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Increasing importance of patients-generated real world data for healthcare policy decisions about medicinal products, volume II

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Increasing importance of patients-generated real world data for healthcare policy decisions about medicinal products, volume II

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Optimal Indicator of Death for Using Real-World Cancer Patients' Data From the Healthcare System

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Background: Information on patient's death is a major outcome of health-related research, but it is not always available in claim-based databases. Herein, we suggested the operational definition of death as an optimal indicator of real death and aim to examine its validity and application in patients with cancer.

Materials and methods: Data of newly diagnosed patients with cancer between 2006 and 2015 from the Korean National Health Insurance Service—National Sample Cohort data were used. Death indicators were operationally defined as follows: 1) in-hospital death (the result of treatment or disease diagnosis code from claims data), or 2) case wherein there are no claims within 365 days of the last claim. We estimated true-positive rates (TPR) and false-positive rates (FPR) for real death and operational definition of death in patients with high-, middle-, and low-mortality cancers. Kaplan–Meier survival curves and log-rank tests were conducted to determine whether real death and operational definition of death rates were consistent.

Results: A total of 40,970 patients with cancer were recruited for this study. Among them, 12,604 patients were officially reported as dead. These patients were stratified into high- (lung, liver, and pancreatic), middle- (stomach, skin, and kidney), and low- (thyroid) mortality groups consisting of 6,626 (death: 4,287), 7,282 (1,858), and 6,316 (93) patients, respectively. The TPR was 97.08% and the FPR was 0.98% in the high mortality group. In the case of the middle and low mortality groups, the TPR (FPR) was 95.86% (1.77%) and 97.85% (0.58%), respectively. The overall TPR and FPR were 96.68 and 1.27%. There was no significant difference between the real and operational definition of death in the log-rank test for all types of cancers except for thyroid cancer.

Conclusion: Defining deaths operationally using in-hospital death data and periods after the last claim is a robust alternative to identifying mortality in patients with cancer. This optimal indicator of death will promote research using claim-based data lacking death information.

Keywords: optimal indicator of death, cancer patients, operational definition of death, claims data, real-world data

INTRODUCTION

Over the decades, abundant data have been produced and used in various fields, including health-related data. The term 'Real-World Data (RWD)' has been introduced with the advent of the big data era, which includes data about patients' health status, health care utilization, or cost collected from sources other than traditional clinical trials. RWD consists of electronic health records, claims and billing data, and registries among others (U.S. Food and Drug Administration, 2017; 2020; 2021). There has been an increasing demand to use RWD as a substitute for clinical trial data under the 21st Century Cures Act, which provides guidance on how RWD can influence decision-making, including label expansion for approved products and post-market commitments (United States Congress legislative information, 2016).

Survival is the most direct indicator of a patient's health status and has a critical impact on health-related decision-making. For this reason, survival-associated outcomes are presented as the major outcomes in most clinical studies, including clinical trials and epidemiological studies; they are also key parameters in studies of health policy, health economics, and outcomes research (Podrid and Myerburg, 2005; Khera et al., 2021; Sanyal et al., 2021). However, death is the most difficult outcome to observe in studies with short-term follow-up. Many clinical trials are not conducted for sufficiently long durations to estimate survival rates, and immature survival data increase the uncertainty in cost-effectiveness studies (Tai et al., 2021). Since the confirmation of death is critical, especially in research targeting severe disease, death information needs to be underpinned by studies using long-term observational data.

RWD, especially insurance claims data, has been considered a valuable resource in health-related research. Although claims data have provided abundant information about patients, including demographics, disease diagnosis codes, and prescription drugs, the patients' death information is not provided in many types of claims data. The National Database of Health Care Claims from Japan, or many United States claims databases were not linked to death information (Ministry of Health, Labour and Welfare, Japan, 2018; Reps et al., 2019; Yasunaga, 2019). Moreover, the patient's death information is limited to the claims data from the Health Insurance Review & Assessment Service, which is most widely used in South Korea (Korean Health Insurance Review and Assessment Service, 2021). The lack of these may pose serious challenges such as censoring in using claims data for health-related research (Johansson and Westerling, 2000; Calvo-Alen et al., 2005).

To circumvent this limitation and investigate the overall survival rates in claims data, many studies have adopted their own definitions for the suspicious indicator for death (Yuk et al., 2016; Shim et al., 2020). However, in these cases, the overall survival rates are likely to be underestimated, as they reported. In this study, we suggested an alternative definition of death that can function as an optimal indicator of real death to investigate the overall survival rates using claims data in which patients' death information is not provided. Since cancer is a disease that is closely related to mortality, we applied this definition to data from groups of patients with cancer, who were stratified based on cancer types as per the mortality rates, for validation.

MATERIALS AND METHODS

Data Source

We used the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) data, the representativeness of which has been verified (Lee et al., 2017). The NHIS database was established for patients' health insurance reimbursements and contained all the information on patient demographic characteristics, disease diagnosis codes, prescription drugs, healthcare resource utilization, and medical expenditures. Codes for disease diagnosis were identified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10, 2016). The NHIS-NSC included data from 2002 to 2015 of approximately 1 million randomly selected Koreans, representing 2% of the Korean population in 2006. The NHIS-NSC is linked to Statistics Korea; thus, it provides official death-related information, such as time and cause of death, making it ideal for this study.

Study Population and Design

In this study, we recruited patients newly diagnosed with cancer having an ICD-10 code of "C" and a critical condition code for cancer (V193 or V194). Since the mortality rates are quite different for different cancer types, we carefully considered several types of cancers and grouped them according to the 5-year relative survival of each cancer as follows: the high-mortality group with 20% less survival (lung [C33 or C34], liver [C22], and pancreatic cancer [C25]), the middle-mortality group with 30–80% of survival (stomach [C16], skin [C43 or C44], and kidney cancer [C64 or C65]), and the low-mortality group with about 98% of survival (thyroid cancer [C73]) (Cancer Research UK, 2014; American Cancer Society, 2018; Bertuccio et al., 2019; Statistics Korea, 2021a). Additionally, all cancer patients not specified with cancer type were considered for presenting the overall trends. The one diagnosed earliest was used to determine their type in patients with multiple cancers. For this study, the cohort entry period was set from 1 January 2006 to 31 December 2015. The cohort entry date was defined as the first day of cancer diagnosis during the cohort entry period. Patients diagnosed with cancer within 365 days before the cohort entry date were excluded from the study, retaining only the newly diagnosed patients. The target patients were followed up until death or till the end of the study (31 December 2015), whichever occurred first.

Operational Definition of Death

The combination of in-hospital death and the length of a period without medical utilization after the last claim was operationally defined as an indicator of death (ODD, **Table 1**). Since the claims data were based on treatment reimbursement, in-hospital death information was provided as a consequence of treatment, which can be identified as follows: 1) death indication as a result of treatment or 2) the ICD-10 codes I461, R96, R98, or R99. These ICD-10 codes have been used to indicate death in previous studies

TABLE 1 | The operational definition of death in claims data.

Type	Description	Date of death
In-hospital death		The date of claim when the code was recorded
(1) Treatment result	The case in which the result of treatment is coded as death	
(2) Disease codes	The case in which the claims data include at least one of the ICD-10 codes – I461 (Sudden cardiac death) – R96 (Other sudden death, cause unknown) – R98 (Unattended death) – R99 (Other ill-defined and unspecified cause of mortality)	
Length of the period without any claims	The case in which there are no claims within 365 days of the last claim. That is, there is none of the medical utilization over 365 days	The date of the last claim

(Shin et al., 2015; Noh et al., 2016; Mentzer et al., 2018). The date of in-hospital death was defined as the date of claim on which the code was recorded. To further observe deaths not recorded as in-hospital deaths, we identified them as cases where there were no claims after the last claim. Several studies (Mealing et al., 2012; Lee et al., 2019) operationally defined death as the cases of no claims for 90 or 180 days. We considered 90/180/270/365 days as the length of a period without any claims. In this case, the date of death was defined as the date on the last claim that identified the patient as dead.

Validity of Operational Definition of Death

We estimated its true-positive rate (TPR) and false-positive rate (FPR) using real death data as the gold standard to validate the ODD. A true positive (TP) means that a dead patient is correctly identified as deceased, whereas a false positive (FP) implies that an alive patient is incorrectly identified as deceased. In contrast, true negative (TN) means that alive patients are correctly identified as alive and false negative (FN) means that dead patients are incorrectly identified as alive. TPR is calculated as TPR = TP/(TP + FN) and represents the proportion of patients who were designated as dead by ODD out of the officially dead patients. Additionally, FPR is determined as FPR = FP/(TN + FP) and represents the proportion of patients who were incorrectly classified as dead by ODD out of the patients alive. TPR and FPR refer to sensitivity and 1-specificity, respectively, and are adequate measures for testing the consistency between real and operational deaths. Based on the estimated TPR and FPR according to the length of periods (90/180/270/365 days), Another measure to validate the usefulness of ODD is the survival probability, based on the time of death and indication of death. NHIS-NSC provides only the death year and month; thus, we arbitrarily set up the date of death to be the last day of the month for computing the overall survival time because every claim should be earlier than the day of death.

Statistical Analysis

Frequency and proportion were applied to the TPR and FPR *via* a confusion matrix, which is a table that is often used to describe the performance of a classifier for which the true values are known. The intervals between medical institution visits of the patients with cancer were presented as the median and interquartile range (IQR) to provide information for defining the length of a period without medical claims. The Kaplan–Meier (KM) survival curves and log-rank tests were performed to compare survival probabilities. This study design allowed a 10-year follow-up period at most. We additionally limited the follow-up periods to 3 and 5 years to show robustness by the length of the follow-up period since a 10-year follow-up period is not expected when analyzing RWD. Descriptive analysis using the box plot was performed to determine the differences between the real and operational death dates. All statistical analyses were performed using R version 4.1 (R Core Team, 2021) and the SAS Enterprise Guide (version 7.1; SAS Institute, Cary, NC, United States).

RESULTS

Study Population

A total of 40,970 patients were newly diagnosed with cancer between 1 January 2006 and 31 December 2015, and 12,604 (30.76%) of them were officially recorded as dead (**Table 2**). In the high-mortality group, 2,896, 2,809, and 921 patients were identified as having lung, liver, and pancreatic cancers, respectively. It was confirmed that 1,917 (66.19%), 1,718 (61.16%), and 652 (70.79%) of these patients with lung, liver, and pancreatic cancers, respectively, were recorded as dead. In the middle-mortality group, 5,681, 828, and 773 patients had stomach, skin, and kidney cancers, respectively. Of the patients with stomach, skin, and kidney cancers, 1,561 (27.48%), 154 (18.60%), and 143 (18.50%), respectively, were recorded as dead. A total of 6,316 patients were diagnosed with thyroid cancer in the low-mortality group, 93 (1.47%) of whom were deceased.

Interval of Medical Institution Visits

Table 3 exhibits the median and IQR of maximum intervals between medical institution visits of patients with cancer as evidence of defining the length of a period without medical claims. We identified 39,434 patients having at least two claims during the follow-up. Among them, 11,252 deceased patients visited the medical institution again within at least 30 days (IQR 36). For alive patients, the median interval was 85 days (IQR 105). Overall, the median interval of visits for alive patients was longer in the low-mortality group, followed by the middle- and high-mortality groups. According to the cancer type,

TABLE 2 | True-positive rate (TPR) and false-positive rate (FPR) according to cancer types.

Cancer type	No. of patients	No. of real death	TP	TN	FN	FP	TPR (%)	FPR (%)
All	40,970	12,604	12,185	28,006	419	360	96.68	1.27
High mortality								
Lung	2,896	1,917	1,854	970	63	9	96.71	0.92
Liver	2,809	1,718	1,671	1,083	47	8	97.26	0.73
Pancreatic	921	652	637	263	15	6	97.70	2.23
Subtotal	6,626	4,287	4,162	2,316	125	23	97.08	0.98
Middle mortality								
Stomach	5,681	1,561	1,506	4,045	55	75	96.48	1.82
Skin	828	154	141	661	13	13	91.56	1.93
Kidney	773	143	134	622	9	8	93.71	1.27
Subtotal	7,282	1,858	1,781	5,328	77	96	95.86	1.77
Low mortality								
Thyroid	6,316	93	91	6,187	2	36	97.85	0.58

TN, true negative; TP, true positive; TPR, true-positive rate; FN, false negative; FP, false positive; FPR, false-positive rate.

TABLE 3 | The maximum intervals between medical institution visits of patients with cancer.

Cancer type	Total		Deceased patients		Alive patients	
	N[a]	Median (IQR, days)	N[a]	Median (IQR, days)	N[a]	Median (IQR, days)
All	39,434	64 (88)	11,252	30 (36)	28,182	85 (105)
High mortality						
Lung	2,631	32 (38)	1,673	27 (26)	958	52 (56)
Liver	2,583	41 (56)	1,513	30 (37)	1,070	70 (60)
Pancreatic	851	28 (36)	587	22 (19)	264	56 (83)
Middle mortality						
Stomach	5,556	72 (111)	1,453	35 (42)	4,103	91 (125)
Skin	820	63 (84)	151	45 (60)	669	66 (91)
Kidney	752	71 (94)	131	31 (33)	621	81 (121)
Low mortality						
Thyroid	6,290	99 (102)	84	36 (39.5)	6,206	100 (103)

IQR, interquartile range; N[a], number of patients who had more than two visits, i.e., who visited medical institutions twice or more.

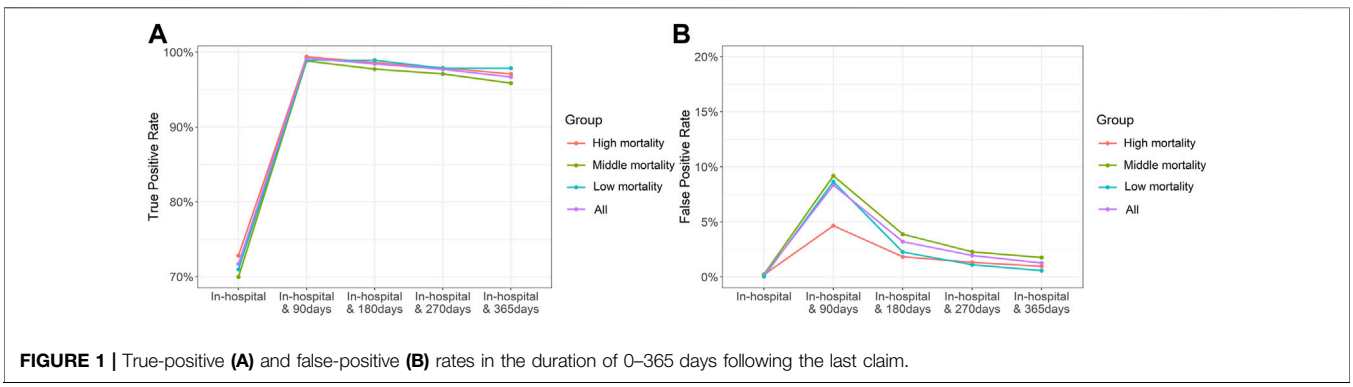

FIGURE 1 | True-positive **(A)** and false-positive **(B)** rates in the duration of 0–365 days following the last claim.

the median interval between medical institution visits of the deceased patients ranged from 22 to 45 days. In contrast, the median interval ranged from 52 to 100 days for patients alive. Additionally, of the 1,536 patients (40,970-39,434 = 1,536) who visited medical institutions once in this study, 1,352 (88.02%) patients died, not having additional claims due to death. Among the remained 184 (11.98%) alive patients, 182 (98.91%) had a follow-up period shorter than 365 days.

Accuracy of Operational Definition of Death

The TPR and FPR according to the length of periods are presented in **Figure 1** (in detail, **Supplementary Tables S1,**

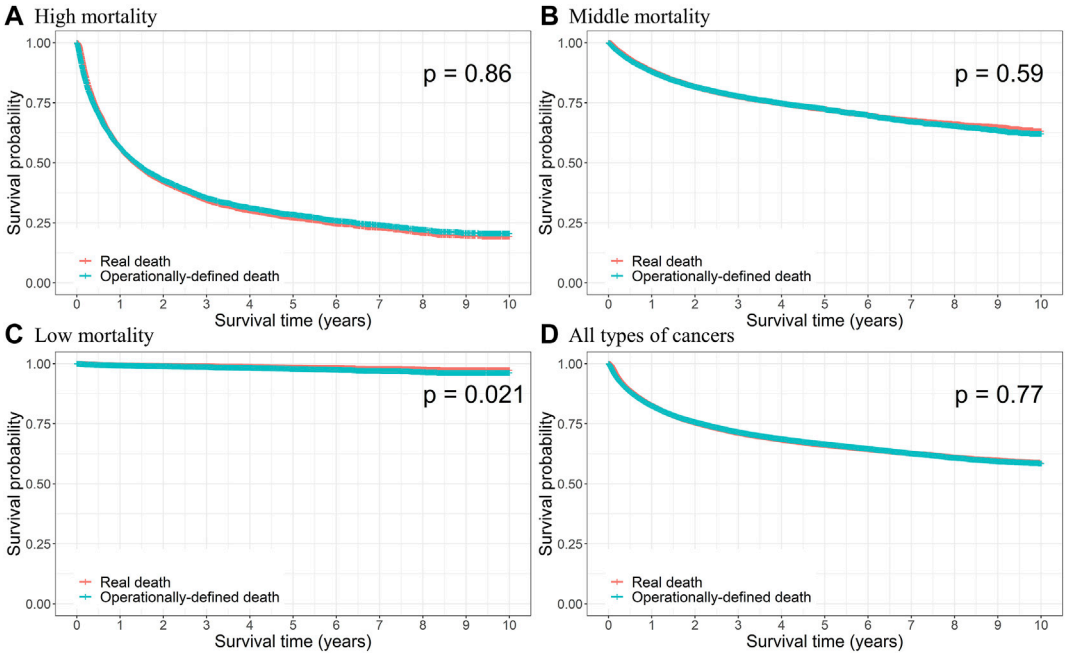

FIGURE 2 | Kaplan–Meier curves of the real and operational definition of death (ODD) and log-rank test *p*-value for **(A)** high, **(B)** middle, and **(C)** low mortalities, and **(D)** all types of cancers.

S2). In cases where only in-hospital death was considered, FPRs were close to 0 but the TPR was approximately 70%. Considering the ODD using the length of periods without medical utilization, TPRs were over 95%. TPRs were slightly decreased after 90 days from the last claim, and FPRs exhibited large variations and high values until 270 days, especially when using the length of 90 days. When using 90 days, FPRs in high-mortality cancer except pancreas were less than 5%, but those in other types of cancers were 7%. When using 365 days, TPRs were 90% over and FPRs were 3% below.

The TPR and FPR from the results determined using a combination of in-hospital deaths and cases in which there were no claims within 365 days of the last claim as an ODD are presented in **Table 2**. Considering all cancers, the overall TPR and FPR were 96.68 and 1.27%. The TPR indicates that 12,185 patients were identified as deceased among 12,604 patients with death records. The FPR indicates that only 360 patients were falsely identified as dead among a total of 28,366 alive patients. In the high-mortality group, the overall TPR and FPR were 97.08 and 0.98%, respectively. In the middle- and low-mortality groups, TPRs were 95.86 and 97.85% and FPRs were 1.77 and 0.58%, respectively.

When not using in-hospital death but using the length of a period without any claims, the results for 365 days revealed that TPR was 86.25% and FPR was 1.14% (**Supplementary Table S2**).

Comparison of Survival Probabilities

For consistency in terms of the overall survival rate between real and operational deaths, we compared the KM curves for the two cases and conducted a log-rank test, and the results observed according to the mortality group are presented in **Figure 2**. The survival probabilities were computed for each death point, and no difference between survival curves was observed for all types of cancers, indicating that there was no significant difference between the dates of real and operational definitions of death ($p = 0.77$). No significant difference was observed for each mortality group, except for the low-mortality group (thyroid cancer; $p = 0.021$). **Supplementary Figure S1** presents the KM curves and log-rank test *p*-values for specific cancer types, and the results were not different from those of the mortality groups.

When we adjusted the period for the case of no claims to 180 days, patients with lung, liver, and pancreatic cancers in the high-mortality group, and skin and kidney cancers in the middle-mortality group did not show significant differences with respect to the KM curves (**Supplementary Figure S2**). We considered 3- and 5-year follow-up periods as well and observed that there were no significant differences for all cancer types in both these periods (**Supplementary Figures S3, S4**).

Most values of the differences between the dates of real and ODD were properly distributed within the 30 days, regardless of the cancer type, which represents the accuracy of the suggested definition of death using claims data in health-related research (**Supplementary Figure S5**).

DISCUSSION

In the present study, we validated ODD *via* TPR and FPR and performed a comparison of survival curves. The TPR was found to be more than 95%, and the FPR was less than 2% in the high-,

middle-, and low-mortality groups. Additionally, there was no significant difference in the survival probability between the real death and the ODD. With robustness confirmed through sensitivity analysis, we have suggested an alternative definition to indicate death and the corresponding date of death to address the absence of death-related information in claims data, especially for patients with cancer. In cases where only in-hospital death was considered, FPRs were perfectly controlled; however, TPRs were disturbed below 80%, and thus, death was not accurately identified. Therefore, researchers who use only administrative data lacking death information could also observe overall survival by defining death based on the pattern of medical utilization.

During the 10-year follow-up, the KM curves were not significantly different for all cancers, except for thyroid cancer. The incidence of thyroid cancer is increasing worldwide with the advancement of diagnostic technology (Davies and Welch, 2014; Cabanillas et al., 2016), which is well-managed enough to cause overdiagnosis, especially in South Korea (Ahn et al., 2014; Park et al., 2016). Because the mortality of thyroid cancer is very low (Statistics Korea, 2021a), it has been presumed that an operational definition could lead to an overestimation of mortality. Similarly, this study showed that cancers with relatively low mortality, including stomach, skin, and kidney cancers, had slightly lower survival probabilities in operationally defined deaths later in the follow-up period, although not significantly different. In the middle-, and low-mortality groups, FPR was more important than TPR due to the size of cases (number of death patients), and they were both controlled well (TPR middle: 95.86%; TPR low: 97.85%, FPR middle: 1.77%; FPR low: 0.58%). Conversely, cancers with poor prognosis, such as lung, liver, and pancreatic cancers, had slightly lower survival probabilities in real deaths later in the follow-up period. In this group, the TPR was relatively more important than the FPR owing to the imbalance problem, in which the proportion of dead cases was higher than that of alive cases. Our results revealed that the TPR and FPR were well-controlled. Considering 3- and 5-year follow-up periods revealed robustness, implying that this definition can be applied to other studies, regardless of follow-up periods. It can be interpreted that our ODD captures the real death well and can be used as an indication of death.

For base-case analysis, we defined death as the case when there were no claims for 365 days from the last claim. The reasoning behind adopting 365 days for ODD is presented in **Figure 1**. It revealed a lower FPR than the case where the claim duration was shorter. The FPR for pancreatic cancer was the highest but only slightly over 2%, and for lung, liver, and thyroid cancers was less than 1%. Additionally, the TPR was greater than 95% overall. We determined the 365-day period, which yielded the lowest FPR and acceptable TPR, as appropriate. As shown in **Table 3**, the medians of a maximum interval between medical institution visits were less than 100 days regardless of cancer type and the maximum of IQRs was 125 days. It implied that 90 days seemed not to be enough to define ODD. Previous studies have defined death as the case of no claims for 180 days, which is shorter than that of our study (Mealing et al., 2012; Lee et al., 2019). When the time period was reduced to 90 days, it resulted in a TPR of over 99% and also an FPR of over 8%. ODD of shorter periods significantly overestimated mortality, especially in cancers with relatively low mortality, including stomach, skin, kidney, and thyroid cancers. However, for cancers with high mortality, such as lung and liver cancers, considering a short period was also worth considering (FPR with 90 days 3.78% in lung cancer; 4.03% in liver cancer). Similarly, our definition may be more accurate for patients with advanced cancer than for patients with early-stage cancer. We also elicited TP and FP results when defining ODD using only the length of a period without any claims for 90–365 days. Although the TPR value was close to 80% for the case of no further claims within 365 days of the last claim, definitions using only the claims gap could be considered in cases of advanced cancer or cancer with low survival.

We identified why FP and FN occurred. The median interval between medical institution visits for FP patients was 252.5 days, which was approximately four times that of all patients. FP patients visited medical institutions infrequently because of which their visit interval was longer than 365 days, resulting in them being considered dead. All FN patients were confirmed to have been dead in 2015. Since the study period was only until 2015, these patients were followed up for less than 365 days of the last claim and were not operationally defined as deaths. The number of FN patients could be reduced if the researcher established a minimum follow-up period, especially a longer period than the period used for the operational definition. In this study, if the cohort entry period was maintained but the follow-up period was extended by 1 year, FN did not occur.

The overall proportion of incidence of all cancers in South Korea from 2006 to 2015 was approximately 4.06%, as per Statistics Korea (Statistics Korea, 2021a). The data used in this study provided by NHIS-NSC represented approximately 4.09%. This indicates that our data were representative datasets. The incidence rates of stomach, liver, and lung cancers were reported to be 0.59, 0.32, and 0.43% (Statistics Korea, 2021a), and those of our data were 0.56, 0.28, and 0.29%, respectively. The proportion of deaths among patients with cancer from our data was slightly lower than the reports (Statistics Korea, 2021a; Statistics Korea, 2021b) (all cancers: 30.76 vs. 35.38%; stomach cancer: 27.47 vs. 32.97%; liver cancer: 61.16 vs. 70.73%; lung cancer: 66.19 vs. 73.74%). However, this may be secondary to the sampling error. Since we utilized real death-related information of the selected patients with cancer recorded by Statistics Korea, no critical problem could affect the study to demonstrate the validity of the suggested ODD.

Despite the significance of these findings, this study had some limitations. First, we applied the ODD to patients with cancer; thus, this definition should be used carefully for other diseases in terms of generalization. However, we confirmed the TPR and FPR across various mortality groups. There is room to adapt the ODD to various diseases, especially with high mortality. Second, the selected patients might be insufficient in this study since we used diagnostic codes recorded in the claims data. However, we included patients with cancer registered under the National Health Insurance Act using critical condition codes. Also, we confirmed that the mortalities in this study were similar to the actual cancer-associated mortalities (Statistics Korea, 2021a).

Third, a lack of the exact date of death and having only the information about the month of death in the database was a limitation. This was the innate limitation of the NHIS-NSC data. Thus, we provided the differences between the last day of the deceased month and the defined date in supplementary as **Supplementary Figure S5**. IQR of gap days was within 20 days across whole groups, even in all cancer groups not specified by cancer type. Even though we do not know the exact date, the gap days in **Supplementary Figure S5** is the maximum value, which can be observed in the real world. Therefore, the difference between the real death date and the operationally-defined date would be close to zero.

Healthcare utilization can differ according to the healthcare system. However, cancer patients worldwide are mainly managed according to consensus and clinical guidelines published by the National Comprehensive Cancer Network, European Society for Medical Oncology, or American Society of Clinical Oncology. Physicians have followed up on cancer patients regularly according to guidelines even if each healthcare system to which they belong has its own system. Although survival rates differ across countries due to race, data collection, analysis, and quality, and are difficult to compare these directly (Gatta et al., 2000; Coleman et al., 2008), the rank and trend of survival rates in South Korea were similar with the United Kingdom and the United States (Cancer Research UK, 2011; Quaresma et al., 2015; Siegel et al., 2022). Therefore, the ODD we offered can be helpful when analyzing claims data to conduct outcomes research regardless of country and healthcare system.

CONCLUSION

In cancer patients, defining the case of no claims within 365 days of the last claim as death can be a robust alternative for death information in claims data lacking it. By determining the appropriate ODD, this study contributes to promoting outcomes research using claim-based data that does not include death information, especially for out-of-hospital deaths.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study, and the data can be found here: Korean National Health Insurance Service (https://nhiss.nhis.or.kr/).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Sungkyunkwan University, Republic of Korea (SKKU-IRB-2021-11-020). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-CJ, S-HK, SM, and JHN designed the research; S-CJ, S-HK, SM, A-RJ, E-KL, and JHN drafted the manuscript; S-CJ, S-HK, SM, A-RJ, E-KL, and JHN performed the research; S-CJ and A-RJ analyzed the data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.906211/full#supplementary-material

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Willingness to pay for and willingness to vaccinate with the COVID-19 vaccine booster dose in China

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Objective: The present study aims to assess the willingness to pay (WTP) for and willingness to vaccinate (WTV) with the Coronavirus (COVID-19) vaccine booster dose in China when the pandemic is under adequate control and the majority of the population is vaccinated. This study is also to identify significant factors associated with the WTP.

Methods: This was a cross-sectional study on adults with no past or present COVID-19 infection. An online questionnaire was distributed to collect data on vaccination status, quarantine experience, and factors related to health beliefs on vaccination. The WTV was assessed through the vaccination preference. The WTP was examined by payment scale (PS) and iterative bidding game (IBG) administered in random order. Three IBG algorithms with different starting-price were presented randomly. The average WTP of PS and IBG were analyzed as primary outcomes using univariate and multivariate analyses. Multivariate ordered logistic regression was performed to identify significant factors for the WTP.

Results: The survey recruited 543 participants with a mean age of 32 years and 57.80% being female. The WTV rate was 86.74%, while 94.66% of participants completed full-schedule or enhanced vaccination. The mean WTP was CNY 149 (±CNY 197) and the median WTP was CNY 80. Regarding significant factors for the WTP, urban residents were 57% more likely (95% CI: 1.11-2.22) to pay for a high-priced vaccine than rural residents. Respondents who completed full-schedule vaccination were 46% more likely (95% CI: 1.03–2.07) to pay for a high-priced vaccine than those who completed enhanced vaccination. Respondents with a low household income of CNY 40k or lower were 62% less likely (95% CI: 0.21–0.66) to pay for a high-priced vaccine than those with a middle household income of CNY 110k–210k. Other significant factors associated with the WTP included the perceived benefit of vaccination and peer environmental pressure in the health belief model.

Conclusion: The WTV with the COVID-19 vaccine booster dose was high in China. The WTP was influenced by the place of residence, vaccination status, household income, perceived benefit of vaccination, and environmental peer pressure. Study findings can inform policymakers to better design vaccination programs and financial schemes involving out-of-pocket payments.

KEYWORDS

willingness to pay, willingness to vaccinate, COVID-19, vaccine, booster, health belief model, iterative bidding game

1 Introduction

The Coronavirus (COVID-19) pandemic continues to be a global public health crisis and has caused huge economic and health damage worldwide. Mass vaccination aiming for herd immunity has been adopted as a national strategy in many countries to protect the population from being infected or developing severe conditions (Ayifah and Ayifah, 2022). Since December 2020, China has launched two rounds of vaccination programs and has been actively promoting the COVID-19 vaccine booster dose (GotPsRo, 2021). Domestically-manufactured vaccines by SinoVac or SinaPharm are provided free of charge to all citizens in light of the zero-COVID policy. Herd immunity of 75%–90% vaccination coverage was obtained in China, as well as in many other countries around the world (Anderson et al., 2020).

The effect of initial mass vaccination is limited as reflected by multiple COVID-19 resurgences worldwide and the recent outbreak in Shanghai. Immunity to COVID-19 can be undermined by the waning effect of vaccination, evolving variants, and virus breakthroughs. To cope with this challenge, the booster dose has been utilized by health authorities. Experts proposed an annual booster dose as a long-term strategy to control cross-border transmission and local outbreaks.

However, a long-term vaccination program is challenging both financially and socially. Providing vaccinations as public goods to a huge population is costly for the government given the current economic decline. Chinese National Healthcare Security Administration announced that the National Medical Fund would no longer subsidize routine nucleic acid amplification tests (Administration, 2022). Copayments or complete out-of-pocket charges may become a requirement in the future in order to sustain vaccination needs.

Vaccine hesitancy has been the major reason for the inability to control the COVID-19 infection (Iyer et al., 2022). Studies found that the success of long-term vaccination is closely related to the willingness to pay (WTP) for and willingness to vaccinate (WTV) against public viruses (Wane et al., 2019; Lai et al., 2020). WTP informs the maximum amount of money a customer is willing to pay for a specific good based on personal valuation and is commonly estimated using contingent valuation methods (CVM). WTV indicates the vaccination intention which can be used to predict actual vaccination behavior. The evidence surrounding WTP and WTV has assisted in policy development, vaccine pricing, government purchasing, and program design (Hynes et al., 2021). At the beginning of the COVID-19 epidemic, WTV and WTP were investigated in the Chinese population. Studies have reported the median WTP for COVID-19 to be CNY 100, 200, or 300 (Wang et al., 2021; Lin et al., 2020; Han et al., 2021) and the mean WTP to be CNY 130.45 and 254 (Qin et al., 2021; Wang et al., 2021). A higher price range of CNY 501–1,000 was once reported as the most preferred price for the general Chinese population (Zhang et al., 2021). On the other hand, WTV rates were estimated to be 83.5%, 77.4%, and 89.1% (Lin et al., 2020; Zhang et al., 2021; Han et al., 2021). Both WTP and WTV were largely affected by socioeconomic variables and variables measuring personal health beliefs, such as perceived risk and perceived benefit of vaccination in line with the health belief model (HBM) (Goruntla et al., 2021).

WTP and WTV varied with the severity of the epidemic (Wang et al., 2022). Early studies were conducted prior to the introduction of the COVID-19 vaccine to the market, therefore the findings may not bear much value to guide future vaccination policy. Now that the target population has been vaccinated and has personally experienced the effect of receiving or abstaining from vaccination, attitudes surrounding WTP and WTV were anticipated to change.

We hypothesized that an annual booster dose of the COVID-19 vaccine will become a national strategy in China for the next several years and that supplying vaccines as public goods may not be sustainable. WTP and WTV change over time, therefore reevaluation is required to inform the feasibility of an alternative financing scheme, as well as program design and adaptation. This study was conducted aiming to assess the WTP and WTV of the general Chinese population for the COVID-19 vaccine booster dose. This study is also designed to identify the significant factors contributing to the WTP.

2 Materials and methods

2.1 Study design

This cross-sectional study was conducted through the largest online survey platform in China, Wen Juan Xing (Changsha

Ranxing Information Technology Co., Ltd., Hunan, China). Wen Juan Xing is equivalent to Qualtrics, SurveyMonkey, or CloudResearch and provides online questionnaire design and survey functions for customers. The questionnaire was posted in January 2022 untill March 2022. Participants were allowed to answer the questionnaire through individual WeChat accounts only once in anonymity. Snowballing sampling was adopted and started with a convenience sample composed of colleagues, friends, and their families. The questionnaire was then circulated *via* the existing respondents. The inclusion criteria were broadly defined, 1) ≥18 years, 2) no history of COVID-19 infection, and 3) ability to read Chinese. The survey was voluntary, and no incentive was offered.

2.2 Data collection

2.2.1 Sample characteristics

The questionnaire inquired respondents about demographic information, socioeconomic status [highest education, marital status, annual household income (AHI), place of residence, medical insurance, etc.], health status (self-rated health status, concurrent chronic diseases), and vaccine dose received. The impact of COVID-19 policies on personal life was explored by asking if respondents had been quarantined at home or in a hotel. Exposure to COVID-19 was measured by the question regarding the presence or absence of recent positive cases in the respondents' community or workplace. Respondents also provided their experience of vaccination and infection.

2.2.2 Health belief

As informed by the HBM theory (Lau et al., 2010), we adapted a previous Chinese HBM questionnaire to investigate the individuals' beliefs in four dimensions with eight questions. These four dimensions included perceived susceptibility ("Infection with COVID-19 is possible for me at present," "The probability of infection is high for me for the next few months"), perceived severity ("I will be very sick if I got COVID-19 infection"), perceived benefits ("Vaccination will decrease my risk of getting an infection or developing severe complications if infected"), and perceived barriers ("I am concerned about the effectiveness of the COVID-19 vaccine," "I am concerned about the safety of the COVID-19 vaccine," "I am concerned about my affordability considering the cost of vaccination"). One question was dedicated to measuring environmental peer pressure ("I will accept vaccination if others accept it"). Each question was assigned four options, "strongly agree," "agree," "disagree" or "strongly disagree" to be consistent with the previous questionnaire (Lin et al., 2020).

2.2.3 Willingness to vaccinate assessment

The WTV in our study is the willingness to receive the COVID-19 vaccine booster dose given respondents have been vaccinated, witnessed the impact of COVID-19 policies, and generally understood the scope and severity of the current COVID-19 epidemic. The WTV question was "Will you accept the COVID-19 vaccine in the future if vaccination is required." The extent of the agreement was ordered as "definitely yes," "probably yes," "not sure," "probably no," and "definitely no." The "definitely no" precludes the subsequent WTP questions and was taken as zero.

2.2.4 Willingness to pay assessment

The WTP in our study examined the maximum amount a person was willing to pay for the booster dose of the COVID-19 vaccine. Based on the CVM methodology, payment scale (PS) and iterative bidding game (IBG) were developed to elicit the stated WTP. Two methods were used in parallel to mitigate the bias inherent in either method (Frew et al., 2004). Price ranges for WTP were derived from the purchase price of category-2 vaccines (out-of-pocket payment and voluntary vaccination), 10% of national monthly income, and medical expense per capita in China from 2016 to 2020 (Catma and Varol, 2021; Ayifah and Ayifah, 2022). A range of CNY 20–800 was deemed reasonable and was applied to both PS and IBG. In order to avoid the artificial between-method difference in WTP solely caused by price cutoffs, the price strata were set consistently for PS and IBG. PS used 10 strata, CNY 20, 80, 110, 140, 170, 200, 350, 425, 500, and 800, while IBG used nine bids, i.e., CNY 20, 80, 140, 170, 200, 350, 425, 500, and 800. Whether for PS or IBG, an open-ended question was followed if a respondent chosed the highest price of CNY 800.

The PS simply asked the correspondents to choose one of 10 preset prices to indicate their WTP or provide an amount if their WTP is above CNY 800. The IBG first gave a brief update regarding the epidemic, prevailing policies, and social effect of COVID-19 vaccination (Frew et al., 2010). Following the update, an usher-in question was presented that stated "Individuals should pay for COVID-19 vaccine out-of-pocket" with five options: "absolutely correct," "probably correct," "not sure," and "probably wrong," and "absolutely wrong." Those answering "absolutely wrong" did not proceed to the subsequent IBG algorithms. Accordingly, their WTP were marked as zero. Three IBG algorithms, IBG20, IBG170, and IBG800, were designed with initial bids of CNY 20, 170, and 800 respectively, to minimize the starting-price bias or anchoring effect (Figure 1) (Frew et al., 2004). Each IBG algorithm would lead to seven ending prices of CNY 20, 80, 140, 200, 350, 500, and 800. Additionally, the respondents were given a chance to state their maximum WTP if it is over CNY 800.

To minimize the information bias due to the ordering effect in estimation, random allocation procedures were taken in two steps. When a respondent was starting to answer WTP questions, one CVM method (PS or IBG) was randomly assigned first and then followed by the other. When it came to IBG algorithms, respondents were instructed to randomly pick a number between

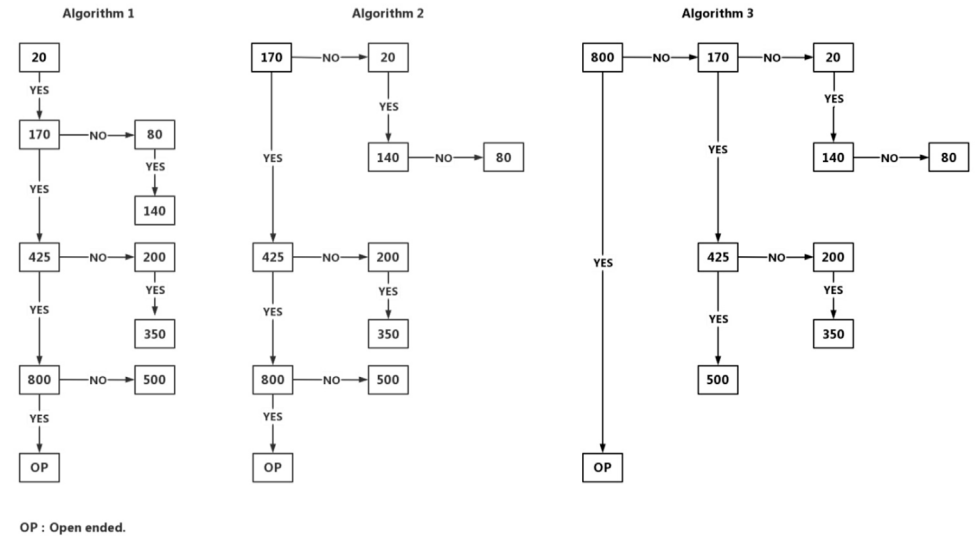

FIGURE 1
Iterative bidding game algorithms.

1, 2, and 3, corresponding to three IBG starting prices, and next move forward to complete the bidding process. As a result, the respondents were randomly assigned to six pathways, IBG20-PS (8.17%), IBG170-PS (18.24%), IBG800-PS (0.87%), PS-IBG20 (34.47%), PS-IBG170 (24.65%) and PS-IBG800 (12.97%).

2.2.5 Statistical analysis

A total of 545 subjects participated in the study by March 2022. Questionnaires of two respondents (COVID-19 positive) were removed for the reasons of ineligibility or missing information. Descriptive statistics were performed to summarize the continuous variables with a mean (standard deviation, SD) and categorical variables with a number (proportion). Univariate analyses included *t*-test, ANOVA, and Chi-square test to carry out comparisons. The WTP derived from PS and IBG were subjected to an agreement test capturing an absolute intra-class correlation coefficient of 0.132, which indicated little agreement of PS with IBG estimates (Koo and Li, 2016). Therefore, the WTP-PS and WTP-IBG were averaged, and the WTP-average was analyzed as the primary outcome.

As the distribution of WTP-average was highly skewed to the right, it was categorized into five levels, CNY 0, 0–80, 81–200, 201–500, >500, with referencing to benchmarks and the parameters of distribution (null or mode, median, mean, 75%, and 95% percentile). Setting the categorical WTP-average as the dependent variable, multivariate ordered logistic regressions were performed to identify the significant predictors of WTP. There were 10 subjects giving extremely opposite WTPs by PS and IBG (e.g., maximum WTP in PS yet minimum WTP in IBG, or vice versa). These data were considered invalid and therefore excluded from the WTP analysis. The analyses were performed with SPSS 26. A $p < 0.05$ was taken as statistically significant.

3 Results

3.1 Characteristics of the sample

The mean age of the sample ($n = 543$) was 32 years with 36 (6.60%) subjects older than 50 years (Table 1). There were more females (57.80%) and urban residents (52.12%). Families ranked in the middle class (AHI from CNY 110 to 210k) accounted for 46.22%. The number of participants from relatively poor families ($n = 67$, AHI < CNY 40k) was almost equal to those from super rich families ($n = 66$, AHI > CNY 450k). Twenty-six (4.78%) persons were not covered by any medical insurance. The majority (89.32%) rated their health good or very good, while 5.89% of the sample had self-reported chronic conditions. There were 96 (17.86%) participants having been quarantined at home and another 15 (2.76%) persons having been quarantined in a hotel. A total of 56 (10.31%) persons have been exposed to either community or workplace infection recently.

3.2 Health belief assessment

As presented in Table 1, the risk perception of COVID-19 in our sample was low, as only 14.36% and 7.92% of the respondents agreed with the current or short-term risk of infection. Only 71

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TABLE 1 Characteristics of study participants and willingness to vaccinate.

Variable	Category	N	Percent (%)
Age (years)	18–24	209	38.49
	25–35	161	29.65
	36–50	137	25.23
	>50	36	6.63
Gender	Male	229	42.17
	Female	314	57.83
Occupation	Professional	124	22.84
	Company staff	90	16.57
	College students and below	96	17.68
	Graduate students and above	121	22.28
	Others	112	20.63
Marital status	Married/Divorced	228	41.99
	Single	315	58.01
Highest education level	Junior college or below	120	22.10
	Bachelor's degree	243	44.75
	Master's degree or above	180	33.15
Place of residence	Urban	260	47.88
	Rural	283	52.12
Annual household income (CNY 1,000)	≤40	67	12.34
	40–70	73	13.44
	70–110	122	22.47
	110–210	129	23.76
	210–450	86	15.84
	>450	66	12.15
Chronic diseases	No	511	94.11
	Yes	32	5.89
Health status self-rated	Very good	224	41.25
	Good	261	48.07
	Fair/Poor/Very poor	58	10.68
Medical insurance	No	26	4.79
	National medical insurance for urban employees	168	30.94
	National medical insurance for urban residents and rural citizens	164	30.20
	National medical insurance and other insurance	127	23.39
	Other insurance	58	10.68
Quarantine experience	Hotel quarantine	17	3.13
	Home quarantine	97	17.86
	No	428	78.82
Recent exposure to COVID-19	No	487	89.69
	Yes	56	10.31
Actual vaccination status	One shot	29	5.34
	Two shots	188	34.62
	Three shots	326	60.04
Willingness to vaccinate	Definitely yes	325	59.85
	Probably yes	146	26.89
	Not sure/Probably no/Definitely no	72	13.26
Out-of-pocket payment for vaccine	Absolutely correct	28	5.20
	Probably correct	116	21.70
	Not sure	249	46.60

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TABLE 1 (*Continued*) Characteristics of study participants and willingness to vaccinate.

Variable	Category	N	Percent (%)
	Probably wrong	52	9.70
	Absolutely wrong	89	16.70
Perceived current risk of infection	Strongly agree/Agree	78	14.36
	Disagree	172	31.68
	Strongly disagree	293	53.96
Perceived short-term risk of infection	Strongly agree/Agree	43	7.92
	Disagree	222	40.88
	Strongly disagree	278	51.20
Perceived severity of infection	Strongly agree/Agree	71	13.08
	Disagree	245	45.12
	Strongly disagree	227	41.80
Perceived benefit of vaccination	Strongly agree	212	39.04
	Agree	277	51.01
	Strongly disagree/Disagree	54	9.94
Concerned about vaccine efficacy	Strongly agree/Agree	178	32.78
	Disagree	267	49.17
	Strongly disagree	98	18.05
Concerned about vaccine safety	Strongly agree/Agree	114	20.99
	Disagree	309	56.91
	Strongly disagree	120	22.10
Environmental peer pressure	Strongly agree/Agree	196	36.10
	Disagree	240	44.20
	Strongly disagree	107	19.71
Concerned about vaccination cost	Strongly agree/Agree	172	31.68
	Disagree	265	48.80
	Strongly disagree	106	19.52

CNY, Chinese Yaun currency; COVID-19, Coronavirus disease 2019.

(13.08%) respondents agreed that COVID-19 was a severe disease, while 489 (90.06%) participants were in agreeance with the protection of the vaccine. The efficacy and safety of the COVID-19 vaccine still concerned 32.78% and 20.99% of the sample respectively. Vaccination cost became an issue for 31.68% of the sample, and 196 (36.10%) participants would accept the vaccination only if others accepted it.

3.3 Willingness to vaccinate and willingness to pay

All participants were vaccinated, and the rates of full-schedule and enhanced vaccination totaled 94.66%. However, the WTV ("Definitely yes" or "probably yes" to vaccination) rate was comparatively lower at 86.74% (Table 1). Still, 9 (1.66%) and 17 (3.13%) subjects chose "definitely not" or" probably not" to the booster dose.

The distributions of WTP and the demand curve of the COVID-19 vaccine were presented in Figure 2. In consistency with the theory, the WTP prices are distributed to the right irrespective of the estimation approach. PS and IBG derived the same median and mode for WTP, which both were CNY 80. IBG derived a significantly higher mean WTP of CNY 189 than PS (mean = CNY 109). The WTP-average captured more intermediate WTPs with the median and mean being CNY 80 and 149 respectively.

3.4 Significant factors for willingness to pay

The WTP-average was presented in Table 2 for different groups. Univariate analyses revealed that gender, place of residence, AHI, chronic disease, actual vaccination status, concerns about safety and cost of vaccination, actual vaccination status, and WTV were significant factors for WTP through between-group comparisons. Specifically, males and urban residents were willing to pay more than their counterparts. The WTP increased with the AHI. Chronic conditions predisposed a person to pay CNY 85 more for the

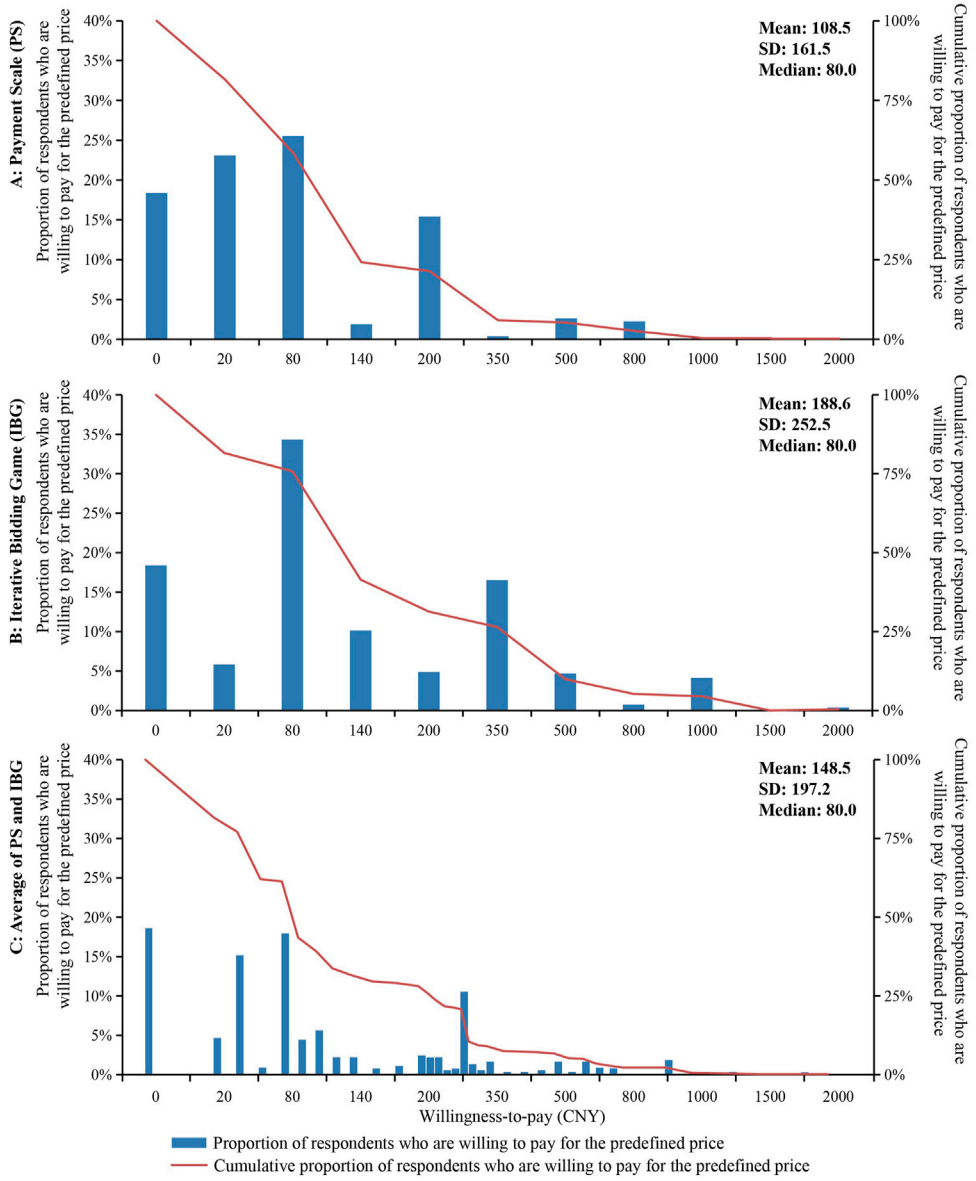

FIGURE 2
Willingness to pay distributions and demand curves of COVID-19 vaccine booster dose.

vaccine. Vaccination predisposed a person to pay less, as those receiving the booster shot preferred a price of CNY 129, notably lower than those receiving one or two shots only. The WTV had a positive relationship with the WTP. "Definitely yes" or "probably yes" to WTV were associated with mean WTPs of CNY 156 and 165, which was higher than the mean WTP (CNY 85) for the group "not sure," "probably no" or definitely no." For HBM variables, respondents who were not concerned about the vaccine safety or vaccination cost were willing to pay CNY 172 and CNY 170 respectively, which was higher than those who were concerned about these issues.

When all variables were submitted to the multiple ordered logistic model, five factors were significant including two socioeconomic variables (place of residence and AHI), two HBM variables (perceived benefit of vaccination and peer environment pressure), and actual vaccination status (Table 3). Urban residents were 57% more likely (95% CI: 1.11–2.22) to pay for a high-priced vaccine than rural residents. Respondents with a low household income of CNY 40,000 or lower were 62% less likely (95% CI: 0.21–0.66) to pay for a high-priced vaccine than those with a middle household income of CNY 10,000–CNY 210,000. Compared to those who

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TABLE 2 Willingness to pay in different groups.

Variable	Category	n	WTP-Average (CNY)			
			Median	Mean	S.D.	P
Age (years)	18–24	206	80	147	208	0.826
	25–35	156	80	148	175	
	36–50	135	80	158	213	
	>50	36	80	124	163	
Gender	Male	222	80	171	218	0.028
	Female	311	80	133	180	
Occupation	Professional worker	120	80	152	210	0.629
	Company staff	89	95	166	189	
	College students and below	95	80	163	254	
	Graduate students and above	118	80	131	140	
	Others	111	80	137	187	
Marital status	Married/Divorced	225	80	149	198	0.969
	Single	308	80	148	197	
Highest education level	Junior college or below	119	80	152	198	0.857
	Bachelor degree	239	80	152	216	
	Master's degree or above	175	80	142	169	
Place of residence	Urban	278	80	170	219	0.008
	Rural	255	80	125	168	
Annual household income (CNY 1,000)	≤40	64	50	86	112	0.001
	40–70	72	80	120	158	
	70–110	120	80	142	169	
	110–210	129	95	148	158	
	210–450	85	80	166	199	
	>450	63	80	235	345	
Chronic diseases	No	503	80	144	181	0.022
	Yes	30	95	229	370	
Health status self-rated	Very good	217	80	144	197	0.819
	Good	259	80	154	202	
	Fair/Poor/Very poor	57	80	142	176	
Medical insurance	No	25	50	88	104	0.082
	National medical insurance for urban workers	164	80	166	218	
	National medical insurance for urban and rural residents	160	80	124	137	
	National medical insurance and other insurance	127	80	153	185	
	Other insurance	57	80	185	300	
Quarantine experience	Hotel quarantine	15	80	199	278	0.586
	Home quarantine	96	80	152	229	
	No	422	80	146	186	
Recent exposure to COVID-19	No	478	80	146	195	0.334
	Yes	55	80	173	217	
Actual vaccination status	One shot only	29	80	224	330	0.008
	Two shots	183	95	171	202	
	Three shots	321	80	129	176	
Willingness to vaccinate	Definitely yes	316	80	156	214	0.011
	Probably yes	145	80	165	189	
	Not sure/Probably no/Definitely no	72	50	85	102	
Perceived current risk of infection	Strongly agree/Agree	78	80	170	239	0.554

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TABLE 2 (*Continued*) Willingness to pay in different groups.

Variable	Category	n	WTP-Average (CNY)			
			Median	Mean	S.D.	P
	Disagree	169	80	147	195	
	Strongly disagree	286	80	143	186	
Perceived short-term risk of infection	Strongly agree/Agree	42	80	145	160	0.310
	Disagree	218	80	164	219	
	Strongly disagree	273	80	137	183	
Perceived severity of infection	Strongly agree/Agree	70	80	195	242	0.087
	Disagree	240	80	147	195	
	Strongly disagree	223	80	136	182	
Perceived benefit of vaccination	Strongly agree	208	80	157	196	0.369
	Agree	273	80	149	202	
	Strongly disagree/Disagree	52	50	114	178	
Concerned about vaccine efficacy	Strongly agree/Agree	175	80	137	207	0.163
	Disagree	264	80	164	202	
	Strongly disagree	94	80	125	161	
Concerned about vaccine safety	Strongly agree/Agree	112	80	123	165	0.006
	Disagree	305	80	172	223	
	Strongly disagree	116	80	112	139	
Environmental peer pressure	Strongly agree/Agree	195	80	162	216	0.067
	Disagree	235	80	155	197	
	Strongly disagree	103	50	108	153	
Concerned about vaccination cost	Strongly agree/Agree	170	80	134	153	0.033
	Disagree	261	80	170	231	
	Strongly disagree	102	65	116	159	

CNY, Chinese Yaun currency; COVID-19, Coronavirus disease 2019.

completed enhanced vaccination, respondents who completed full-schedule vaccination were 46% more likely (95% CI: 1.03–2.07) to pay for a high-priced vaccine. Respondents who do not see the perceived benefit of vaccination were 51% less likely (95% CI: 0.26–0.95) to pay for a high-priced vaccine than those who see the perceived benefit of vaccination. Respondents who do not have peer environmental pressure were 52% less likely (95% CI: 0.26–0.87) to pay for a high-priced vaccine than those who have peer environmental pressure.

4 Discussion

COVID-19 has had drastic economic, social, and public health implications, and continues to pose a significant threat worldwide. The COVID-19 vaccine booster dose has been implemented globally and is becoming a long-term public health safety measure. The WTP and WTV are important indicators of the population's attitude toward continuous vaccination, and these measures fluctuate with the progression of the epidemic and its effect on policies. Therefore, continuous assessment of the WTP and WTV is of great significance. With this in mind, this study was conducted and found that the overall WTV rate was 86.74% in China given a 100% coverage rate and a 94.66% full vaccination rate. The median and mean WTPs were CNY 80 (USD 12.40) and CNY 149 (USD 23.02) respectively. Place of residence, AHI, vaccination status, perceived benefit of vaccination, and environmental peer pressure can significantly predict the concurrent WTP.

Our results appear encouraging, as both the actual vaccination rate and WTV are high. Compared to the WTV rates of 83.50%, 77.40%, and 89.10% in the early phase of the COVID-19 epidemic in China (Lin et al., 2020; Zhang et al., 2021; Han et al., 2021), the current WTV rate of 86.74% did not drop at a time that COVID-19 was under adequate control. Previous studies were conducted before the COVID-19 vaccine was available, and vaccination programs were not yet implemented. Theoretically, WTV at that time should have been higher because the strong wish to terminate the epidemic altogether would have predisposed more people to accept the vaccine. The WTV in our study represented the vaccination intention of vaccinated persons, who were more

TABLE 3 Factors associated with the willingness to pay a high price for the COVID-19 vaccine booster dose.

Variables	Categories	Ordered logistic regression for WTP		
		Odds ratio	95% confidence interval	*p*-Value
Age (years)	18–24	1	—	—
	25–35	1.26	0.75–2.11	0.392
	36–50	1.56	0.72–3.39	0.259
	>50	0.99	0.37–2.66	0.982
Gender	Male	1.22	0.86–1.73	0.262
	Female	1	—	—
Occupation	Professional worker	1	—	—
	Company staff	1.75	1.01–3.03	0.045
	College students and below	1.46	0.72–2.98	0.293
	Graduate students and above	1.43	0.65–3.17	0.374
	Others	1.13	0.64–2.00	0.665
Marital status	Married/Divorced	0.55	0.28–1.07	0.078
	Single	1	—	—
Highest education level	Junior college or below	1	—	—
	Bachelor degree	0.88	0.51–1.53	0.657
	Master's degree or above	0.67	0.29–1.54	0.344
Place of residence	Urban	1.57	1.11–2.22	0.012
	Rural	1	—	—
Annual household income (CNY 1,000)	<40	0.38	0.21–0.66	0.001
	40–70	0.58	0.34–1.02	0.057
	70–110	0.73	0.46–1.18	0.200
	110–210	1	—	—
	210–450	0.82	0.48–1.40	0.466
	>450	0.91	0.50–1.68	0.770
Chronic diseases	No	1	—	—
	Yes	1.17	0.57–2.41	0.669
Health status self-rated	Very good	1.22	0.68–2.20	0.500
	Good	1.36	0.78–2.36	0.281
	Fair/Poor/Very poor	1	—	—
Medical insurance	No	0.5	0.22–1.14	0.097
	National medical insurance for urban workers	1	—	—
	National medical insurance for urban and rural residents	1.09	0.67–1.77	0.723
	National medical insurance and other insurance	1.09	0.67–1.80	0.721
	Other insurance	1.08	0.61–1.90	0.793
Quarantine experience	Hotel quarantine	0.75	0.26–2.14	0.584
	Home quarantine	1.11	0.72–1.72	0.630
	No	1	—	—
Recent exposure to COVID-19	No	1	—	—
	Yes	1.49	0.89–2.48	0.126
Actual vaccination status	One shot only	1.47	0.64–3.41	0.368
	Two shots	1.46	1.03–2.07	0.032
	Three shots	1	—	—
Perceived current risk of infection	Strongly agree/agree	0.85	0.45–1.60	0.617
	Disagree	0.81	0.49–1.33	0.396
	Strongly disagree	1	—	—
Perceived short-term risk of infection	Strongly agree/Agree	1.35	0.60–3.02	0.470

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TABLE 3 (*Continued*) Factors associated with the willingness to pay a high price for the COVID-19 vaccine booster dose.

Variables	Categories	Ordered logistic regression for WTP		
		Odds ratio	95% confidence interval	*p*-Value
	Disagree	1.46	0.88–2.43	0.141
	Strongly Disagree	1	—	—
Perceived severity of infection	Strongly agree/Agree	1.21	0.65–2.27	0.551
	Disagree	0.86	0.54–1.36	0.508
	Strongly Disagree	1	—	—
Perceived benefit of vaccination	Strongly agree	1	—	—
	Agree	0.83	0.57–1.20	0.311
	Disagree/Strongly disagree	0.49	0.26–0.95	0.036
Concerned about vaccine efficacy	Strongly agree/Agree	1	—	—
	Disagree	1.17	0.73–1.86	0.522
	Strongly disagree	1.23	0.59–2.57	0.586
Concerned about vaccine safety	Strongly agree/Agree	1	—	—
	Disagree	1.32	0.78–2.24	0.307
	Strongly disagree	1.06	0.47–2.42	0.885
Environmental peer pressure	Strongly agree/Agree	1	—	—
	Disagree	1.01	0.70–1.47	0.946
	Strongly disagree	0.48	0.26–0.87	0.017
Concerned about vaccination cost	Strongly agree/Agree	1	—	—
	Disagree	1.00	0.68–1.47	0.991
	Strongly disagree	0.82	0.45–1.50	0.525

CNY, Chinese Yaun currency; COVID-19, Coronavirus disease 2019.

informed and realistic about the vaccination effect and witnessed the success of non-medical measures. The WTV rate remained satisfactory suggesting a promising prospect for the long-term vaccination strategy in China. As a developing country, the WTV rate of China was similar to that of other developing countries such as India and Kenya (Carpio et al., 2021; Goruntla et al., 2021), yet higher than that of developed countries such as Germany, the Netherland, and France (Neumann-Bohme et al., 2020).

Contrary to the theory and empirical evidence that the actual vaccination rate was always lower than the WTV rate (Wang et al., 2022), our study found the opposite. The full-schedule vaccination rate among our participants was 7.92% higher than the WTV rate. There were 61 subjects showing reluctance to vaccination, yet vaccinated anyhow. The high vaccination rate discovered in our study was generally consistent with the high acceptance of other personal protective measurements, such as mask-wearing and hand-washing in the Chinese population (Zhong et al., 2020). The extra vaccination above WTV indicates that external factors in addition to personal intention were taking effect. This is in line with the theory about the influence of external action plans on public willingness. An Indian study proved that governmental propagation of the COVID-19 vaccine enhanced the WTV rate significantly (Goruntla et al., 2021). This is most likely the case in China, as the Chinese government had implemented the zero-COVID policy, in contrast to "Live with COVID-19" in advanced countries (Kirby, 2022). Under the umbrella of the zero-COVID strategy, 1) vaccination was mandated to some institutionalized populations such as students and government officers (Ioannidis, 2021), 2) non-vaccination restricts people from essential activities like working in office or business traveling, 3) authorities provide powerful education about the severity and fatality of COVID-19 infection and benefit of vaccines (Zhang et al., 2021; Zhang et al., 2022), 4) some cities provided incentives to push for the vaccination, 5) last but not least, the vaccine is free. All these interventions would boost the vaccination rate as proven in other populations (Iyer et al., 2022).

Our study illustrated an expected, yet concerning, phenomenon that high vaccination status would dissuade a person from paying for a vaccine. The WTP estimated from our sample was lower than previously observed. The median WTP-average was CNY 80, below the median WTPs of CNY 100, 200, and CNY 300 previously reported for the Chinese population (Wang et al., 2021; Lin et al., 2020; Han et al., 2021). Likewise, the mean WTP in our study was CNY 149, lower than the mean WTPs of CNY 254 and 130 (Qin et al., 2021;

Wang et al., 2021). One study published that the most preferred WTP range was CNY 501–1,000 (Zhang et al., 2021). Additionally, WTP was negatively associated with the number of shots. Full-schedule and booster-vaccinated persons would pay CNY 95 and 563, less than that of those who had received one shot only. This was further consolidated in multivariate analyses showing respondents boosted with the third shot were significantly reluctant to pay a higher price for the COVID-19 vaccine. This downward trend of WTP is not surprising in that the perceived current risk of infection was low at 14.36%, and the perceived risk in the next months was even lower at 7.92%. Studies have already shown that higher perceived risk is positively associated with WTP (Adigwe, 2021; Han et al., 2021; Zhang et al., 2021). Across the study period, the number of domestic cases were below 100, while sporadic outbreaks were confined to one or two cities (Organization, 2021), therefore, the urgency and value of vaccination was not sensed by individuals living in such environment. Our findings anticipate difficulties in changing from the currently free vaccine to a required co-payment or even a complete out-of-pocket payment if most people have been vaccinated. Targeted measures to improve public awareness of COVID resurgence and the importance of vaccine effect were suggested.

The HBM theory, which was specifically developed to study preventive interventions (Orji et al., 2012; Wong et al., 2020), has illustrated that personal belief is powerful in the vaccination decision-making process (Han et al., 2021). According to the multivariate analyses, the perceived benefit of vaccination and environmental peer pressure would enhance WTP. Those who strongly agreed with the benefit of vaccination are more than two times as likely to pay for high-priced vaccines than those who strongly disagreed. Those who would accept vaccination if others took it were twice as likely to pay for high-priced vaccines relative to those immune to peers' behavior. Perceived benefit and susceptibility were known predictors for WTP in various populations (Han et al., 2021; Harapan et al., 2020). Additionally, interventions targeting these HBM constructs have improved the effectiveness of vaccination (Jones et al., 2012; Myers, 2017). Based on our findings, it makes sense to strengthen beliefs surrounding vaccination benefits and to leverage environmental pressure.

Regarding the relation between socioeconomic factors and WTP, our study found that people with lower AHI tend to pay less for the COVID-19 vaccine. The multivariate analyses confirmed the trend, and specifically, AHI < 40k was shown to be significantly associated with the lower WTP. Urban residents were 1.57 times as likely to pay a high vaccine price. These findings were consistent with local and international studies that economically disadvantaged people were unwilling to pay irrespective of other factors (Wang et al., 2021). This highlights the need to consider the affordability of the COVID-19 vaccine, especially in low-middle-income countries. If the COVID-19 vaccine was priced at CNY 149 (the grand mean WTP in our study), over 70% of the sample and families with AHI < 210K were unwilling to pay (Figure 2; Table 2). This can be extrapolated to one billion people considering the size of Chinese population (EBoNBoSo, 2022). Domestically made vaccines have been priced at CNY 200 or 234 per dose to local governments and individual customers (Times, 2020; Author Anonymous, 2020). It seems that the COVID-19 vaccines have been over-priced and exceeded common affordability.

WTP is useful, informative evidence for a government to utilize in the provision of public goods and decision-making surrounding issues such as financing, pricing, and subsidization. In the scenario that public goods transit to private goods, WTP can inform the affordability of the public, especially in low- and middle-income countries (LMICs) where public financing is difficult. In Nigeria, only a quarter of respondents were willing to pay for vaccination, and half of the respondents were not willing to pay more than USD1.20 (Adigwe, 2021). Studies from other LMICs have reported mean WTPs of USD 30.66, 57.20, and 85.92 respectively in Malaysia, Indonesia, and Vietnam (Harapan et al., 2020; Wong et al., 2020; Vo et al., 2021), as well as WTP ranges of USD 6.81-13.62 for India and USD 49.81-68.25 for Kenya (Carpio et al., 2021; Goruntla et al., 2021). Our estimate of CNY 149, which is equivalent to USD 23.09 according to the exchange rate in 2021, has seemingly confirmed that China still belongs to the class of LMIC, and that the affordability of the population needs to be considered. On the other hand, high-income countries reported much higher mean WTPs of USD 232 and USD 318.76 for the COVID-19 vaccine in Chile and the USA respectively (Catma and Varol, 2021; Cerda and Garcia, 2021). The WTP varies greatly across the countries indicating the uneven affordability of different populations. This heterogeneity may form a barrier in the global war on the COVID-19 epidemic (Acharya et al., 2021).

Some advantages of our study were of note. The biggest advantage distinguishing this study from others could be that the validity of WTP is high. We used randomization and averaging to minimize bias. Respondents were first randomly allocated to PS or IBG method, and then further randomized to one of three IBG biding algorithms with different starting-price. The WTPs by two CVM methods were averaged and analyzed. It turned out that the IBG derived significantly higher WTPs than the PS, though methodologically expected (Frew et al., 2004). Moreover, the WTPs by two CVM methods from the same person had a poor agreement, even in extremely opposite directions observed in 10 cases. Within IBG itself, the mean WTPs were CNY 435, 329, and 309 for IBG800, IBG170, and IBG20 respectively, reflecting the "anchoring effect" inherent in this method. All these facts mean that random allocation and data averaging are necessary and have reduced the methodology-induced bias in estimating the true WTP. Another advantage is that WTP and WTV for the booster dose at the time of adequate epidemic control were rarely reported. Our study filled the gap and allowed policy-makers to keep track of WTP and WTV trajectories.

This study has some limitations. The sample size of 543 was considered small to represent the national population. In this regard, a study using Monte Carlo simulation showed that a sample size of 400 is sufficient to produce a valid WTP with little impact from the number of bidding prices (Judez et al., 2000). The representativeness may also be undermined by our sampling methods and the online-survey format. Respondents with high internet utilization may be systematically different from the general population. Snowballing sampling is limited to reaching a wide population base. Considering that two rounds of vaccination programs have been completed, and the effectiveness and safety of the vaccine are generally known to everyone, the IBG scenario did not provide data or facts about the vaccine. The social benefit of vaccination and the negative effect of non-vaccination were delineated instead. This needs to be considered when our results were compared with the early studies which were conducted before the vaccine was available. Finally, a cross-sectional study was unable to substantiate a causal relationship.

5 Conclusion

The willingness to vaccinate with the COVID-19 vaccine booster dose was generally high in China, especially in the younger populations. The wiliness to pay was influenced by the place of residence, vaccination status, household income, perceived benefit of vaccination, and environmental peer pressure. Study findings can inform policymakers to better design future vaccination programs and financial schemes involving out-of-pocket payments. Financial support is necessary for disadvantaged populations in view of their affordability problems.

Data availability statement

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

Ethics statement

Ethical review and approval was 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

HJZ and LP share the first authorship as they conceptualized the study, designed the questionnaire, analyzed the data and drafted the manuscript. HS and JL interpreted the results and provided important ideas for discussion. PW and YB compiled the data and did the preliminary analyses. HJZ and LP wrote the first draft of the manuscript. HJZ, LP, HP, and ML wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Rivaroxaban in heart failure patients with left ventricular thrombus: A retrospective study

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Background: The role of rivaroxaban in patients with heart failure (HF) combined with left ventricular (LV) thrombus remains unknown in current guideline-directed anticoagulant therapy. The aim of this study was to investigate the impact on clinical outcomes of rivaroxaban compared to vitamin K antagonists (VKAs) in patients with HF combined with LV thrombus.

Methods: We retrospectively extracted clinical, echocardiographic and follow-up data of HF patients (all classifications) admitted at China-Japan Union Hospital of Jilin University from January 2017 to June 2021. A total of 198 patients with HF were identified with LV thrombus by echocardiography, 78 of them were managed with VKAs, 109 with rivaroxaban.

Results: The median follow-up was 17.0 months (interquartile range: 6.0–24.0 months). High rates of major cardiovascular adverse events (MACEs) were observed in both the rivaroxaban and VKAs groups (49.5% vs. 57.7%). However, rivaroxaban *versus* VKAs observed a decrease in MACEs (adjusted HR:0.636; 95%CI:0.418–0.970; $p = 0.035$) and systemic embolism (4.6% vs. 12.8%; adjusted HR:0.318; 95%CI:0.108–0.933; $p = 0.037$; Gray's test $p = 0.041$) but was not found to have a benefit with regard to LV thrombus resolution (59.6% vs. 70.6%; adjusted HR: 1.303; 95% CI:0.898–1.890; $p = 0.163$; Gray's test $p = 0.073$). Additionally, there was no significant between-group difference in the rate of International Society on Thrombosis and Hemostasis (ISTH) bleeding events.

Conclusion: Our data found that in populations with HF combined with LV thrombus, the overall prognosis in both the rivaroxaban and VKAs groups was catastrophic. Although rivaroxaban improved the prognosis to some extent, a considerable need remains for new treatments to improve their clinical course.

KEYWORDS

heart failure, left ventricular thrombus, anticoagulation management, rivaroxaban, vitamin K antagonists

Introduction

Despite the considerable progresses made during the last few years in heart failure (HF) management, there remain many aspects of HF therapy in clinical practice which lack strong trial evidence (Siliste et al., 2018; Maggioni and Andreotti, 2019). Anticoagulation therapy in patients with HF combined with left ventricular (LV) thrombus constitutes one of these examples (Ezekowitz et al., 2017). Patients with HF are at increased risk for the development of left ventricular (LV) thrombus owing to stasis of blood in hypokinetic or akinetic regions (Zannad et al., 2013; Lin et al., 2021; Levine et al., 2022). Meanwhile, HF patients with LV thrombus tend to experience higher rates of adverse events than those without LV thrombus. Currently, treatment with oral anticoagulants (Either warfarin or a direct oral anticoagulant) has emerged as a possible strategy for improving outcomes in this area (Ezekowitz et al., 2017). However, the guidelines also acknowledge that this recommendation was made on the basis of the lack of trial evidence and mechanism of action (Ezekowitz et al., 2017). Since previous large studies have not specifically focused on HF patients with LV thrombus (Homma et al., 2012; Zannad et al., 2018), the prognosis in this population remains mostly unknown under the current guideline-directed medical therapy. A recent retrospective study reported that under the anticoagulation management of vitamin K antagonists (VKAs), the prognosis of HF complicated with LV thrombus was catastrophic, with a high rate of 20% 1-year systemic embolism and mortality (Lemaître et al., 2021). However, the prognosis of the anticoagulation management of direct oral anticoagulants (DOACs) has not been reported in this area.

Rivaroxaban, as a type of DOACs, has been observed with more positive results than VKAs in other clinical settings (Sherwood et al., 2014; van Es et al., 2014). Given the lack of data on the application of rivaroxaban in HF patients with LV thrombus, we designed a retrospective study to investigate the impact on clinical outcomes of rivaroxaban compared with VKAs under the current guideline-directed anticoagulant management in HF patients with LV thrombus.

Materials and methods

Study population

This study is a retrospective observational study from a large tertiary referral center. We conducted a computerized search for all HF patients (all classifications) admitted at China-Japan Union Hospital of Jilin University from January 2017 to June 2021. HF patients with LV thrombus on echocardiography, regardless of underlying disease causing the HF, were screened, and only patients with confirmed LV thrombus by two independent cardiologists and with documented routine follow-up were included in this study. In the event of disagreement between cardiologists reviewing the LV thrombus images, the images were submitted to another independent cardiologist for confirmation of the final review. We extracted information from the available medical record, and retrieved information regarding all-cause mortality, rehospitalization for cardiovascular events, systemic embolism, or bleeding events from routine clinical follow-up after LV thrombus diagnosis. Patients who had not yet documented a review event in the medical record were contacted individually by telephone to finalize the accuracy. Detailed definitions of HF and LV thrombus echocardiographic evaluation were presented in the Supplementary Appendix. Written consent was waived due to the minimal patient risk and the retrospective study design. The study protocol was reviewed and approved by the ethical review board of China-Japan Union Hospital of Jilin University.

Antithrombotic management

According to current guidelines for the management of heart failure (Ezekowitz et al., 2017), anticoagulation management with either a VKAs (warfarin) or DOACs (mostly rivaroxaban and a few dabigatran) was initiated when LV thrombus was diagnosed in HF patients in our center. Periodic re-evaluation of LV thrombus status was performed to adjust anticoagulation duration. In patients at high risk of bleeding (i.e., previous history of bleeding, renal failure, or anemia), the dose of anticoagulant was individualized according to the guidance from responsible physician. Whether or not to administer antiplatelet therapy was determined by the responsible physician at the time, depending on the patient's underlying disease and the management strategy for that disease.

Clinical covariates

All clinical covariates including demographic data, past medical history, underlying disease, laboratory biochemical parameters, and echocardiographic data were collected through medical records or by interaction with patients or their family members. Those clinical covariates were associated with the prognosis of thrombosis and heart failure in previous studies (Zannad et al., 2018; Lemaître et al., 2021). To address and minimize bias in retrospective study design, data collection was standardized with precise definitions for each clinical covariate and measure. Since the final missing data were small (<5%), the missing data in clinical covariates were imputed using the mean or mode.

Endpoints and definitions

In this study, we mainly investigated the three endpoints: LV thrombus resolution, major adverse cardiovascular events

(MACEs) and bleeding. LV thrombus status was defined based on the method of Lattuca et al. (2020). LV thrombus resolution was defined as the complete disappearance of LV thrombus on all echocardiographic views at the last available follow-up visit. LV thrombus persistence was defined as the visibility of thrombus on all echocardiographic views at the last available follow-up visit. Major adverse cardiovascular events (MACEs) were defined as a composite of all-cause mortality, systemic embolism, and rehospitalization for cardiovascular events following an LV thrombus diagnosis. Bleeding events were defined as major bleeding, clinically relevant non-major bleeding and minor bleeding according to International Society on Thrombosis and Hemostasis (ISTH) criteria (Schulman and Kearon, 2005; Kaatz et al., 2015). All endpoint events were reviewed by a clinical academic group independent of this study based on pre-specified event definition criteria. The detailed adjudication procedures and definitions of endpoint events were shown in the Supplementary Appendix.

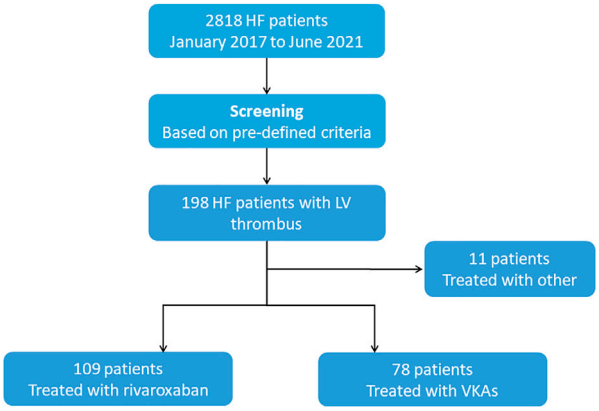

FIGURE 1
Study Chart Flow. HF = heart failure; VKAs = vitamin K antagonists.

Statistical analysis

Baseline characteristics were described as continuous or categorical variables. Continuous variables were represented as mean (SD) or median (IQR), and comparisons between groups were performed using Student's t-test or Mann-Whitney *U* test, as appropriate. Categorical variables were presented as number (%), and comparisons were performed using the $\chi 2$ or Fisher's exact test as appropriate.

The influence of anticoagulant types (Rivaroxaban vs. VKAs) on outcomes in patients with HF combined with LV thrombus was assessed by hazard ratios and their 95% confidence intervals (CIs) using Cox proportional hazard regression models. All clinical covariates were assessed by univariate Cox proportional hazards regression to determine whether they were significantly associated with outcomes. Then, covariates with $p \leq 0.05$ in the univariate models were included in the multivariate Cox proportional hazards regression models to identify the independent effect of anticoagulant types on outcomes (Agoritsas et al., 2017). Meanwhile, considering the analytical effect of the number of events on the multivariate proportional hazards regression models, we used the principle of EPV = 10 for determining the number of covariates to improve the accuracy and precision of the multivariate models (the covariates incorporated in each model were detailed in the in the Supplementary Table SA6) (Peduzzi et al., 1995). Validity of the proportionality assumption was verified by a visually examining Schoenfeld-type residual plot or a weighted residuals test. Kaplan-Meier curves and log-rank test were used to examine differences in the rate of LV thrombus resolution across study groups.

Additionally, considering the impact of higher mortality in the heart failure population on other non-mortality endpoints, we used the Fine-Gray models as the sensitivity analyses to assess the robustness of these non-mortality study findings (Scrucca et al., 2010). These sensitivity analyses were conducted after adjusting for the competing risk for mortality. Finally, exploratory analyses were performed in various subgroups to investigate the influence of anticoagulant types on outcomes in each subgroup. The exploratory endpoints included LV thrombus resolution, MACEs, all-cause mortality, systemic embolism, rehospitalization for cardiovascular events. We used the Cox proportional Hazard joint test to assess the interaction between treatment effect and these subgroup characteristics. All analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 24.0 (IBM Corp, Armonk, NY, United States) with a 2-sided p value < 0.05 indicating statistical significance.

Results

Patients

During the study period, a total of 198 patients with HF were identified with LV thrombus by echocardiography, 78 of them were managed with VKAs, 109 with rivaroxaban (Figure 1). Median anticoagulation durations were 4.0 months (IQR: 1.0–10.0 months) in the VKAs group and 2.0 months (IQR: 1.0–7.0 months) in the rivaroxaban group, respectively. The baseline characteristics of patients with confirmed LV thrombus were shown in Table 1. At baseline, compared to the VKAs group, patients with rivaroxaban had a higher proportion of ischemic heart disease accompanied by higher levels of haemostatic markers (Fibrinogen), larger LVEDD, and lower LVEF. Other baseline characteristics including age, sex, antiplatelet therapy and coronary risk factors did not differ significantly between the two groups. A more exhaustive

TABLE 1 Clinical characteristics in heart failure patients with LVT.

Baseline characteristics	VKAs (*n* = 78)	Rivaroxaban (*n* = 109)	Other (*n* = 11)	p value[a]
Male, n (%)	66 (84.6)	85 (78.0)	11 (100.0)	0.257
Age, yrs	63.0 (54.5–71.0)	64.5 (54.2–70.8)	64.0 (49.0–67.0)	0.882
Body mass index, kg/m^2	24.0 (21.0–26.3)	24.3 (22.1–27.0)	24.6 ± 2.4	0.292
Prior SSE, n (%)	28 (35.9)	33 (30.6)	1 (9.1)	0.444
Hypertension, n (%)	33 (42.3)	45 (41.3)	3 (27.3)	0.889
Diabetes mellitus, n (%)	21 (26.9)	57 (30.5)	1 (9.1)	0.371
Current smoker, n (%)	41 (52.6)	42 (38.5)	5 (45.5)	0.057
Chronic heart failure, n (%)	39 (50.0)	59 (54.1)	7 (63.7)	0.577
Ischemic heart disease, n (%)	61 (78.2)	97 (89.0)	6 (54.5)	0.045
Atrial fibrillation, n (%)	6 (7.7)	7 (6.4)	0 (0)	0.736
Antiplatelet therapy	63 (80.8)	80 (73.4)	7 (63.6)	0.241
Creatinine clearance, mL/min/1.73 m^2	70.6 (53.2–87.9)	63.6 (55.3–87.9)	80.1 ± 26.4	0.638
WBC, ×10^9	8.2 (6.8–10.5)	8.3 (6.6–10.9)	9.0 (6.0–11.7)	0.981
Hemoglobin, g/L	144.0 (128.0–158.0)	146.0 (130.3–157.0)	142.0 ± 22.7	0.809
NT-proBNP, pg/mL	5530.0 (1465.0–7910.0)	4580.0 (1752.5–9305.0)	6060.0 (1490.0–10000.0)	0.904
D-dimer, mg/L	1.4 (0.7–3.0)	1.6 (0.7–3.0)	1.7 (1.0–3.0)	0.642
Fibrinogen, mg/dl	4.0 (3.2–4.2)	3.5 (2.8–4.0)	4.3 ± 1.7	0.028
LV ejection fraction, %	39.0 (31.0–51.0)	35.0 (27.0–44.0)	35.4 ± 13.5	0.005
LVEDD, mm	51.7 (45.5–59.7)	55.9 (49.1–63.5)	55.2 ± 11.2	0.042
LV aneurysm,n (%)	16 (20.5)	18 (16.5)	1 (9.1)	0.484
Mitral regurgitation area, cm^2	2.5 (0–5.6)	3.6 (1.8–6.3)	2.9 (0–4.2)	0.113
Thrombus size, mm^2	256.0 (136.5–474.5)	284.0 (177.3–498.5)	387.1 (130.5–666.0)	0.589

[a]P value was for rivaroxaban group as compared with VKAs group.
Abbreviations: WBC, white blood cell count; MPV, mean platelet volume; LV ejection fraction:left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LV aneurysm:left ventricular aneurysm.

TABLE 2 Outcomes of Cox Proportional Hazards Regression Analysis in Patients who received Rivaroxaban or VKAs Therapy.

Outcomes	VKAs (*n* = 78)	Rivaroxaban (*n* = 109)	Adjusted HR (95%CI)	*p* value[a]
LV thrombus resolution	46 (59.0)	77 (70.6)	1.303 (0.898–1.890)	0.163
Major adverse cardiovascular events: composite of all-cause mortality, systemic embolism, and rehospitalization	45 (57.7)	54 (49.5)	0.636 (0.418–0.970)	0.035
All-cause mortality	27 (34.6)	31 (28.4)	1.515 (0.891–2.575)	0.125
Systemic embolism	10 (12.8)	5 (4.6)	0.318 (0.108–0.933)	0.037
Rehospitalization for cardiovascular events	21 (26.9)	31 (28.4)	1.064 (0.611–1.852)	0.826
Bleeding events	5 (6.4)	8 (7.3)	1.124 (0.368–3.437)	0.837
Major bleeding	1 (1.3)	0 (0)	—	—
CRNM bleeding	1 (1.3)	0 (0)	—	—
Minor bleeding	3 (3.8)	8 (7.3)	—	—

[a]P value is for rivaroxaban group as compared with VKAs group.
Abbreviations: LVT, left ventricular thrombus; CRNM, clinically relevant non-major.

review of the study population was included in the supplemental appendix, including the types of underlying disease (Supplementary Table SA1), and antiplatelet drug administration (Supplementary Table SA2).

Left ventricular thrombus resolution

During the follow-up period (median: 17 months; IQR: 6.0–24.0 months), LV thrombus resolution that confirmed by

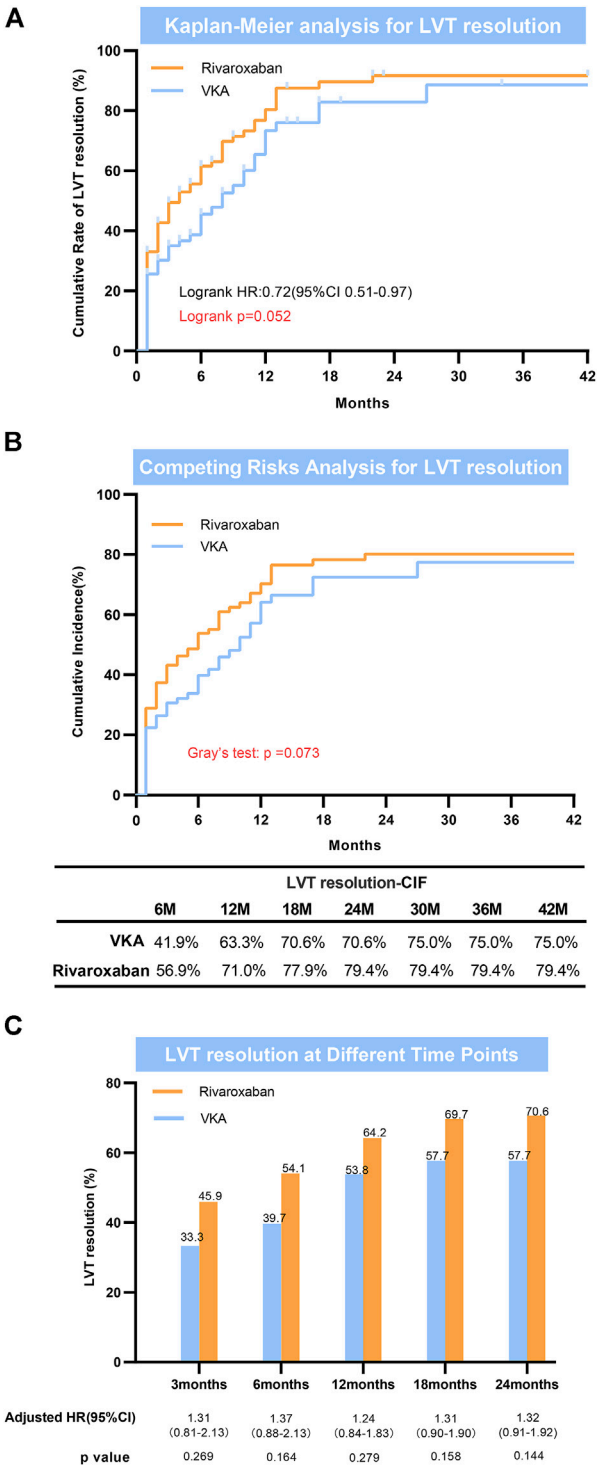

FIGURE 2
Left ventricular thrombus resolution. **(A)** Kaplan-Meier analysis for LVT resolution; **(B)** Competing risks analysis for LVT resolution; **(C)** LVT resolution at different time points. LVT = left ventricular thrombus.

echocardiography occurred in 46 of 78 (59.6%) patients in the VKAS group and 77 of 109 (70.6%) in the rivaroxaban group (Table 2). Despite the direct observation that the thrombus resolution rates were higher in the rivaroxaban group than in the VKAs group (59.6% vs. 70.6%), the thrombus resolution rates between the two groups did not achieve a statistically significant difference in the adjusted Cox proportional hazards regression model (adjusted HR: 1.303; 95% CI:0.898–1.890; $p = 0.163$) (Table 2). Similar results were obtained in the Fine-Gray model after adjusting for mortality and in the log rank test, with no statistically significant improvement in LV thrombus resolution with rivaroxaban compared to VKAs (Gray's test $p = 0.073$; log rank $p = 0.052$) (Figure 2A, Figure 2B). In view of these, for a better observation of the difference in the thrombus resolution due to the types of anticoagulants (rivaroxaban vs. VKAs), we compared the thrombus resolution rates according to the time points, and similarly, no statistically significant differences were observed between the two groups (Figure 2C).

Clinical outcomes

MACEs occurred in 57.7% ($n = 45$) in the VKAs group and 49.5% ($n = 54$) in the rivaroxaban group during the follow-up period (Table 2). A total of 27 patients (34.6%) in the VKAs group and 31 (28.7%) in the rivaroxaban group died. Systemic embolism occurred in 12.8% ($n = 10$) in the VKAs group and 4.6% ($n = 5$) in the rivaroxaban group, respectively. Meanwhile, the incidence of rehospitalization for cardiovascular events was 26.9% ($n = 21$) in the VKAs group and 28.4% ($n = 31$) in the rivaroxaban group. After adjusting for potential confounders in the multivariate Cox proportional hazards regression model, in comparison with the VKAs group, HR for MACEs was lower in the rivaroxaban group (adjusted HR: 0.636; 95% CI:0.418–0.970; $p = 0.035$). For systemic embolism, in the multivariate Cox regression model, relatively low HR was also observed in the rivaroxaban group (adjusted HR:0.318; 95% CI:0.108–0.933; $p = 0.037$), which was consistent with observation in the Fine-Gray model (Gray's test $p = 0.041$) (Supplementary Table SA4). For all-cause mortality and rehospitalization for cardiovascular events, no statistical differences were observed between the two groups (Table 2, Supplementary Table SA3). Additionally, there was no statistically significant difference in the incidence of ISTH bleeding events between the rivaroxaban and VKAs groups. This result observed in the multivariate COX regression model and the Fine-Gray model was consistent (Table 2, Supplementary Table SA5).

Exploratory analyses

In the exploratory analysis, subgroups were stratified according to age, sex, types of heart disease, antiplatelet therapy, types of heart

failure, and left ventricular ejection fraction. The outcomes were consistent across most subgroups, with no statistically significant interactions, except for in LV thrombus resolution (Supplementary Figures SA1–SA5). In terms of LV thrombus resolution, interaction tests showed a potentially different effects of rivaroxaban in the ischemic heart disease population and the non-ischemic heart disease population (p value for interaction = 0.05), but with a wide confidence interval in the non-ischemic heart disease population (HR: 4.215; 95% CI:1.418–12.525) (Supplementary Figure SA1).

Discussion

Advances in the understanding of the contribution of thrombin generation to thrombosis and the role of DOACs in thrombosis have prompted new anticoagulation paradigms. Since no clinical data on rivaroxaban in HF patients with LV thrombus have been reported, this retrospective study was performed. In this study, we investigated the impact on clinical outcomes of rivaroxaban compared to VKAs in HF patients with LV thrombus in terms of LV thrombus resolution, major adverse cardiovascular events, and bleeding events. In this population, rivaroxaban *versus* VKAs was not found to have a benefit with regard to LV thrombus resolution but observed a decrease in major adverse cardiovascular events and systemic embolism in the setting of the poor prognosis for both groups. Additionally, there was no significant between-group difference in the rate of bleeding events. These findings provide new insights into the anticoagulation management of LV thrombus in the HF setting.

Management of LV thrombus remains a challenge in various clinical settings. In the presence of a definite LV thrombus, no strong trials evidence was available to guide therapeutic strategies or to compare different antithrombotic treatment regimens (Di Odoardo et al., 2021). In this dilemma, the 2017 Canadian Heart Failure Guidelines state that either VKAs or DOACs could be used for LV thrombus on the basis of the lack of trial evidence and mechanism of action (Ezekowitz et al., 2017). Hence, with the available clinical evidence, the management of LV thrombus still presents a considerable uncertainty (Massussi et al., 2021). Some evidence suggested that DOACs, including rivaroxaban, have a quicker resolution rate of LV thrombus than VKAs in the AMI setting, which may be associated with a better clinical benefit (Jones et al., 2021). Furthermore, the No-LVT trial in the all-disease population reported the odds ratio of LV thrombus resolution in the rivaroxaban group was significantly higher than in the warfarin group at 1 month (N = 79; odds ratio: 2.813; p = 0.03) (Abdelnabi et al., 2021). These studies underscored that rivaroxaban *versus* VKAs perhaps provides a better benefit-risk profile in other clinical settings where LV thrombus exists, yet its role in the clinical setting of HF combined with LV thrombus has not been investigated.

In this study, rivaroxaban *versus* VKAs was not found to have a benefit with regard to LV thrombus resolution; to test the stability of this finding, we used various statistical models, and the finding was generally consistent across statistical models, which was different from some previous LV thrombus-related studies in the non-HF setting (Abdelnabi et al., 2021; Jones et al., 2021; Zhang et al., 2022). The reason for this observation is unclear, which may be that the intrinsic differences of LV thrombus formation in various clinical settings contributed to the complicating interchangeability. Although LV thrombus is considered to be caused primarily by the Virchow triad, left ventricular thrombosis is not equally associated with blood stasis, endocardial alterations, inflammation, and fibrosis in different clinical settings (Massussi et al., 2021). These differences in thrombosis may reasonably translate into differences in antithrombotic activity, resulting in different anticoagulant responsiveness. Notably, although no statistical difference was observed between rivaroxaban and VKAs in terms of LV thrombus resolution, we found a higher rate of resolution with rivaroxaban than with VKAs when observed at all time points. To some extent, it could be considered that rivaroxaban is no worse than VKAs in terms of LV thrombus resolution. However, due to the cohort size and retrospective design, the result should be interpreted with caution.

In the HF population with LV thrombus, prognosis after anticoagulation management is another issue of concern. This study showed that with current guideline-directed anticoagulant therapy, these patients remain at long-term risk for mortality and cardiovascular events. Both groups maintained a high rate of MACEs, but fewer MACE were observed in the rivaroxaban group than in VKAs (49.5% vs. 57.7%, p = 0.035), with no significant between-group difference in the rate of bleeding events (7.3% vs. 6.4, p = 0.837). This rivaroxaban-related benefit was also reported in other large randomized clinical trials (RCTs) (Mega et al., 2013; Korjian et al., 2018; Branch et al., 2019). A post-hoc analysis of the ATLAS ACS 2-TIMI 51 trial showed that in patients with a history of HF, rivaroxaban at 2.5 mg dose and 5 mg dose significantly reduced the primary efficacy endpoint, cardiovascular mortality, and all-cause mortality without increasing the risk of major bleeding (Korjian et al., 2018). In a post hoc analysis for HF patients in the COMPASS trial, a dose of 2.5 mg rivaroxaban plus aspirin was associated with a greater absolute risk reduction and similar relative risk reduction in MACE compared with non-HF patients (Branch et al., 2019). Furthermore, our study observed that the administration of rivaroxaban in this population reduces systemic embolic events (4.6% vs.12.8%) but has a relatively small impact on death and rehospitalization driven by pump failure-related. This result was similar to the COMMANDER HF results (Zannad et al., 2018; Greenberg et al., 2019), which reported that rivaroxaban in the population in sinus rhythm with heart failure and reduced ejection fraction (HFrEF) prevented thrombo-embolic events, but with little impact on outcome measures that include mortality for the clinical condition of HFrEF; of noted, our study included an all-classified HF population with LV thrombus, whereas the COMMANDER HF investigated population was an HFrEF population in sinus rhythm.

In these different HF subsets, the pathophysiological mechanisms leading to patient prognosis are multifaceted, and we need to recognize the impact of the various degrees of left ventricular dysfunction, dilatation, and prothrombotic state associated with HF on the anticoagulant effects of rivaroxaban. However, regardless, clinicians must decide which oral anticoagulant to recommend for these HF patients with LV thrombus. Based on the results of ATLAS ACS 2-TIMI 51, COMPASS, COMMANDER HF, and this study, in the background of current guideline recommendations for administration, perhaps rivaroxaban could be a plausible option, yet more large-scale studies are also needed to confirm the generalizability of our findings, as well as further investigations in pragmatic RCTs in this subset of HF.

Limitations

First, the retrospective nature of this study predisposes it to selection bias; in particular, LV thrombus was only evaluated by echocardiography. Although we adopted an additional standardized procedure for the final confirmation of LV thrombus to reduce this bias (details in the Supplemental Appendix), this may still contribute to an underestimation of the number of HF patients with LV thrombus. Second, event data was mostly obtained from medical records, which may produce omissions of clinical events. Although we conducted direct telephone follow-up to confirm clinical events, and data was obtained from a highly specialized large-scale heart failure center, which maintained a high level of data recruitment and follow-up, it may still have confounded the analysis of outcomes. Third, we were unable to evaluate the impact of antiplatelet therapy on LV thrombus in detail. Several studies have reported the beneficial effects of antiplatelet therapy on LV thrombus (Altıntaş et al., 2019). Meanwhile, in this study, there was no significant between-group difference in the use of antiplatelet therapy. However, the absence of difference between groups did make our cohort homogenous, allowing us to specifically examine the effect of different anticoagulants. Finally, we are unable to standardize the dose of anticoagulants, but this also reflects the current dilemma of anticoagulation management in this population in the real world. In summary, our findings should not be considered conclusive but rather as a status response to the current anticoagulation management.

Conclusion

Our data found that in populations with heart failure combined with LV thrombus, the overall prognosis in both the rivaroxaban and VKAs groups was catastrophic. Although rivaroxaban improved the prognosis compared with VKAs to some extent, a considerable need remains for new treatments to improve their clinical course. Further research is needed to provide more robust evidences.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by this study was approved by the China-Japan Union Hospital of Jilin University Ethics Committee (Approval No. 20211130014).

Author contributions

QZ and ZZ drafted the article and contributed to the study concept and design. ZZ analyzed the data. DS and WZ interpreted the data. MQ, HZ, and SL contributed to data collection. PY, DS, and WZ designed and revised the manuscript. All authors read and approved the final version to be published.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1008031/full#supplementary-material

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New insight into the analgesic recipe: A cohort study based on smart patient-controlled analgesia pumps records

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Purpose: Intravenous patient-controlled analgesia (IV-PCA) has been widely used; however, regimen criteria have not yet been established. In China, the most often used opioid is sufentanil, for which repeated doses are a concern, and empirical flurbiprofen axetil (FBP) as an adjuvant. We hypothesized that hydromorphone would be a better choice and also evaluated the effectiveness of FBP as an adjuvant.

Methods: This historical cohort study was conducted in two tertiary hospitals in China and included 12,674 patients using hydromorphone or sufentanil for IV-PCA between April 1, 2017, and January 30, 2021. The primary outcome was analgesic insufficiency at static (AIS). The secondary outcomes included analgesic insufficiency with movement (AIM) and common opioid-related adverse effects such as postoperative nausea and vomiting (PONV) and dizziness.

Results: Sufentanil, but not the sufentanil-FBP combination, was associated with higher risks of AIS and AIM compared to those for hydromorphone (OR 1.64 [1.23, 2.19], $p < 0.001$ and OR 1.42 [1.16, 1.73], $p < 0.001$). Hydromorphone combined with FBP also decreased the risk of both AIS and AIM compared to those for pure hydromorphone (OR 0.74 [0.61, 0.90], $p = 0.003$ and OR 0.80 [0.71, 0.91], $p < 0.001$). However, the risk of PONV was higher in patients aged ≤35 years using FBP (hydromorphone-FBP vs. hydromorphone and sufentanil-FBP vs. hydromorphone, OR 1.69 [1.22, 2.33], $p = 0.001$ and 1.79 [1.12, 2.86], $p = 0.015$).

Conclusion: Hydromorphone was superior to sufentanil for IV-PCA in postoperative analgesia. Adding FBP may improve the analgesic effects of both hydromorphone and sufentanil but was associated with an increased risk of PONV in patients <35 years of age.

KEYWORDS

patient-controlled analgesia, sufentanil, hydromorphone, flurbiprofen, postoperative nausea and vomiting, generalized estimation equation, analgesic insufficiency, dizziness

Introduction

Proper management of postoperative pain is important as it may reduce the length of hospital stay and the incidence of complications including atelectasis, pneumonia, and thromboembolism (Muehling et al., 2008; Tenenbein et al., 2008; Ghosh and Chatterji, 2019; Turan et al., 2019). Patient-controlled analgesia (PCA) is a widely used technique that allows personalized dosing and timely access to pain medication. Intravenous PCA (IV-PCA) is one of the most favored modalities due to its convenience (Momeni et al., 2006). Unexpectedly, PCA showed small advantages over conventional non-patient-controlled analgesia in achieving lower pain scores, as supported by moderate to low-level evidence, with higher opioid consumption (Hudcova et al., 2006; McNicol et al., 2015). Although opioids remain the main analgesics of IV-PCA, their effectiveness in clinical practice is restricted by their side effects (Momeni et al., 2006), mainly postoperative nausea and vomiting (PONV), respiratory depression, dizziness, etc. Adjuvants including NSAIDs, lidocaine, clonidine, dexmedetomidine, and magnesium have been evaluated for their effectiveness in improving analgesic efficiency and reducing opioid-related side effects by reducing opioid consumption, (Yy et al., 1998; Burstal et al., 2001; Jeffs et al., 2002; Unlügenç et al., 2003; Nie et al., 2018; Xiang et al., 2018; Shim and Gan, 2019). However, these studies rarely found differences in side effect profiles between different opioids.

According to a recent national survey in Chinese hospitals, sufentanil ranked first in opioids used for PCA (>80% of hospitals) (Wang et al., 2021). Due to the lack of a well-established standard, the choice of opioid and adjuvant in IV-PCA depends on anesthesiologist familiarity and drug accessibility, rather than evidence (Grass, 2005; Fernandes et al., 2017). Although sufentanil has been proven to be effective in IV-PCA, its extremely rapid onset and short duration have raised concerns about repeated dosing (Lehmann et al., 1991; Minkowitz et al., 2013). Moreover, despite its higher plasma protein binding (~90% vs. 8%–19%), the free fraction of sufentanil was more dependent on total drug concentration and volume balance, while the free fraction of hydromorphone was nearly constant (Saari et al., 2014; Drugs.com, 2021a; Drugs.com, 2021b). However, few studies have compared analgesic efficacy and adverse effects between hydromorphone and sufentanil in postoperative IV-PCA, with conflicting results (Yan et al., 2018; Yang et al., 2018). In addition to opioids, flurbiprofen axetil (FBP), a nonsteroid anti-inflammatory drug (NSAID) that is commonly administered on a scheduled rather than on an as-needed basis, is often empirically used as an adjuvant for IV-PCA in Chinese hospitals (Wick et al., 2017; Shi et al., 2021). However, gastrointestinal adverse effects occur more frequently with FBP than with other NSAIDs, among which nausea is representative with an incidence of >3% (Brogden et al., 1979; Drugs.com, 2022). Therefore, we hypothesized that hydromorphone might be a better choice and performed further evaluations of the effectiveness of FBP (Wang et al., 2021).

This study compared the efficacy and adverse effect profiles between hydromorphone and sufentanil and evaluated the effect of adding FBP as an adjuvant to the IV-PCA pump. With the help of intelligent PCA pumps, this study included a larger population with higher coverage of the postoperative period than traditional PCA research to provide evidence to inform IV-PCA formulation.

Methods

Study design

We conducted this retrospective cohort study in two tertiary medical centers in Guangdong, China. The study included patients who underwent surgery in one of five specialties (gynecology [GYN], major abdominal, thoracic, orthopedics, or urology) between April 1, 2017, and January 30, 2021. The requirement for written consent was waived and this study was approved by the ethics committees of the First and Fifth Affiliated Hospitals of Sun Yat-sen University according to the China Good Clinical Practice (GCP) guidelines and the tenets of the Declaration of Helsinki.

Data source

The data used in this study were extracted from the analgesic information database of the RHEN® PCA infusion pump system (RHEN Meditech Inc., Jiangsu, China), which recorded infusion activities and synchronized patient characteristics and surgery information from the DoCare® anesthesia clinical information system (MedicalSystem Co., Ltd., Suzhou, China). Infusion data such as the number of patient bolus attempts, the number of valid boluses, and the total volume delivered in milliliters was automatically documented every 20 min by the RHEN® smart PCA pump. The analgesic recipes and postoperative assessments

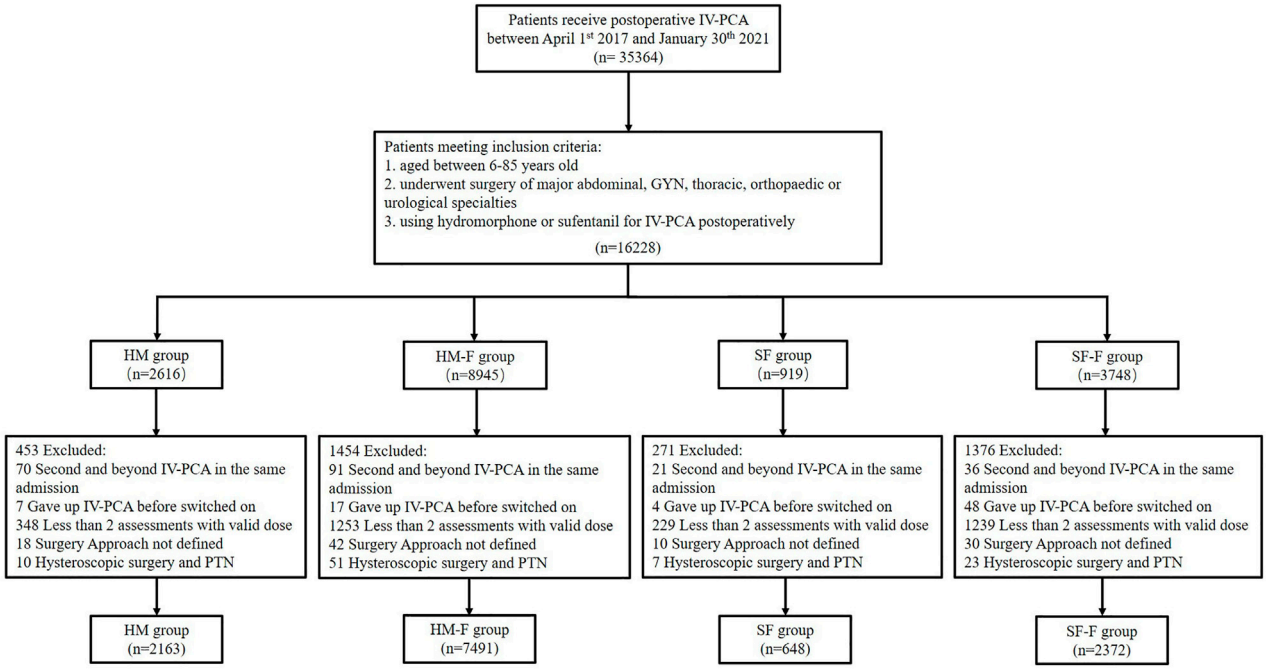

FIGURE 1
Flow chart showing the study organization, including patient inclusion, exclusion, and classification.

were recorded manually by anesthesiologists. Multifaceted evaluation of analgesic effects using the visual analogue scale (VAS, range 0–10) to measure pain intensity both at static and with movement, and opioid-related side effects such as PONV, dizziness, sedation, confusion, respiratory depression, and decreased muscle strength was performed by the acute pain service (APS) team that regularly visited the wards. The end time of the surgery varied by individual; hence, the analgesic evaluations covered most of the postoperative time points.

Study patients

This study included patients aged 6–85 years who underwent one of the five surgical specialties described above and received either hydromorphone or sufentanil for IV-PCA during the study period. The exclusion criteria included: 1) second and beyond PCA therapy in the same admission; 2) discontinued IV-PCA use for personal reasons or mechanical failure before the pump was switched on; 3) <2 postoperative analgesic assessments with valid real-time doses; 4. unknown surgery approaches for GYN, major abdominal, and urologic surgery; 5) hysteroscopic surgery and percutaneous nephrolithotripsy (PTN) (due to extremely small sample sizes). To improve the model efficiency, assessments beyond the sixth record for each participant were also removed (n = 99, mostly >48 h after surgery). Patients were assigned to the hydromorphone (HM) or sufentanil (SF) groups if they received hydromorphone or sufentanil, respectively, as single opioids for IV-PCA without adding FBP as an adjuvant. In contrast, patients receiving FBP were assigned to the hydromorphone-flurbiprofen (HM-F) or sufentanil-flurbiprofen (SF-F) groups according to the opioid used. The workflow is shown in Figure 1.

Institutional standards for anesthesia and analgesic practice

In the two institutions included in this study, the anesthesiologists were randomly assigned to surgeries. General anesthesia was induced by target-controlled infusion of propofol (3–6 g/ml) and injection of sufentanil (0.3–0.5 g/kg) and muscle relaxants (rocuronium of cis-atracurium). Anesthesia was routinely maintained with target-controlled infusions of propofol (2–3 g/ml) and remifentanil (2–4 ng/ml) in routine, while sevoflurane (1%–2%) was added according to patient status and anesthesiologist preference. Additional intraoperative sufentanil was administered at the discretion of the anesthesiologist. NSAIDs and serotonin receptor-3 antagonists were routinely administered 1h before

the end of surgery. Upon surgery completion, IV-PCA was started, and the patients were transferred to the postanesthetic care unit, where they received extubation and extra analgesia as needed. The choice of opioid in IV-PCA was hydromorphone (50–80 g/ml), sufentanil (0.6–1 g/ml) or other opioids, as decided solely by the anesthesiologist.

The parameters for the intravenous analgesia pump (RHEN Meditech Inc., Nantong, Jiangsu province, ISO9001:2008) were as follows: background dose 0–2 ml/h, PCA dose 2–3 ml, lockout time 10–15 min, and hour limit 10–16 ml. After analgesic assessment, the parameter settings were adjusted according to the following rules: 1) the background dose was increased by 25% if the VAS was static at >3; 2) the PCA dose was increased by 25% and the lockout time was reduced by 25% if the VAS with movement was >5 despite appropriate patient pump control or the hourly limit was reached. A rescue dose (usually 0.05–0.1 g tramadol) was prescribed by the surgeons according to patient complaints.

Outcomes

The primary outcome was analgesic insufficiency at static (AIS, defined as VAS at static >3). The secondary outcomes were analgesic insufficiency with movement (AIM, defined as VAS with movement >3), PONV, and dizziness. The VAS cutoff was chosen because the patients were instructed to maintain a pain score of 1–3. This study did not consider other opioid relative adverse effects such as sedation, confusion, respiratory depression, and decreased muscle strength because their extremely low incidences made it difficult to draw reliable conclusions.

Covariates

Among all patient characteristics, our study included only age and sex. Height and weight were not considered as previous studies demonstrated no correlation between patient weight and morphine consumption (Grass, 2005). Surgical type was classified according to specialties and approaches, with 11 levels (laparoscopic GYN, open GYN, laparoscopic abdominal, open abdominal, limb, spine, open thoracic, video-assisted thoracoscopy surgery [VATS], laparoscopic urologic, cystoscopy and ureteroscopy, and open urologic). Time was a continuous covariate representing the duration since the end of the operation, which was also the start of IV-PCA pump use. The infused doses of hydromorphone (m_H), sufentanil (m_S), and flurbiprofen (m_F) were defined as the doses of these drugs that were infused at the time of assessment. Opioid consumption was calculated as morphine milligram equivalent using the multipliers 4 or 0.5 for hydromorphone and sufentanil, respectively.

Statistical analysis

Baseline characteristics were calculated and stratified by group. Normally distributed variables were shown as means±standard deviations. Analysis of variance (ANOVA) and Tukey HSD tests were used for intergroup comparisons. Categorical variables were shown as cases and frequencies and compared using chi-square tests. A two-level (individual and hospital) generalized estimation equation (GEE) model with an exchangeable correlation matrix was used to account for the clustering effect introduced by repeated measurements of an individual and the heterogeneous populations of different hospitals. The covariates in the GEE model included sex, age, surgery type, and time. Infused doses, including such as m_H, m_S, and m_F, were also controlled in the model for comparisons between groups. Spline functions were used to address nonlinearity between the risk of developing analgesic insufficiency and time. The optimal parameters were chosen to minimize the quasi-likelihood under the independence model information criterion (QIC). The HM group was chosen as the reference in multigroup comparisons.

As this study included pediatrics, adults, and geriatrics and age is an important factor affecting analgesic selection, a stratified analysis according to age was further performed to assess the association between treatment group and outcomes that might vary with age (≤35 years, 35–65 years, or ≥65 years), sex and surgery type. The estimated incidence of the outcomes over time was calculated using an explorative GEE model. Differences with $p < 0.05$ were considered significant. All analyses were conducted using R software (version 4.0.5).

Sample size

Due to the retrospective cohort study design, the sample size was based on available data. No formal statistical power calculation was conducted.

Missing data

Only complete data were used in the analyses.

Results

Patients

Finally, a total of 12,674 patients and 34,926 observations were identified from the PCA pump database (Figure 1). Most of the study population received a hydromorphone-based recipe, among which 7,491 (59.1%) received FBP as adjuvant and 2,163 (17.1%) did not. Sufentanil-based recipes were administered less

frequently, with 648 (5.1%) and 2,372 (18.7%) in the SF and SF-F groups, respectively. The sufentanil-based groups showed significantly higher average opioid consumption than those in the hydromorphone-based groups (HM: 7.07 [5.59], HM-F: 7.42 [4.37], SF: 15.94 [11.08], SF-F: 17.56 [10.91], $p < 0.001$]. The average opioid consumption was significantly higher in the SF-F group compared to that in the SF group ($p < 0.001$), but similar between the HM and HM-F groups ($p = 0.138$). These four groups differed significantly in baseline characteristics including age, sex, surgery type, and distribution of analgesic assessments, as summarized in Table 1.

Primary analysis

Multivariate analysis of the outcomes revealed a higher risk of AIS in the SF group compared to the HM group, which was not observed when FBP was added (SF vs. HM: OR 1.64 [1.23, 2.19], $p < 0.001$ and SF-F vs. HM: OR 1.08 [0.84, 1.38], $p = 0.561$). Moreover, the risk of AIS decreased by 26% in the HM-F group compared to the HM group (OR 0.74 [0.61, 0.90], $p = 0.003$). The differences in AIM between groups were similar to those at static, with the HM-F group showing a lower risk (OR 0.81 [0.71, 0.91], $p < 0.001$).

Both the HM-F and SF-F groups administered FBP as an adjuvant showed higher risks of PONV compared to that in the HM group (OR 1.20 [1.03, 1.40], $p = 0.018$, and OR 1.27 [1.04, 1.55], $p = 0.021$ respectively). The risk of dizziness also increased in the HM-F group compared to that in the HM group (OR 1.28 [1.01, 1.62], $p = 0.040$). PONV and dizziness did not differ between sufentanil and hydromorphone. The results are summarized in Table 2.

Subgroup analysis

The incidence rates of AIS and AIM were not affected by age, sex, or surgery type (p for interaction >0.05, Supplementary Figures S1, S2). The incidence of PONV was not affected by sex or surgery type (p for interaction >0.05, Supplementary

TABLE 1 Characteristics of the study cohort.

Characteristic	HM (n = 2163)	HM-F (n = 7491)	SF (n = 648)	SF-F (n = 2372)	P value[a]
Age, mean(SD), y	50.29 (21.31)	51.46 (15.29)	54.49 (19.32)	51.38 (14.58)	<0.001
Sex, No.(%)	—	—	—	—	<0.001
Male	1154 (53.4)	3464 (46.2)	315 (48.6)	962 (40.6)	
Female	1009 (46.6)	4027 (53.8)	333 (51.4)	1410 (59.4)	
Height, mean (SD), cm	161.26 (10.69)	162.91 (8.02)	161.67 (9.79)	162.49 (7.82)	<0.001
Weight, mean (SD), kg	58.60 (13.13)	60.09 (10.98)	59.06 (12.13)	59.80 (10.73)	<0.001
Surgery type, No.(%)	—	—	—	<0.001	—
Laparoscopic GYN	72 (3.3)	659 (8.8)	24 (3.7)	213 (9.0)	—
Open GYN	138 (6.4)	885 (11.8)	46 (7.1)	345 (14.5)	—
Laparoscopic abdominal	228 (10.5)	950 (12.7)	94 (14.5)	333 (14.0)	—
Open abdominal	506 (23.4)	1961 (26.2)	125 (19.3)	570 (24.0)	—
Limb surgery	287 (13.3)	582 (7.8)	84 (13.0)	146 (6.2)	—
Spine surgery	217 (10.0)	510 (6.8)	50 (7.7)	152 (6.4)	—
Open thoracic	196 (9.1)	805 (10.7)	74 (11.4)	239 (10.1)	—
VATS	83 (3.8)	270 (3.6)	36 (5.6)	168 (7.1)	—
Laparoscopic urologic	84 (3.9)	169 (2.3)	31 (4.8)	39 (1.6)	—
Cystoscopy and ureteroscopy	42 (1.9)	92 (1.2)	10 (1.5)	26 (1.1)	—
Open urologic	310 (14.3)	608 (8.1)	74 (11.4)	141 (5.9)	—
Average opioid consumption mean (SD), mg/d	7.07 (5.59)	7.42 (4.37)	15.94 (11.08)	17.56 (10.91)	<0.001
Observations per patient, No. (%)	—	—	—	—	<0.001
2	642 (29.7)	2087 (27.9)	208 (32.1)	802 (33.8)	—
3	1426 (65.9)	5124 (68.4)	405 (62.5)	1461 (61.6)	—
≥4	95 (4.4)	280 (3.7)	35 (5.4)	109 (4.6)	—
Time of first assessment, median (IQR), h	9.86 (6.76, 14.62)	9.64 (6.18, 14.26)	10.69 (7.32, 15.89)	11.61 (7.61, 19.04)	<0.001

Abbreviations: HM, Hydromorphone; HM-F, Hydromorhone-Flubiprofen Axetil; SF, Sufentanil; SF-F, Sufentanil-Flurbiprofen Axetil; GYN, gynecologic; VATS, Video-assisted thoracoscopic surgery.

[a]Continuous variables were compared using analysis of variance if they followed normal distribution, otherwise compared with Kruskal-Wallis test, and categorical variables were compared using chi-squared test.

TABLE 2 Multivariable analysis of factors associated with the primary outcome and secondary outcome.

	Adjusted Odds Ratio (95% CI)			
	AIS	**AIM**	**PONV**	**Dizziness**
Treatment Group	—	—	—	—
HM	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
HM-F	**0.74 (0.61,0.90)**	**0.80 (0.71,0.91)**	**1.20 (1.03,1.40)**	**1.28 (1.01,1.62)**
SF	**1.64 (1.23,2.19)**	**1.42 (1.16,1.73)**	0.91 (0.70,1.19)	1.14 (0.79,1.63)
SF-F	1.08 (0.84,1.38)	1.10 (0.93,1.30)	**1.27 (1.04,1.55)**	1.25 (0.92,1.69)
Sex	—	—	—	—
Male	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	**1.18 (1.03,1.36)**	**1.27 (1.17,1.39)**	**3.00 (2.69,3.35)**	**1.97 (1.68,2.30)**
Age*	**0.99 (0.99,0.99)**	**0.99 (0.99,0.99)**	**0.99 (0.99,0.99)**	1.00 (0.99,1.00)
Surgery type	—	—	—	—
Laparoscopic GYN	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Open GYN	1.23 (0.93,1.63)	**1.33 (1.10,1.61)**	0.87 (0.73,1.03)	0.80 (0.63,1.02)
Laparoscopic abdominal	0.96 (0.71,1.30)	**1.42 (1.17,1.73)**	0.83 (0.68,1.00)	0.80 (0.60,1.07)
Open abodominal	**1.45 (1.10,1.90)**	**1.63 (1.36,1.95)**	**0.80 (0.67,0.94)**	**0.73 (0.57,0.93)**
Limb surgery	0.89 (0.64,1.24)	1.08 (0.87,1.33)	**0.78 (0.64,0.96)**	**0.69 (0.52,0.93)**
Spine surgery	**0.69 (0.47,0.99)**	1.11 (0.88,1.39)	**0.63 (0.50,0.79)**	**0.39 (0.27,0.57)**
Open thoracic	**1.79 (1.34,2.39)**	**2.20 (1.81,2.67)**	**0.77 (0.63,0.95)**	0.92 (0.70,1.20)
VATS	1.25 (0.84,1.85)	**1.87 (1.47,2.39)**	0.81 (0.62,1.07)	0.82 (0.55,1.21)
Laparoscopic urologic	0.89 (0.53,1.48)	1.08 (0.80,1.46)	1.02 (0.75,1.37)	0.70 (0.43,1.14)
Cystoscopy and ureteroscopy	0.78 (0.37,1.64)	0.63 (0.39,1.04)	0.80 (0.51,1.26)	**0.25 (0.10,0.61)**
Open urologic	1.07 (0.78,1.48)	**1.36 (1.10,1.68)**	0.97 (0.79,1.19)	**0.71 (0.53,0.95)**
m_H*	**1.08 (1.02,1.14)**	**1.13 (1.08,1.18)**	1.00 (0.95,1.04)	**1.10 (1.03,1.17)**
m_S*	**1.01 (1.00,1.01)**	**1.01 (1.00,1.01)**	1.00 (0.99,1.00)	1.00 (1.00,1.01)
m_F*	1.00 (1.00,1.00)	1.00 (1.00,1.00)	1.00 (1.00,1.00)	1.00 (1.00,1.00)

Abbreviations: HM, Hydromorphone; HM-F, Hydromorhone-Flubiprofen Axetil; SF, Sufentanil; SF-F, Sufentanil-Flurbiprofen Axetil; GYN, gynecologic; VATS, Video-assisted thoracoscopic surgery. Significant results with $p < 0.05$ are in bold.

*The odd ratios are for each 1-year increase in age, each 1mg increase in m_H or m_F and 1μg increase in m_S respectively.

Figure S3) but was significantly affected by age (p for interaction = 0.047, Figure 2). The HM-F and SF-F groups showed increased risks of PONV only in the ≤35 years subgroup (OR 1.69 [1.22, 2.33] p = 0.001 and 1.79 [1.12, 2.86], p = 0.015, Figure 2). Dizziness was affected by age, with the HM-F group showing a higher risk of dizziness in the ≤35 years subgroup (OR 1.76 [1.04, 2.98], p = 0.04, and p for interaction = 0.014, Figure 3). Meanwhile, the interaction effects between treatment group and sex and between treatment group and surgery type were significant considering dizziness (p for interaction <0.001). However, no difference in dizziness between regimens was observed when stratified by sex and surgery type (Figure 3).

Explorative analysis

The estimated incidences of both AIS and AIM differed most significantly in the first 24 h postoperatively. Adding FBP as an adjuvant lowered the risk of analgesic insufficiency in the first 24 h but not afterward (Supplementary Figures S4A,B). However, the estimated incidence rates of PONV and dizziness remained higher in the HM-F and SF-F groups than those in the HM group at 24–48 h postoperatively as well as in the first 24 h (Supplementary Figures S4C,D).

Discussion

The results of this historical cohort study of 12,674 patients receiving postoperative IV-PCA demonstrated that adding FBP as an adjuvant significantly improved the analgesic effect, although the potential risk of PONV was increased in patients <35 years of age, and hydromorphone was associated with a lower risk of analgesic insufficiency compared to sufentanil.

Comparison between opioids is difficult. Morphine remains the gold standard in the treatment of acute postoperative pain

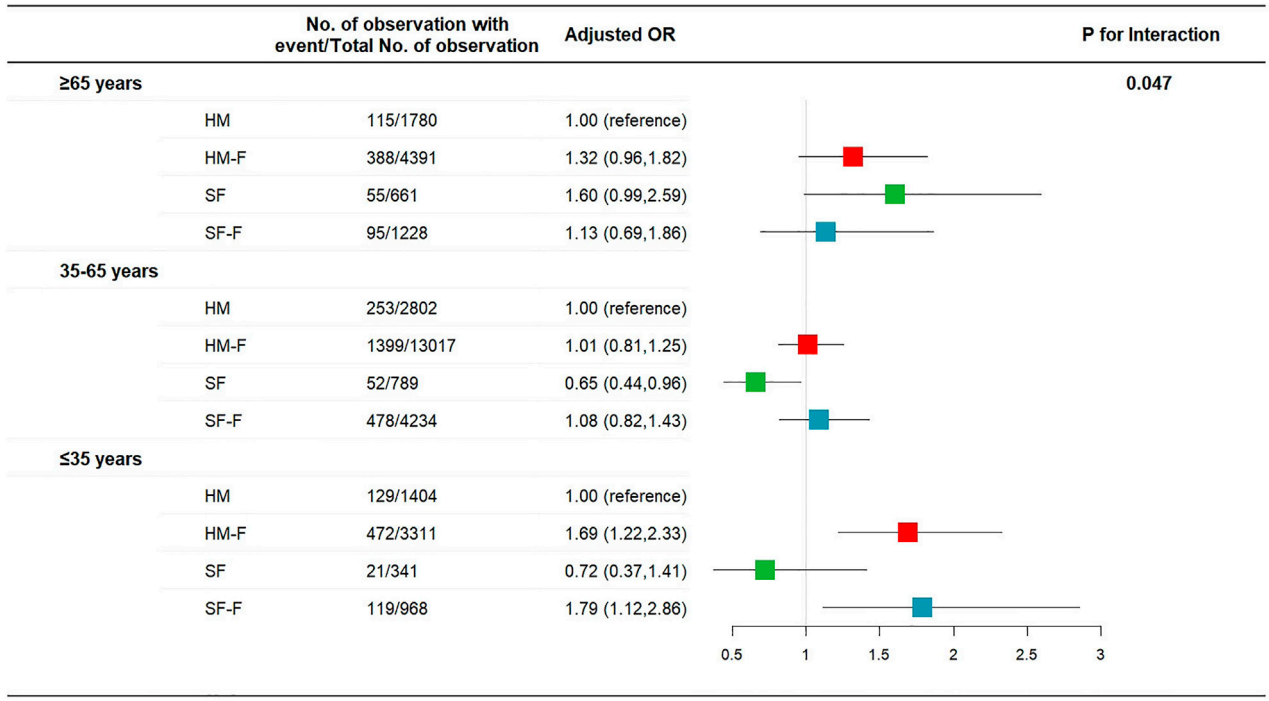

FIGURE 2
Risk of PONV for patients receiving hydromorphone plus FBP, sufentanil, or sufentanil plus FBP for IV-PCA, as compared to patients receiving hydromorphone, stratified according to patient age.

even though hydromorphone is considered superior in both potency and pharmacokinetics (Hong et al., 2008). Previous publications seldom reported differences between different opioids due to limitations related to sample size, statistical analysis, and high variation in individual responses (Drewes et al., 2013). Most PCA studies utilized small sample sizes, ranging from 500 patients or more, with varied surgical types, making it difficult to compare and pool even in systematic reviews (Dinges et al., 2019). Additionally, PCA used to assess analgesic effectiveness is based on an assumption that the analgesic demand directly reflected pain intensity; thus, both opioid consumption and pain score were important outcome measures in PCA studies (Sechzer, 1990). However, several factors affect the relationship between pain intensity and opioid consumption (Kissin, 2009). First, not all patients in clinical practice achieve complete and pain spontaneous relief due to a fear of opioid-related side effects. As patients were educated to maintain a VAS at rest of ≤3, it is hard to say that two mean VAS <3 had significant differences that were attributable to treatment effects or individual factors. Moore et al. first expressed skepticism regarding the validity of VAS as an outcome measure in 2005 (Moore et al., 2005). A series of studies showed that pain intensity and pain relief were highly skewed data that cannot be appropriately reported as means (Moore et al., 2010; Moore et al., 2011). This was confirmed in the 10-year experience of acute pain service in Italy, in which the mean VAS was relatively low in clinical practice because most patients achieved satisfactory pain relief (Deni et al., 2019). Therefore, the percentage and pain intensity of patients with VAS >3 were concealed by the mean VAS; these populations were inclined to withdraw from clinical trials due o analgesic failure, which introduced bias. Based on these findings, Moore et al. advocated using no worse than mild pain as an outcome, defined as NRS (0–10) ≤3 or VAS (0–100) ≤30, which was better correlated with other pain-related symptoms such as insomnia and depression and more precisely reflected analgesic requirements in clinical practice (Moore et al., 2013a; Moore et al., 2013b). Similarly defined moderate-to-severe pain has been used as an important parameter in population studies and clinical trials (Bulilete et al., 2019; Melcer et al., 2021). Second, while opioid consumption was compared in MME, the conversion factors were controversial, with manual selection introducing bias (Anderson et al., 2001). Finally, varied individual responses to specific opioids played an important role in conflicting results between different trials (Kent et al., 2010).

This study used a cohort including the largest number of common noncardiac surgeries to date. Some surgery types were not included due to the high risk of bias from unmeasured confounders: 1) patients who underwent neurosurgery, cardiothoracic surgery, and oral and maxillofacial surgery

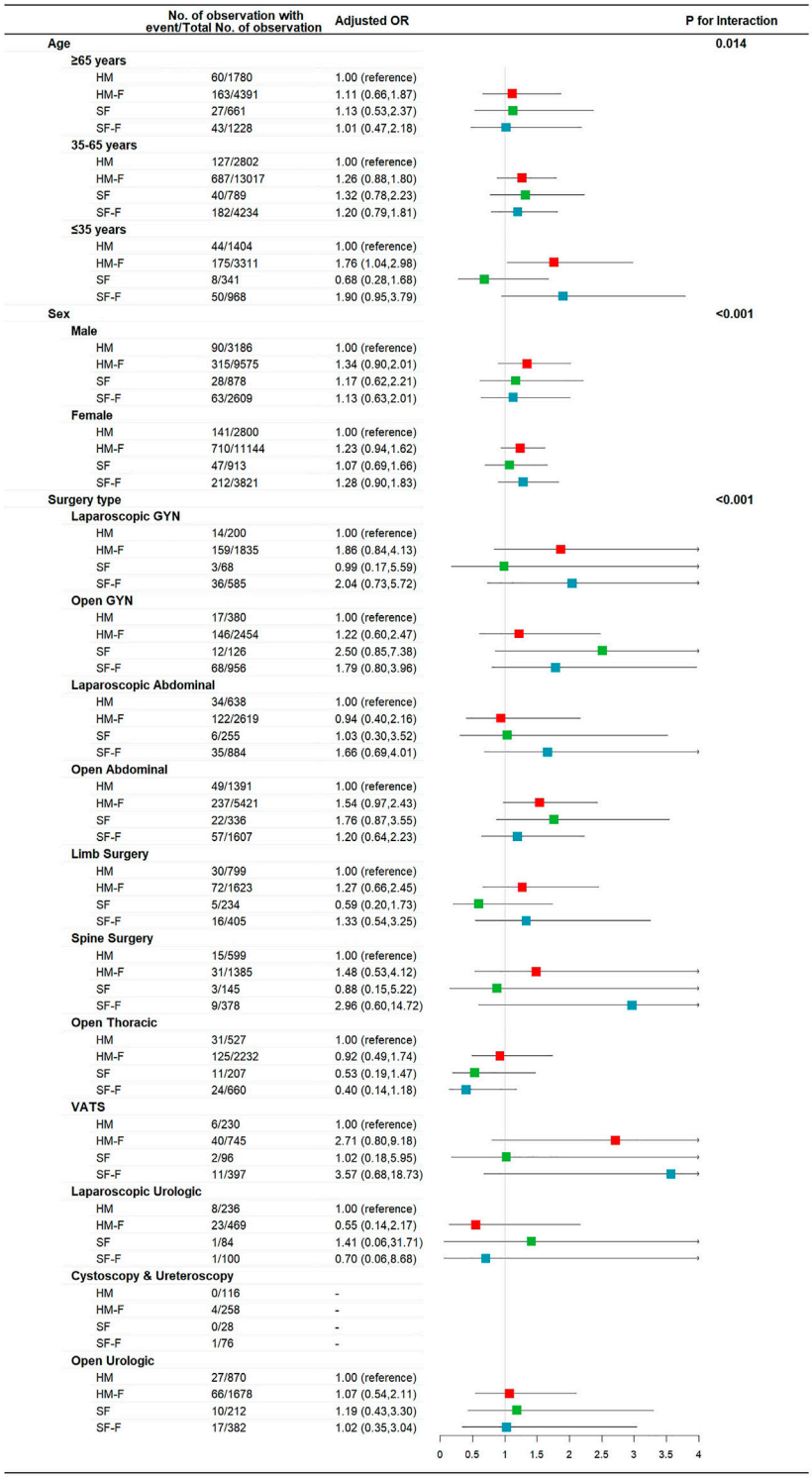

FIGURE 3
Risk of dizziness for patients receiving hydromorphone plus FBP, sufentanil, or sufentanil plus FBP for IV-PCA, as compared to patients receiving hydromorphone, stratified according to patient age, sex, and surgery type.

were routinely monitored in the intensive care unit immediately after surgery, where they were possibly exposed to opioid analgesics and sedatives; 2) patients who underwent vascular surgery, burn surgery, and plastic surgery were not included because this population was likely to have diabetic neuropathy and chronic pain; and 3) IV-PCA was rarely used after obstetric surgery, thyroid surgery, breast surgery, and eye, nose, and throat surgery. The remaining five specialties included in this study followed similar perioperative care standards in both institutions. To focus on patients who could not achieve a target pain relief by PCA, we chose analgesic insufficiency (defined as VAS score ≥4) as the main measure of analgesic effectiveness, as advocated in the serial studies by Moore et al. (2011; 2013a; 2013b). A two-level GEE model (individual and hospital) was adapted to flexibly include unbalanced analgesic assessments at various time points for up to h, which allowed the construction of a dynamic scope of the postoperative analgesia with less information loss. This model included the real-time drug consumption of hydromorphone, sufentanil, and FBP covariates to adjust the relationship between pain intensity, adverse effects, and drug consumption.

We compared hydromorphone and sufentanil, which represented two typical opioid classes with different pharmacokinetics that are seldom directly compared (Drewes et al., 2013). Consistent with Yan et al., the results of our primary analysis showed better analgesic effects of hydromorphone, with similar risks of PONV and dizziness (Yan et al., 2018). Yan et al. assessed the pain score at five time points (0, 6, 12, 24, and 48 h postoperatively), reporting that the pain score in the sufentanil group was only higher than that in the hydromorphone group at 6 h, which they attributed to the increasing free fraction of sufentanil over time, as reported by Saari et al. (2014). We included more time points in our study and found that the risk of analgesic insufficiency of the sufentanil group remained higher than that in the hydromorphone group at approximately 72 h postoperatively, which was not fully explained by the plasm protein binding rate. Therefore, we speculated that acute tolerance may also contribute to these findings. Coda et al. suggested the development of acute tolerance in the sufentanil group compared to morphine and hydromorphone in patients with oral mucositis pain following bone transplantation (Coda et al., 1997). Preclinical experiments by Kissin et al. revealed that acute tolerance developed within 8 h and was faster in both sufentanil and alfentanil groups compared to morphine (Kissin et al., 1991). However, evidence in a longer timeframe and in comparison with hydromorphone are lacking.

Preemptive or postoperative FBP has long been recommended in multimodal analgesic regimens for the treatment of postoperative acute pain (Yamashita et al., 2006; Wang et al., 2012; Martinez et al., 2019). However, its use as an adjuvant in IV-PCA was not thoroughly studied (Wick et al., 2017). FBP reportedly enhances the analgesic effect of sufentanil and fentanyl in IV-PCA, while its combination with morphine and hydromorphone is rare (Liu et al., 2011; Geng et al., 2015). The results of our primary analysis showed that FBP combined with either hydromorphone or sufentanil was associated with a better analgesic efficacy compared to the respective opioid-only groups. Subgroup analysis revealed that FBP significantly increased the risk of PONV and that the hydromorphone-FBP combination also increased the risk of dizziness in patients aged ≤35 years, findings that were not previously reported. A bolus dose of FBP was believed to reduce opioid-associated adverse effects including PONV; however, no study had examined its influence on adverse effects in continuous use. Therefore, the clinical significance of our findings is unclear (Martinez et al., 2019). As younger age was an independent risk factor of PONV in our GEE model (Table 2), our finding suggests the need for care in the continuous use of FBP in IV-PCA in patients aged ≤35 years. Further clinical and mechanism research are needed to confirm and fully explain this association.

Our study has several limitations arising from its retrospective design. First, the intelligent analgesic research database did not include potential confounders such as primary diagnosis, comorbidities, preoperative medication, preoperative opioid exposure, and postoperative medication prescribed in the ward. Second, while we reclassified surgery types according to specialties and approaches, heterogeneity in pain intensity still existed among each surgery type. Moreover, this 11-level classification resulted in a wide confidence interval in subgroup analysis stratified by surgery type owing to the inadequate sample sizes in some subgroups. Third, due to the diminishing use of morphine in Chinese tertiary hospitals, we could not compare hydromorphone and sufentanil to morphine, which remains the gold standard (Wang et al., 2021). Fourth, the two medical centers in this study are both located in southern China. Given the high variability in individual responsiveness to certain opioids and the unknown underlying mechanisms, the generalizability of our results requires further assessment.

In conclusion, the results of this study demonstrated the superiority of hydromorphone over sufentanil for IV-PCA in the management of acute postoperative pain. Adding FBP as an adjuvant may improve the analgesic effects of both hydromorphone and sufentanil; however, its use was associated with an increased risk of PONV in patients ≤35 years of age. The combination of hydromorphone and FBP was related to an increased risk of dizziness in the same patient population.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. Written informed consent from the participants' legal guardians/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Study design: WH, QH, and SZ. Coordination: LY and ZW. Data acquisition: YS, QH, and XX. Data interpretation: YS, WH, and QH. Drafting: YS and QH. Final approval of manuscript: All authors.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.988070/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Risk of AIS in patients receiving hydromorphone plus FBP, sufentanil, or sufentanil plus FBP for IV-PCA, as compared to patients receiving hydromorphone, stratified according to patient age, sex, and surgery type.

SUPPLEMENTARY FIGURE 2
Risk of AIM in patients receiving hydromorphone plus FBP, sufentanil, or sufentanil plus FBP for IV-PCA, as compared to patients receiving hydromorphone, stratified according to patient age, sex, and surgery type.

SUPPLEMENTARY FIGURE 3
Risk of PONV in patients receiving hydromorphone plus FBP, sufentanil, or sufentanil plus FBP for IV-PCA, as compared to patients receiving hydromorphone, stratified according to patient sex and surgery type.

SUPPLEMENTARY FIGURE 4
Estimated incidence of the outcomes. Incidence-time curves of **(A)** AIS, **(B)** AIM, **(C)** PONV, and **(D)** dizziness.

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Cost-utility analysis of empagliflozin in heart failure patients with reduced and preserved ejection fraction in China

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Objective: EMPEROR-Reduced and EMPEROR-Preserved studies showed the benefits of empagliflozin along with a reduction in cardiovascular death or hospitalisation for heart failure (HF). Our aim was to evaluate the economics and effectiveness of adding empagliflozin to the standard therapy for HF with reduced ejection fraction (HFrEF) and HF preserved ejection fraction (HFpEF) in China.

Methods: A multistate Markov model was constructed to yield the clinical and economic outcomes of adding empagliflozin to the standard therapy for 65-year-old patients with HFrEF and HFpEF. A cost-utility analysis was conducted, mostly derived from the EMPEROR-Reduced study, EMPEROR-Preserved study, and national statistical database. All costs and outcomes were discounted at the rate of 5% per annum. The primary outcomes were total and incremental costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). Sensitivity analyses were also performed.

Results: In the HFrEF population, the 10-year incremental cost was $827.52 and the 10-year incremental QALY was 0.15 QALYs, resulting in an ICER of $5,612.06/QALY, which was below the WTP of $12,652.5/QALY. In the HFpEF population, compared with the control group, the incremental cost was $1,271.27, and the incremental QALY was 0.11 QALYs, yielding an ICER of 11,312.65 $/QALY, which was also below the WTP of $12,652.5/QALY. In the HFrEF and HFpEF populations, the results of a one-way sensitivity analysis showed that the risk of cardiovascular death in both groups was the most influential parameter. In the HFrEF population, a probability sensitivity analysis (PSA) revealed that when the WTP thresholds were $12,652.5/QALY and $37,957.5/QALY, the probabilities of being cost-effective with empagliflozin as an add-on were 59.4% and 72.6%, respectively. In the HFpEF population, the PSA results revealed that the probabilities of being cost-effective with empagliflozin as an add-on were 53.1% and 72.2%, respectively.

Conclusion: Considering that the WTP threshold was $12,652.5/QALY, adding empagliflozin to standard therapy was proven to be a slightly more cost-effective option for the treatment of HFrEF and HFpEF from a Chinese

healthcare system perspective, which promoted the rational use of empagliflozin for HF.

KEYWORDS

empagliflozin, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, cost-utility analysis, China

Introduction

Heart failure (HF) is a clinical syndrome in which the cardiac systolic and/or diastolic functions are significantly inadequate, resulting in an inadequate pump function, which is the leading cause of human death and/or hospitalisation, and it has become a serious global public health problem (Hao et al., 2019). Notably, HF is divided into HF with mildly reduced ejection fraction (HFmrEF), HF with reduced ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF), which is more prevalent among the elderly. The clinical characteristics of HFmrEF are more similar to those of HFpEF. Based on the high incidence of poor prognosis and lack of clinically proven therapies thus far, HFpEF is considered to be the only and/or largest unmet demand in the cardiovascular (CV) medicine field (Dunlay et al., 2017). Approximately 1%–2% of the global population over 40 years of age suffer from HF; among the population aged 60–70 years, this proportion would add to 10% and continue to increase with the aging population. The prevalence of HF in China is approximately 1.3%, and it has increased by 44% over the past 15 years (Cook et al., 2014; Conrad et al., 2018). Moreover, HF not only lowers the quality of life but also causes a heavy economic burden for patients and their families. It is estimated that the economic burden of HF care in China will increase significantly in the next few decades. Furthermore, HF is an economically burdensome disease. The cost of hospitalisation for HF in China has increased to approximately $26.3 billion, representing an increase of 87% in 10 years (Cook et al., 2014).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are new therapeutic agents for diabetes mellitus that decrease blood sugar levels by inhibiting the proximal renal tubular SGLT protein family reabsorption of glucose (Chao and Henry, 2010). The EMPA-REG OUTCOME study demonstrated that the CV safety of empagliflozin was related to a 14% reduction in CV outcomes and a 35% decrease in HF associated with hospitalisation in a diabetic population (Zinman et al., 2016). An EMPEROR-Reduced study found that empagliflozin was associated with a 25% reduction in CV death or hospitalisation for HF and a 30% reduction in HF associated with hospitalisation in patients with HFrEF with or without diabetes (Packer et al., 2020). SGLT2 inhibitors were recommended as the first-line drugs for the treatment of HFrEF based on promising evidence from EMPEROR-Reduced and DAPA-HF studies (Colombo et al., 2020; Packer et al., 2020; Mcdonagh et al., 2021). The EMPEROR-Preserved study also provided evidence of empagliflozin related to a 21% reduction in CV death or hospitalisation for HF and a 29% reduction in HF hospitalisation in patients with HFpEF with or without diabetes (Anker et al., 2021). Based on the satisfactory results of the EMPEROR-Preserved study, the United States Food and Drug Administration has approved that empagliflozin could be used to treat HFpEF in February 2022 (Michael O'Riordan, 2022).

Considering the curative effect, economic benefit was also an important factor in medical decision-making. Empagliflozin contributed to a higher cost of HF that significantly limited its promotion. Cost-utility analysis is a useful method to evaluate the value of drugs by quantifying and comparing the cost and effectiveness of different therapeutic strategies. The previous pharmacoeconomic evaluation focussed on HFrEF or HF as a homogenous group and lacked a pharmacoeconomic evaluation of HFpEF (Griffiths et al., 2014; Park et al., 2019). Therefore, we evaluated the cost-utility of empagliflozin in HFrEF and HFpEF from the perspective of healthcare systems in China.

Materials and methods

Simulated population

Two simulated cohorts were employed in this study. The first cohort comprised the HFrEF population, whose characteristics were consistent with those of the EMPEROR-Reduced study.[7] The second cohort was composed of the HFpEF population, whose characteristics were similar to those of the EMPEROR-Preserved study.[10] The simulated population in the EMPEROR-Reduced study was not completely different from that in the EMPEROR-Preserved study. The major difference from the EMPEROR-Reduced population was that patients with HFrEF were defined by a left ventricular ejection fraction (LVEF) ≤ 40%, while the population with HFmrEF had an LVEF of 40%–50% and those with HFpEF had an LVEF > 50% in the EMPEROR-Preserved study. The empagliflozin group in both hypothetical cohorts comprised patients who received empagliflozin (10 mg daily) as an add-on to the standard therapy for HF. The control group received placebo and standard treatment for HFrEF and HFpEF. The initial age

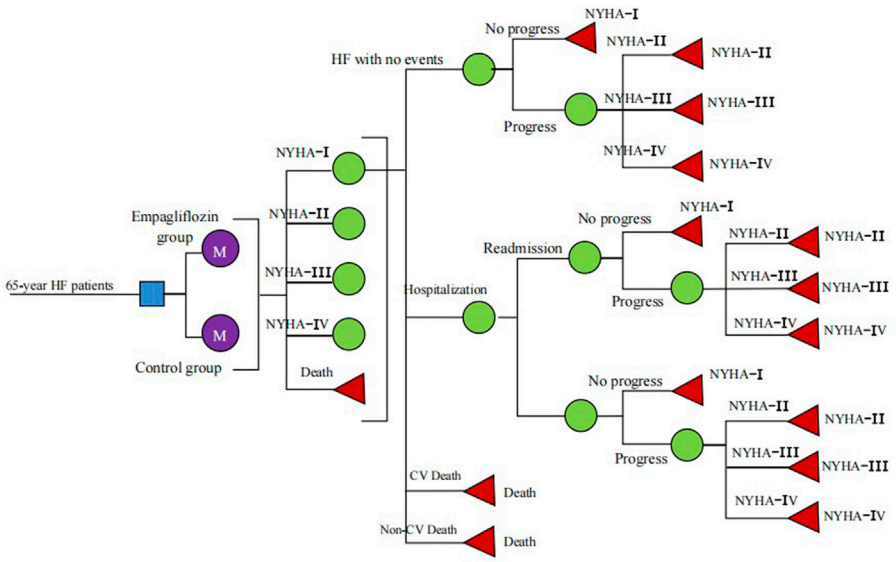

FIGURE 1
Schematic representation of the Markov model.

of the simulated patients in the model was 65 years, and the majority of HF cases were reported in the elderly in the real world (Li et al., 2020). A Markov model was created using Microsoft Excel 2010.

Model structure

Based on the clinical outcomes of the EMPEROR-Reduced and EMPEROR-Preserved studies, including CV death, hospitalisation, and readmission for HF, we constructed a multistate Markov model to evaluate the cost-utility analysis of the intervention (empagliflozin) for patients with HFrEF and HFpEF. We defined five mutually independent and transferable Markov states (Figure 1), including New York Heart Association (NYHA) function classes I, II, III, and IV, and death (CV death and non-CV death). At the end of each cycle, the patient would switch between different NYHA function classes, and the symptoms would improve or worsen. Because the purpose of our study was to calculate the long-term costs and outcomes of HF patients, a lifetime (10 years) horizon with a 3-month cycle length was applied for the cost-utility analyses. The rate of HF readmission was high during the early post-discharge period, especially within the first 90 days after discharge from HF hospitalisation (Khan et al., 2021; Wideqvist et al., 2021). Based on "The Guidelines of Pharmacoeconomic Evaluations of China (2020)," an annual discount rate of 5% was applied to minimise the impact of inflation on future costs and QALYs, and a half-cycle correction was applied to prevent the overestimate of expected survival (Liu, 2020).

Clinical event probabilities

As we could not directly obtain the age-dependent incidence of each clinical event from the EMPEROR Reduced and EMPEROR Preserved studies, we proposed an assumption that the rate of each clinical event and the efficacy of empagliflozin on HFrEF and HFpEF were fixed. We chose some data from other published literature and national statistical databases in cases where relevant data could not be directly obtained from the EMPEROR-Reduced and EMPEROR-Preserved studies. In the HFrEF population, the risks of CV death were 10.0% and 10.8% in the empagliflozin and control groups, respectively, while the risks of hospitalisation for HF were 13.2% and 18.3% (Packer et al., 2020). The risk of readmission for HF after discharge (13.4%) within 30 days in HFrEF patients was derived from the PARADIGM-HF study (Desai et al., 2016). In the HFpEF population, the incidences of CV death were 8.3% and 7.2% in the empagliflozin and control groups, respectively, and the incidences of HF-related hospitalisation were 16.2% and 12.1%, respectively (Anker et al., 2021; Packer et al., 2021). The incidence of readmission for HF within 30 days after discharge in HFpEF patients was 18% in the I-PRESERVE trial (Carson et al., 2015). Considering that there was no difference in age-dependent non-CV death between both groups, it was assumed that the non-CV death of both groups was the same, as obtained from the China Center for Disease Control and Prevention (National Center for Chronic and Noncommunicable Disease Control and Prevention, 2019). The formula $r = -1/t \ln(S)$, $P = 1\text{-}e^{(-r^{*}T)}$ was applied to calculate the event probabilities (S is the rate, t is the time,

TABLE 1 Selected model inputs.

Variables	Value	Range	Distribution	Reference
Clinical event probabilities				
HFrEF population				
Cardiovascular death				
Control group	0.0212	0.01908–0.02332	Beta	Packer et al. (2020)
Empagliflozin group	0.01956	0.01760–0.02152	Beta	Packer et al. (2020)
Hospitalization for heart faliure				
Control group	0.03719	0.03347–0.04091	Beta	Packer et al. (2020)
Empagliflozin group	0.02619	0.02357–0.02881	Beta	Packer et al. (2020)
Readmission for heat faliure	0.331	0.2979–0.3641	Beta	Desai et al. (2016)
HFpEF population				
Cardiovascular death				
Control group	0.00975	0.00877–0.01072	Beta	Anker et al. (2021)
Empagliflozin group	0.00864	0.00778–0.00951	Beta	Anker et al. (2021)
Hospitalization for heart faliure				
Control group	0.02003	0.01803–0.02204	Beta	Packer et al. (2021)
Empagliflozin group	0.01466	0.01319–0.01613	Beta	Packer et al. (2021)
Readmission for heat faliure	0.417	0.3753–0.4587	Beta	Carson et al. (2015)
Probability of non-CV mortality by age				
65–69 years	0.2430%			(National Center for Chronic and Noncommunicable Disease Control and Prevention, 2019)
70–74 years	0.3042%			(National Center for Chronic and Noncommunicable Disease Control and Prevention, 2019)
75–79 years	0.4185%			(National Center for Chronic and Noncommunicable Disease Control and Prevention, 2019)
Utility (HFrEF)				
NYHA I	1.000	0.950–1.000	Beta	Di Tanna et al. (2021)
NYHA II	0.860	0.817–0.903	Beta	Di Tanna et al. (2021)
NYHA III	0.600	0.570–0.630	Beta	Di Tanna et al. (2021)
NYHA IV	0.280	0.266–0.294	Beta	Di Tanna et al. (2021)
Utility (HFpEF)				
NYHA I	1.000	0.950–1.000	Beta	Di Tanna et al. (2021)
NYHA II	0.830	0.789–0.872	Beta	Di Tanna et al. (2021)
NYHA III	0.550	0.523–0.578	Beta	Di Tanna et al. (2021)
NYHA IV	0.270	0.257–0.284	Beta	Di Tanna et al. (2021)
Hospitalization and readmission	−0.1	−0.13–-0.08	Beta	King et al. (2016)
Cost				
Standard therapy	$131.96	$131.96–310.83	Gammma	Huang et al. (2017)
Empagliflozin	$59.63	$47.70–71.55	Gammma	Local data
Hospitalization and readmission	$1,783.39	$1,029.73–3,336.39	Gammma	Ma, (2021)
Discounted rate	5%	0%–8%		Liu (2020)

and P is the clinical event probability) (Park et al., 2019) (Table 1). The transition probabilities between different NYHA function classes at the end of every cycle were assumed to be similar. The 3-month transition probability between NYHA function classes was obtained from the published literature (King et al., 2016) (Table 2).

Cost and utility

From a Chinese healthcare system perspective, we only enrolled the direct medical costs because they could be measured easily and objectively. The cost in the study included the costs of hospitalisation for HF, standard

TABLE 2 New York Heart Association classes transition probabilities per cycle (3 months).

To	I	II	III	IV	Distribution
From					
I	0.977	0.019	0.004	0	Dirichlet
II	0.008	0.981	0.010	0.001	Dirichlet
III	0	0.034	0.960	0.006	Dirichlet
IV	0	0	0.055	0.945	Dirichlet

therapy, and empagliflozin. The cost of hospitalisation for HF, including medical, operation, examination, inspection, berth, administration fees, and medical staff, were obtained from the China Health Statistics Yearbook 2021 (Ma, 2021). Standard therapy consisted of sacubitril/valsartan (SAC/VAL), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta blockers, and spironolactone. Although HFpEF therapy lacked specific drugs, most were already treated with diuretics, SAC/VAL, ACEI, ARB, beta-blockers, and spironolactone. The standard therapy cost was derived from the National Claims Sampling Database (Huang et al., 2017). According to the latest national negotiation price in 2022, empagliflozin was $0.6625 per 10 mg, while SAC/VAL was $0.497 per 100 mg; thus, we could calculate the range of standard therapy and the cost of empagliflozin of each cycle (Table 1). All costs of this study were converted into US dollars at an exchange rate of 1 $ = 6.4 RMB (The People's Bank of China, 2021).

Owing to the simultaneous lack of evidence on the health utility of HFrEF and HFpEF in China, the published literature was chosen. The visual analogue scale and time trade-off were used to calculate the utility scores of HFrEF and HFpEF (Di Tanna et al., 2021). Additionally, a higher rate of hospitalisations leads to a greater utility decrease; thus, each HF-related hospitalisation would reduce the utility by 0.1 (King et al., 2016) (Table 1). The expenses and QALYs in the model were inflated to 2022 by adopting the consumer price index in the medical care category.

Outcome

The primary endpoints in this study were the total discounted cost, total discounted QALYs, and ICER. The ICER was calculated by dividing the difference in total cost by the difference in outcomes for both groups. In view of "The Guidelines of Pharmacoeconomic Evaluations of China (2020)": ICER < 1 fold of gross domestic product (GDP) per capita, the incremental cost was totally deserved and very cost-effective; 1 fold of GDP per capita < ICER < 3-fold of GDP per capita, the incremental cost was receivable and cost-effective; ICER > 3-fold of GDP per capita, the incremental cost was not deserved and not cost-effective (Liu, 2020). Considering that there was no fixed willingness-to-pay (WTP) to evaluate cost utility in China, we defined the WTP thresholds of $12,652.5/QALY and $37,687.5/QALY related to the one-time and three-times GDP per capita of China in 2021, respectively, to judge whether adding empagliflozin in HFrEF and HFpEF was very cost-effective (ICER ≤ $12,652.5) or only a cost-effective (i.e., ICER ≤ $37,687.5) (Eichler et al., 2004).

Sensitivity analyses

A series of sensitivity analyses, including one-way sensitivity analysis and probability sensitivity analysis (PSA), was adopted in this study to validate the stability of the model. One-way sensitivity analysis was used to calculate all ICERs by changing the reasonable range of one parameter and keeping the other parameters fixed in the model to evaluate the impact of this parameter on cost utility (Table 1). The results are presented in a tornado diagram. Notably, PSA can simultaneously consider the impact of changes of multi-parameters in the model on the ICER. The parameters in the model were randomly sampled (1,000 repetitions) based on their relevant distributions. The cost parameters suited the gamma distribution, while the utility parameters and event probability

TABLE 3 The results from base-case analysis.

	Total cost ($)	Total life years (QALY)	Incremental cost ($)	Incremental life years (QALY)	ICER ($ per QALY)
HFrEF population					
Empagliflozin group	5,501.48	4.27	827.52	0.15	5,612.06
Control group	4,673.96	4.12			
HFpEF population					
Empagliflozin group	5,916.20	4.96	1,271.27	0.11	11,312.65
Control group	4,645.23	4.85			

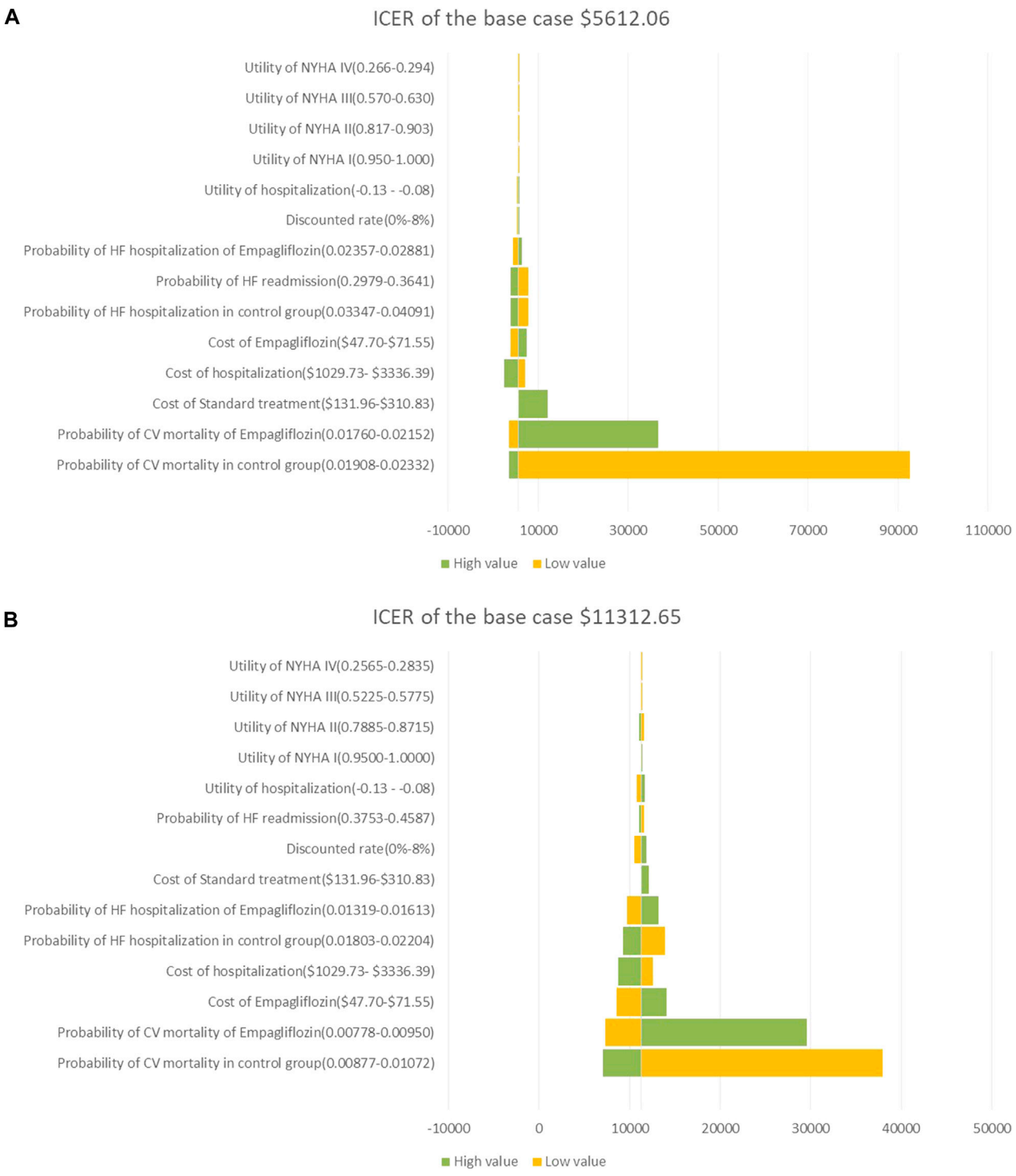

FIGURE 2
(A) Tornado diagram showing the univariate sensitivity analysis of the Markov model simulation in HFrEF population. **(B)** Tornado diagram showing the univariate sensitivity analysis of the Markov model simulation in HFpEF population.

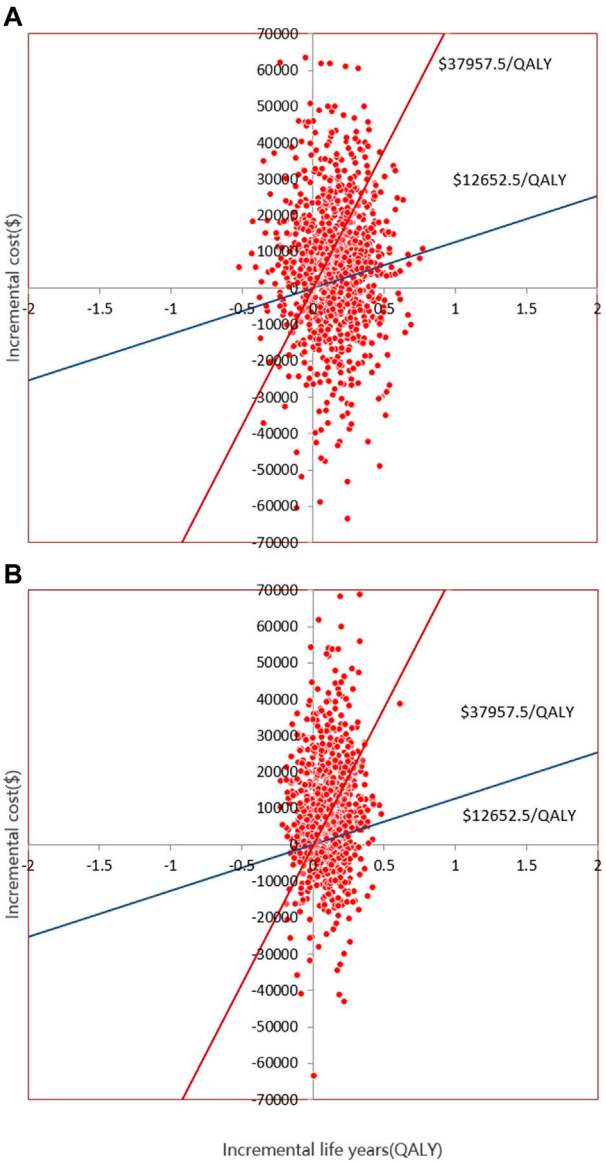

FIGURE 3
(A) Scatter plot showing the incremental costs and incremental quality-adjusted life-year of a thousand simulations for Empagliflozin group and Control group in HFrEF population. **(B)** Scatter plot showing the incremental costs and incremental qualityadjusted life-year of a thousand simulations for Empagliflozin group and Control group in HFpEF population.

parameters suited the beta distribution, and the results were represented by cost-effectiveness-acceptability curves and scatter diagrams.

Scenario analysis was also performed by changing the cost of empagliflozin (national purchase price, $0.275 per 10 mg, once daily), the time horizon (15 and 20 years), and the hospital level [town-level hospitals ($1,029.73), county-level hospitals ($1,231.06), municipal hospitals ($1,783.39), provincial hospitals ($1,949.55), and ministerial hospitals ($3,336.39)] (Ma, 2021).

Results

HFrEF population

The 10-year total cost in the empagliflozin group was higher than that in the control group ($5,501.48 vs. $4,673.96), projecting an incremental cost of $827.52. However, the 10-year total QALYs in the empagliflozin group was higher than that in the control group (4.27 QALYs vs. 4.12 QALYs), thereby projecting an incremental QALY of 0.15 QALYs. This yielded an ICER of $5,612.06/QALY, which was below the WTP of $12,652.5/QALY. Empagliflozin was associated with a 1.2% reduction in CV death and a 28.7% decrease in HF hospitalisation from our simulated results (Table 3).

HFpEF population

Compared with the control group, the 10-year total cost in the empagliflozin group was more expensive ($5,916.20 vs. $4,645.23) and an incremental cost of $1,271.27. However, the 10-year total QALYs in the empagliflozin group was higher (4.96 QALYs vs. 4.85 QALYs), along with an incremental QALY of 0.11 QALYs. This yielded an ICER of $11,312.65/QALY, which was below the WTP of $12,652.5/QALY. Empagliflozin was associated with a 7.8% reduction in CV death and a 25.5% decrease in HF hospitalisation based on our simulated results (Table 3).

Sensitivity analyses

In the HFrEF and HFpEF populations, the results of the one-way sensitivity analysis showed that the risk of CV death in both groups was the most influential parameter, which was more than three times the GDP of $37,957.5/QALY; followed by the cost of empagliflozin and the cost of hospitalization for HF, which was lower than three times the GDP of $37,957.5/QALY; and the ICER calculated by changing a reasonable range of parameters was represented as a tornado diagram (Figures 2A,B).

In the HFrEF and HFpEF populations, most of the 1,000 iterations fell in the upper-right quadrant, demonstrating that the add-on empagliflozin treatment for HFrEF and HFpEF usually incurred a higher cost but gained higher QALYs (Figures 3A,B). In the HFrEF population, the PSA results revealed that when the WTP thresholds were $12,652.5/QALY and $37,957.5/QALY, the probabilities of being cost-effective for the add-on empagliflozin treatment were 59.4% and 72.6%, respectively (Figure 4A). In the HFpEF

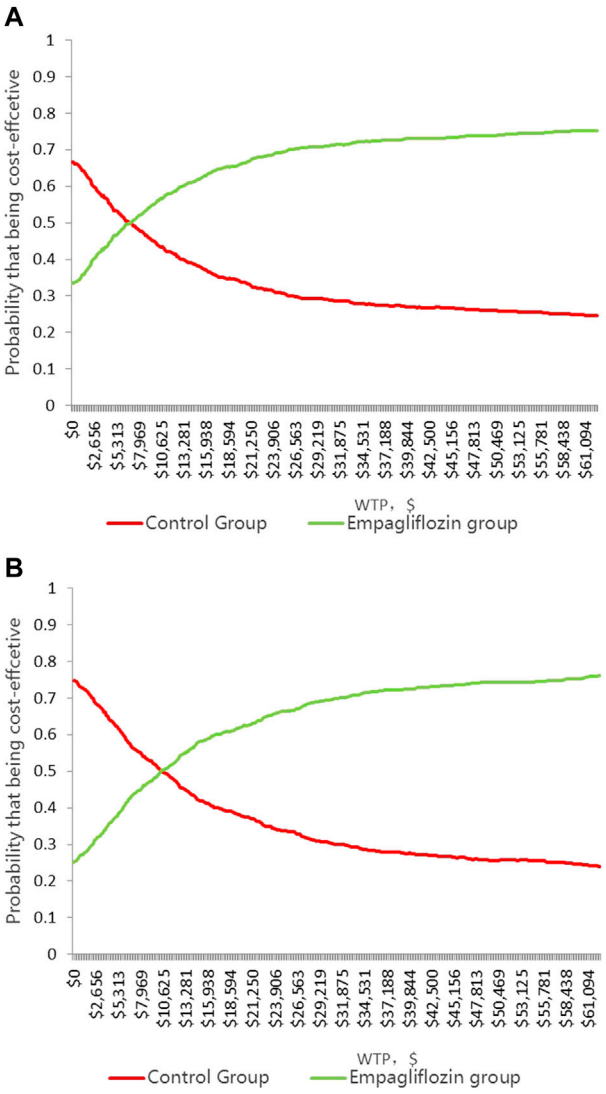

FIGURE 4
(A) Cost-effectiveness acceptability curve showing the maximum willingness to pay and the corresponding probability of cost-effectiveness for Empagliflozin group and Control group in HFrEF population. **(B)** Cost-effectiveness acceptability curve showing the maximum willingness to pay and the corresponding probability of cost-effectiveness for Empagliflozin group and Control group in HFpEF population.

population, the PSA results revealed that when the WTP thresholds were \$12,652.5/QALY and \$37,957.5/QALY, the probabilities of being cost-effective for the add-on empagliflozin were 53.1% and 72.2%, respectively (Figure 4B).

Based on the scenario analysis, when the national purchase price of empagliflozin was slightly lower, the cost of hospitalisation for HF was much higher, the time horizon was longer, and it was more cost-effective to add empagliflozin to the HFrEF and HFpEF populations (Table 4).

Discussion

This study aimed to explore the cost utility of an intervention (empagliflozin) on HFrEF and HFpEF populations based on the EMPEROR-Reduced study, EMPEROR-Preserved study, and national statistical database. In our study, we found that adding empagliflozin to the standard therapy for HFrEF was cost-effective from a Chinese healthcare system perspective with an ICER of 5,612.06 \$/QALY, which was below the WTP of \$12,652.5/QALY. Adding empagliflozin to the standard therapy for HFpEF generated advantages in cost utility. One HFpEF patient gained a QALY by spending \$11,312.65, which was also below the WTP of \$12,652.5/QALY. A series of sensitivity analysis was conducted to validate the stability of the model. Generally, the results in the model provided decision-makers and healthcare payers with a valuable quantitative assessment of empagliflozin in the HFrEF and HFpEF populations.

Initial clinical trials showed that SGLT2 inhibitors were very promising antidiabetic drugs but reduced CV death and hospitalisation for HF in the diabetic population (Zinman et al., 2016; Wiviott et al., 2019). The EMPEROR-Reduced and DAPA-HF studies demonstrated that SGLT2 inhibitors benefited HFrEF along with a reduction in CV death and/or hospitalisation for HF in both diabetic and non-diabetic patients (Colombo et al., 2020; Packer et al., 2020). In HFrEF, empagliflozin induced reverse remodeling with regression in LV dilatation, improved exercise capacity and enhanced quality of life (Santos-Gallego et al., 2021; Requena-Ibanez et al., 2022). This was due to empagliflozin causing a shift in myocardial metabolism away from glucose utilization towards consumption of free fatty acids and ketone bodies (Garcia-Ropero et al., 2019; Santos-Gallego et al., 2019; Santos-Gallego et al., 2022). In HFpEF, empagliflozin improved diastolic dysfunction and myocardial fibrosis that caused HFpEF; moreover, empagliflozin also improved other mechanisms contributing to HFpEF such as renal dysfunction and vascular stiffness/systemic vascular resistance (Requena-Ibanez et al., 2021; Santos-Gallego et al., 2021; Santos-Gallego and Van Spall, 2021). A series of studies have proven that adding dapagliflozin to the standard therapy of HFrEF generated cost-effectiveness advantages in different economic systems and medical environments, including the United States, Australia, Thailand, and China (Mcewan et al., 2020; Jiang et al., 2021; Krittayaphong and Permsuwan, 2021). Although the study reported a cost-utility analysis of empagliflozin in patients with chronic HF from the healthcare system perspectives of the United States and the United Kingdom, all the parameters were derived from subgroup data from the EMPA-REG OUTCOME trial, which only included the diabetic population. Therefore, this study might not fully demonstrate the advantages of empagliflozin in HFrEF (Reifsnider et al., 2020). The add-on empagliflozin treatment for HFrEF was a cost-effective choice in Thailand, and it also considered adverse reaction events, including urinary tract infections

TABLE 4 The result of scenario analyses presented as ICER.

Scenario	ICER($ per QALY)	
	HFrEF population	HFrEF population
Price for empagliflozin		
National negotiation price	5,612.06	11,312.65
National purchase price	520.36	3,298.60
Hospital Level		
Town Hospital	7,145.36	1,257.86
County Hospital	6,735.76	12,235.49
Municipal Hospital	5,612.06	11,312.65
Provincial Hospital	5,274.02	11,035.04
Ministerial Hospital	2,452.50	8,717.90
Time horizon		
10 years	5,612.06	11,312.65
15 years	5,147.52	9,842.18
20 years	4,882.05	8,907.66

(Krittayaphong and Permsuwan, 2022). Empagliflozin in HFrEF also generated advantages in cost-effectiveness in the total, diabetic, and non-diabetic populations in China (Lin et al., 2022).

Owing to the lack of specific drugs for HFpEF therapy, SAC/VAL, ACEI, ARB, and spironolactone were unable to reduce the risk of CV or hospitalisation for HF (Yusuf et al., 2003; Massie et al., 2008; Hegde et al., 2017). Empagliflozin was the first to provide promising evidence towards improving HFpEF (Anker et al., 2021). There was little evidence of the cost-utility analysis of empagliflozin in the treatment of HFpEF. A study in Thailand showed that one HFpEF patient gained a QALY by spending $11,809, which was not worthwhile, as the WTP was lower (4,773.27 $/QALY) (Krittayaphong and Permsuwan, 2022). Additionally, several studies have shown that empagliflozin is cost-effective in the treatment of diabetes (Ramos et al., 2020); therefore, adding empagliflozin to standard therapy was a duly cost-effective choice for HFrEF and HFpEF patients with diabetes.

There were several reasons why empagliflozin was more cost-effective in HFrEF than in HFpEF. First, the data in the model were mostly based on the EMPEROR-Reduced and EMPEROR-Preserved studies (Packer et al., 2020; Anker et al., 2021). Empagliflozin could reduce more hospitalisation times for HFrEF than HFpEF, which reduced hospitalisation costs and increased QALYs. The hazard ratio (0.69, 95% CI, 0.59–0.81) of hospitalisation for HF in the EMPEROR-Reduced study was lower than that in the EMPEROR-Preserved study (0.72, 95% CI, 0.63–0.82) (Packer et al., 2020; Anker et al., 2021). Second, the severity of HFrEF was higher than that of HFpEF in the EMPEROR-Preserved study, and the EMPEROR-Reduced study showed a higher mortality rate for HFrEF.

In the one-way sensitivity analysis, CV death in both groups was the most important driver in cost utility, regardless of HFrEF or HFpEF population, which had more than three times the GDP of $37,957.5/QALY, and other parameters had little impact on the model. This finding was expected in our study because empagliflozin could not reduce the risk of CV death in the HFrEF and HFpEF populations from the EMPEROR-Reduced and EMPEROR-Preserved studies (Packer et al., 2020; Anker et al., 2021). If the parameter range was slightly changed, the ICER would change significantly, which could not be attributed to model instability. To determine the cost-utility of the add-on empagliflozin treatment for HFrEF and HFpEF population was a reduction of CV death and/or hospitalization for HF, which also urged us to explore the cost-utility of adding empagliflozin to standard therapy in HFrEF and HFpEF population.

This study has some limitations that should be discussed. First, we derived clinical event probabilities based on the median follow-up times and carried fixed transitional probabilities forward, which might not reflect the real HF course, but the sensitivity analysis validated that our model was stable over a relatively wide range of parameters. Second, hospitalisation for non-HF which was complicated in the real world, was not enrolled in our model, but the EMPEROR-Reduced and EMPEROR-Preserved studies showed that empagliflozin could also reduce the risk of all-cause hospitalisation by 15% and 7%, respectively (Packer et al., 2020; Anker et al., 2021). Our results may be more cost-effective when considering the condition. Third, data on clinical events and utility came from other sources, which might cause racial bias, but we solved the problem that might have occurred *via* sensitivity analysis.

Fourth, we assumed that HF patients in the model could tolerate the recommended dose without adverse reaction events, but the EMPEROR-Reduced and EMPEROR-Preserved studies showed that the most common adverse reaction events, including urinary tract infection and hypovolaemia, were not significantly different. Finally, this was a mathematical model combined with national conditions in China, and the generalisability of our findings should be limited to settings or contexts similar to those of this study.

Conclusion

At a WTP level of $12,652.5/QALY, empagliflozin was proven to be a cost-effective add-on therapy for both HFrEF and HFpEF, from a Chinese healthcare system perspective. The results may serve as a reference for rational drug use and health decision-making, but further cost-utility analyses based on real-world evidence of populations in China need to be performed. Liu, 2020, National Bureau, 2019, Santos-Gallego et al., 2021, The People's Bank of China, 2020.

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

YT collected the data regarding heart failure; YT analyzed the data and developed a Markov model; HS was the leader of the study. All authors have read and approved the final manuscript.

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Conflict of interest

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

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Cost-effectiveness of fuzuloparib compared to routine surveillance, niraparib and olaparib for maintenance treatment of patients with germline BRCA1/2 mutation and platinum-sensitive recurrent ovarian carcinoma in China

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Background: Maintenance therapy with the poly (ADP-ribose) polymerase inhibitors (PARPis) for platinum-sensitive recurrent ovarian carcinoma (OC) have proven to be effective compared with placebo. We aimed to evaluate the cost-effectiveness (CE) of maintenance fuzuloparib compared to routine surveillance (RS), niraparib and olaparib for platinum-sensitive recurrent OC from the Chinese healthcare systems.

Method: A partitioned survival model with three-state (progression-free, progressed, death) was constructed utilizing TreeAge Pro 2011 software to evaluate the economic value of fuzuloparib, niraparib and olaparib maintenance treatment for platinum-sensitive recurrent OC based on the clinical data derived from FZOCUS-2, ENGOT-OV16/NOVA and ENGOT-Ov21/SOLO2. Transition probabilities were estimated from the reported survival probabilities in those trials. Cost and health preference data were derived from the literature. The quality-adjusted life-years (QALYs) and lifetime costs were measured for this analysis. A 5 years horizon and 5%/year discount rates were used. One-way analysis, and probabilistic sensitivity analysis (PSA) were performed to explore the model uncertainties.

Results: Total cost of fuzuloparib, niraparib and olaparib were $31628.10, $48183.48 and $54605.54, whereas they had an incremental cost-utility ratio of $31992.69, $32216.08 and $23359.26 per additional progression-free survival (PFS) QALYs gained compared with RS, relatively. Model showed that maintenance fuzuloparib achieved at least an 85.5% probability of CE at the threshold of $37654.50/QALY. One-way sensitivity analysis revealed that the results were sensitive to the PFS and the price of medicines.

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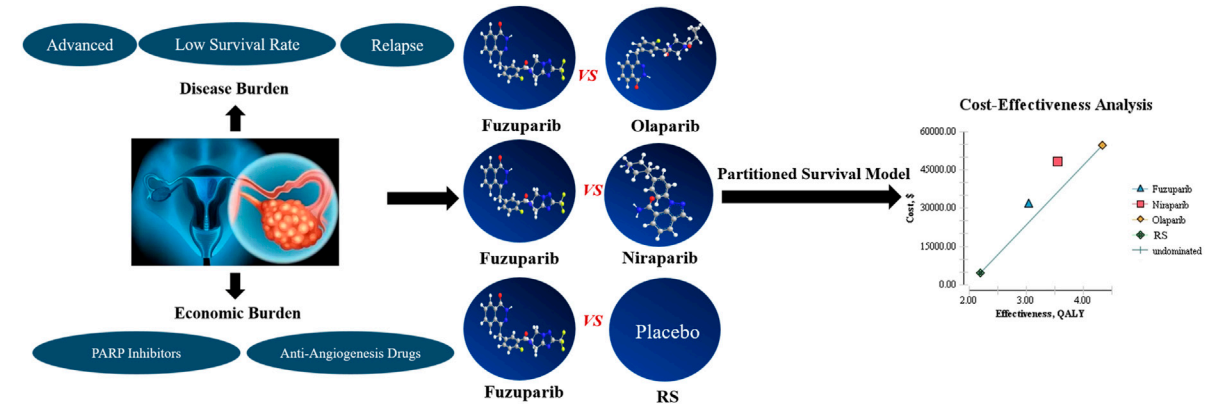
Conclusion: Fuzuloparib was less cost-effective for patients with germline BRCA1/2 mutation and platinum-sensitive recurrent OC compared to olaparib, but was superior to niraparib from the Chinese healthcare systems perspective.

KEYWORDS

fuzuloparib, niraparib, olaparib, cost-effectiveness, maintenance treatment, ovarian cancer, BRCA1/2 mutation



GRAPHICAL ABSTRACT

1 Introduction

Ovarian carcinoma (OC), including fallopian tube cancer and primary peritoneal cancer, is one of the most common gynecological cancers. The incidence of OC is rising yearly with the mortality ranking first in gynecologic tumors, which imperils the health of female (Smith, 2015). In 2016, data from National Cancer Center indicates that in China, 27,200 deaths and 57,200 new cases of OC were reported. The latter accounted for 20% of all new cases globally (Rongshou et al., 2022). The onset of OC is latent with 70% of patients diagnosed in advanced stage, and it is prone to recurrence. The main forms of treatment are surgery and postoperative platinum containing chemotherapy (Ledermann and Raja, 2011). For platinum sensitive relapsed patients, platinum containing combination chemotherapy schemes (carboplatin/paclitaxel, carboplatin/gemcitabine, carboplatin/docetaxel, cisplatin/gemcitabine, etc.,), with or without bevacizumab, are often used (Orr and Edwards, 2018). Nevertheless, platinum retreatment is accompanied with diminishing effectiveness and cumulative toxicity. Therefore, there is an urgent need for new treatment strategies that are well tolerated and able to effectively improve the progression-free survival (PFS) rate of patients suffering from relapsed OC.

Maintenance treatment retards the recurrence or reduces the incidence of relapse. For a long time, few drugs are applicable for maintenance treatment of recurrent OC, and the duration of bevacizumab maintenance treatment is limited. In recent years, poly (ADP-ribose) polymerase inhibitors (PARPis) have made breakthroughs as the maintenance treatment of recurrent OC with BRCA1/2 mutations, and have become a new treatment mode (Smith et al., 2015; Pujade-Lauraine et al., 2017). The advent of PARPis have changed the treatment modality of OC, making maintenance therapy an important part of the whole management process of OC, with milestone significance.

Loss-of-function mutations in BRCA1/2 have been found in 28.5% of patients among Chinese OC patients, which interferes normal repair of DNA double-strand breaks (Li et al., 2021a). PARPis enhance the efficacy of radiotherapy and chemotherapy with alkylating agents and platinum containing drugs *via* interrupting DNA single strand repairs and promoting tumor cells apoptosis through the mechanism that PARPis can block the alternative DNA repair pathway of BRCA1/2 mutated tumor cells resulting in synthetic lethality (Gong et al., 2020).

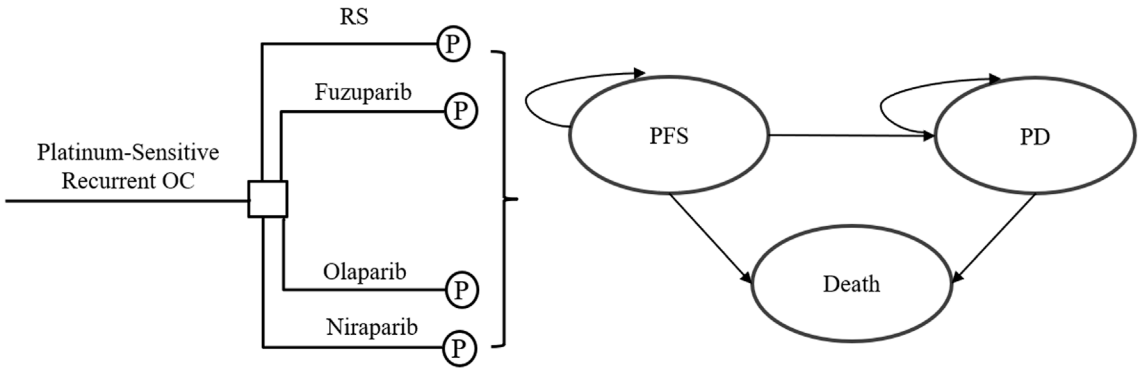


FIGURE 1
Model structure for platinum-sensitive recurrent ovarian carcinoma. OC, ovarian carcinoma; P, partitioned survival model; RS, routine surveillance; PFS, progression-free survival; PD, progressed disease.

Currently, PARPis including olaparib (AstraZeneca), niraparib (Tesaro), fuzuloparib (Hengrui) have been approved by the National Medical Products Administration (NMPA) as maintenance treatment for platinum-sensitive, recurrent OC, which bring about delayed OC progression. Accordingly, the median PFS and quality of life of OC patients have also been notably improved (Wolford et al., 2020). In a double-blind, randomized, placebo-controlled, phase III trial (SOLO2/ENGOT-Ov21), olaparib maintenance therapy afforded in 19.1 months of median PFS *versus* 5.5 months in placebo [hazard ratio (HR), 0.30; 95% CI, 0.22–0.41; $p <$ .0001] (Pujade-Lauraine et al., 2017), 51.7 months of median OS *versus* 38.8 months in placebo [hazard ratio (HR), 0.74; 95% CI, 0.54–1.00; $p = .054$[(Poveda et al., 2021). In an international, multicenter, double blind, randomized, placebo-controlled, phase III trial (ENGOT-OV16/NOVA), the median PFS was significantly longer in the niraparib arm (21 months) than the placebo arm (5.5 months) in a niraparib cohort [hazard ratio (HR), 0.27; 95% CI, 0.17–0.41; $p < .001$] (Mirza et al., 2016). Also, in an ongoing, randomized, double-blind, placebo-controlled, phase III, multicenter study (FZOCUS-2) (Li. et al., 2022), fuzuloparib as a maintenance drug in patients with platinum-sensitive recurrent OC significantly prolonged PFS compared with placebo [12.9 vs. 5.5 months; hazard ratio (HR), 0.25; 95% CI, 0.17–0.36; $p < .0001$]. Thus, PARPis seem to be attractive options for the treatment of platinum-sensitive, recurrent OC. Nevertheless, considering the high treatment cost of PARPis, it is crucial to optimize the allocation of limited health resources. Several relevant studies have evaluated the cost-effectiveness (CE) of different PARPis in the treatment of OC(Guy et al., 2019; Armeni et al., 2020; Muston et al., 2020), but they are not assessed on fuzuloparib. This study aimed to investigate the CE of fuzuloparib compared with routine surveillance (RS), olaparib and niraparib for platinum-sensitive recurrent OC from the Chinese healthcare systems. The results provide appropriate standards and theoretical basis for national medical insurance policy and a reference for more cost-efficient clinical treatment options for patients.

2 Methods

2.1 Model structure

The hypothetical target population for this analysis was patients with platinum-sensitive, recurrent OC, according to the patient characteristics of the clinical trials (Mirza et al., 2016; Pujade-Lauraine et al., 2017; Poveda et al., 2021; Li et al., 2022). A partitioned survival model with three health states was constructed to estimate the cost and treatment efficacy of therapy with RS, fuzuloparib, olaparib or niraparib (Wu and Shi, 2020). As shown in Figure 1, three mutually exclusive states were progression-free survival (PFS), progressed disease (PD), and death, respectively. It was assumed that all patients were in PFS state when entering the model. At the end of each cycle, the patient may stay in the original state or progress to the next state. FZOCUS-2 is a study completely based on the Chinese population, so the inclusion criteria and treatment regimen for the study target population were consistent with the FZOCUS-2 trial in this study. The study hypothesized that the patients entering the model had the same characteristics as the patients enrolled in the clinical trial, namely serous OC, primary peritoneal or fallopian tube cancer, or grade ≥2 endometrioid OC, platinum-sensitive after the last platinum dose of their penultimate line of chemotherapy, and an eastern

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

Parameter	Expected value	Range	Distribution	Source
Drug costs				
Fuzuloparib/cycle	1394.73	1115.78~1,394.73	fixed	Shandong drug centralized procurement platforms (2022)
Olaparib/cycle	1770.75	1416.60~1770.75	fixed	Shandong drug centralized procurement platforms (2022)
Niraparib/cycle	1989.49	1,591.59~1989.49	fixed	Shandong drug centralized procurement platforms (2022)
AEs costs				
Anemia	801.28	488.29~1,114.27	gamma	Guy et al. (2019)
Thrombocytopenia	195.44	156.35~234.52	gamma	Zhang et al. (2021)
Neutropenia	552.98	442.38~663.57	gamma	Zhang et al. (2021)
Leukopenia	503.31	377.48~629.14	gamma	Zhou et al. (2019)
Follow up monitoring cost				
CA 125 test	14.44	11.55~17.33	gamma	Cheng et al. (2021)
Complete blood count	3.57	2.85~4.28	gamma	Li et al. (2021b)
CT scan	95.53	76.42~114.63	gamma	Li et al. (2021b)
BSC cost	126.49	101.18~151.78	gamma	Zhou et al. (2019)
Terminal care cost	2,104.25	1,683.41~2,525.10	gamma	Li et al. (2021b) (Zhou et al., 2019) Li et al. (2021b)
Utility				
PFS	0.84	0.67~1.00	beta	Mirza et al. (2016)
PD	0.79	0.63~0.95	beta	Mirza et al. (2016)
PFS life-years				
Fuzuloparib	1.08	0.93~1.08	fixed	Li et al. (2022)
Olaparib	1.59	1.36~2.14	fixed	Pujade-Lauraine et al. (2017)
Niraparib	1.75	1.46~1.75	fixed	Mirza et al. (2016)
RS	0.46	0.32~0.47	fixed	Li et al. (2022)
Discount	0.05	0.00~0.08	fixed	Guoen, (2020)

AE, adverse event; CT, computed tomography; BSC, best supportive care; PFS, progression-free survival; PD, progressed disease; RS, routine surveillance.

cooperative oncology group (ECOG) performance status at a baseline of 0–1, and adequate organ function.

The GetData Graph Digitizer (version 2.20) was used to gather the data points from the PFS curves and OS curves, then data points were used to fit the following parametric survival function: Weibull, log-logistic, exponential, log-normal, gompertz and gamma. Akaike information criterion (AIC) and Bayesian information criterion (BIC) are both standards for measuring the goodness of model fitting, and the smaller value represents better goodness (Gao et al., 2021). In this model, the log-logistic and log-normal distribution are suitable for PFS and OS in RS group, respectively. Besides, The Weibull model was the most reasonable functions for extrapolating OS of niraparib group, and that the log-normal model was best for PFS and OS in other groups (see the Supplementary Appendix). Therefore, in our analysis, Weibull distribution, log-logistic distribution and log-normal distribution were used to calculate transition probability. Parametric survival curve was delineated by RStudio 2022.02.0 software. The distribution parameters of survival curve and the partitioned survival model were developed in TreeAge Pro 2011. General population mortality was derived from mortality tables of resident population in 2021 published by National Bureau of Statistics.

Recurrent OC is typically incurable with a low 5 year survival rate (Dottino et al., 2019; Ni et al., 2019). The time horizon was limited to 60 months, and each model cycle represents 28 days, which is in accordance to the treatment cycle of FZOCUS-2. The primary output of the model includes PFS quality-adjusted life years (PFS-QALYs) of the treatment scheme, and incremental CE ratios (ICERs). Based on the China guidelines for pharmacoeconomic evaluations (2020) (Guoen, 2020), 5%

TABLE 2 Results of cost-effectiveness of fuzuloparib, olaparib and niraparib.

Treatment strategy	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	Incremental		ICER ($) *versus* baseline (QALYs)	ICER ($) incremental (QALYs)
					Costs ($)	QALYs		
RS	4,471.42	2.20						
Olaparib	54,605.54	4.34	50,134.12	2.15	50,134.12	2.15	23,359.26	23,359.26
Niraparib	48,183.48	3.55	−6,422.06	−0.79	43,712.06	1.36	32,216.08	Dominated
Fuzuloparib	31,628.10	3.05	−16555.38	−0.51	27,156.68	0.85	31,992.69	Dominated

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; RS, routine surveillance.

discount rate was adopted, and 1–3 times of Chinese *per capita* GDP in 2021 was used as the willingness-to-pay (WTP) threshold (12551.50$–37654.50$/QALY) (statistics, 2022). The incremental CE ratio was calculated to estimate the economic efficiency of treatment scheme.

2.2 Costs and utility values

The analysis was conducted from the perspective of the Chinese healthcare system, therefore, only direct medical expenses were considered, including the cost of drugs, follow-up test, best supportive care (BSC), terminal care and management of serious adverse effects (SAEs). The unit price of fuzuloparib, olaparib and niraparib in China was obtained from Shandong drug centralized procurement platforms, and other cost data was derived from literatures. All the costs were adjusted for inflation to reflect 2021 United States dollars according to Chinese Consumer Price Index (CPI) and based on the 2021 exchange rate (6.4515 RMB/United States dollar).

In order to simplify the model, only SAEs (≥3 grade according to NCI-CTCAE V5.0 criteria) with an incidence of more than 10% was considered in our research. It was assumed that adverse events occurred independently and probability remained constant over the 60-month time horizon. Discontinuation resulting from severe adverse reaction was not taken into account. For our base case, all adverse events of grade 3 and above were presumed to be incurred in the first cycle (Wu and Shi, 2020). All patients in the model were assumed to have regular laboratory testing with a carbohydrate antigen 125 (CA 125) and computed tomography (CT) every 2 months, and have a weekly complete blood count (CBC) for the first 4 weeks of treatment, followed by a CBC monthly, regardless of receipt of maintenance therapy strategy. The cost of BSC was the only cost included in this analysis after disease progression, and terminal care costs (TCC) were included in the final state. It is assumed that patients enter the model after receipt of platinum-based chemotherapy for their recurrence, and therefore clinical estimates and costs related to cytotoxic chemotherapy were not included. All information is listed in Table 1.

In the clinical trials mentioned in the article, PFS was the primary endpoint. Consequently, in our model, PFS life-years were applied as the effectiveness measure for our base-case analysis and sensitivity analysis. QALYs were calculated by multiplying the PFS life-years with health-state utility values (HSUV), which was reported in the literature (Table 1). Regardless of the country assessed and the therapy applied, the utility values of the PFS and PS states in the same disease were the same (Li et al., 2021b).

2.3 Sensitivity analysis

One-way and probabilistic sensitivity analysis (PSA) were conducted using TreeAge Pro 2011 software to validate the model's robustness when the results vary across a reasonable range. In one-way sensitivity analysis, the influence of parameter change on ICER value was calculated one by one according to the lower and upper limits obtained from credible intervals or a range of ±20% of the base case value (Wan et al., 2019), and the tornado graph was drawn using the obtained results. PSA was carried out *via* 1000 Monte Carlo simulations according to the distribution form of parameters (gamma distribution for cost, beta distribution for utility and incidence data) (Briggs et al., 2012). The ranges and distributions of the parameters used in the sensitivity analysis are given in Table 1.

3 Results

3.1 Base-case analysis

The costs for a 28-day medication were $1394.73, $1989.49 and $1770.75 for fuzuloparib, niraparib and olaparib, respectively, following the recommended dosing regimen in the package insert of drugs. In the base-case analysis, niraparib was associated with the longest PFS-life year (1.75), followed by olaparib (1.59), fuzuloparib (1.08) and RS (0.46). Compared with RS, the other three strategies showed positive effects in maintenance treatment of platinum-

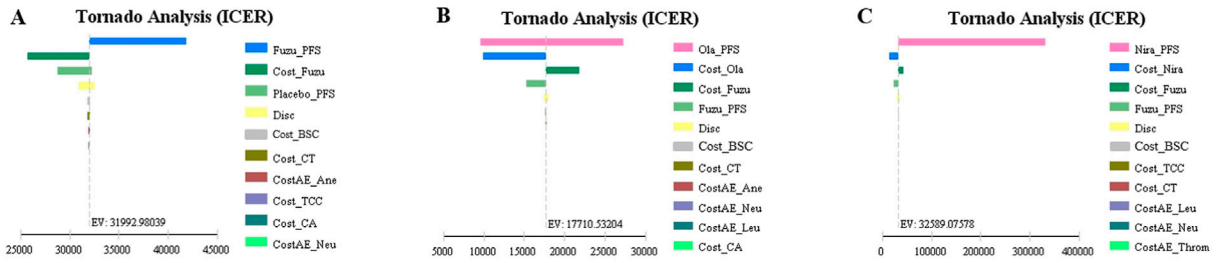


FIGURE 2
Tornado diagram of the one-way deterministic sensitivity analysis. **(A)** is the result of fuzuloparib maintenance therapy vs. RS, **(B)** is the result of fuzuloparib maintenance therapy vs. olaparib maintenance therapy, and **(C)** is the result of fuzuloparib maintenance therapy vs. niraparib maintenance therapy. PFS, progression-free survival; PD, progressed disease; AE, Adverse Event; CT, computed tomography; BSC, best supportive care; TCC, terminal care costs; RS, routine surveillance.

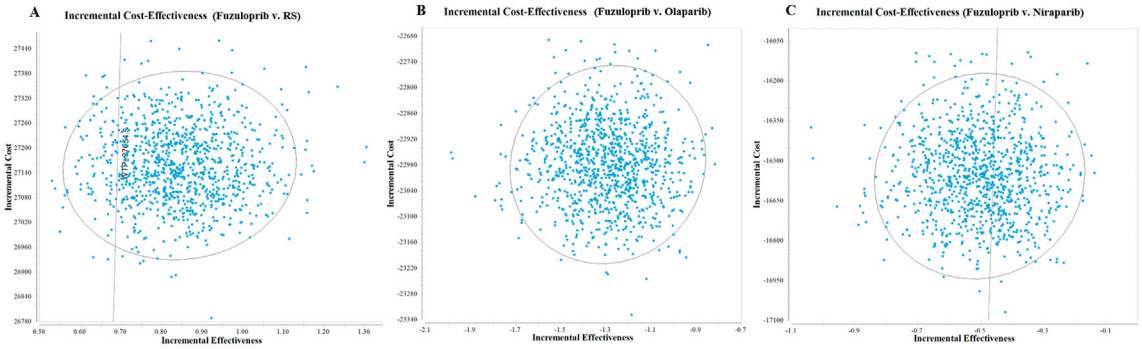


FIGURE 3
1,000 monte carlo simulation diagram of the probabilistic sensitivity analysis. **(A)** is the result of fuzuloparib vs. RS, **(B)** is the result of fuzuloparib vs. olaparib, and **(C)** is the result of fuzuloparib vs. niraparib. RS, routine surveillance.

sensitive recurrent OC, and results of baseline CEA are show in Table 2. Total cost of fuzuloparib, niraparib and olaparib were $31628.10, $48183.48 and $54605.54. Compared with RS, the ICERs of olaparib, niraparib and fuzuloparib groups are all below WTP threshold, which is $23359.26, $31992.69 and $32216.08 respectively. Olaparib is superior to niraparib and fuzuloparib, with -$6,422.06 and -$16555.38 incremental costs and –0.79 and –0.51 incremental QALYs, respectively. Olaparib regimen is the highest cost therapy among all treatments, but with highest QALY, which means it is more cost-effective.

3.2 Sensitivity analysis

The tornado diagram showed that the ICERs of fuzuloparib vs. RS, fuzuloparib vs. olaparib, fuzuloparib vs. niraparib were all most sensitive to the PFS, followed by the cost of those medicines (Figure 2). In the fuzuloparib vs. RS, the ICER was higher than WTP threshold of $37654.50 per QALY when the PFS of fuzuloparib (0.93~1.08) reduced to the lower threshold. In each group, other variables (such as discount rate, follow-up monitoring cost and adverse reaction treatment cost) had moderate or mild effects on ICER.

The results of probabilistic sensitivity analysis suggested that the probability of fuzuloparib being CE compared with RS, oraparib and niraparib is 85.5%, 0% and 33.3% at a WTP threshold of $37654.50 per QALY, respectively (Figure 3). The results showed that olaparib was most cost-effective for patients.

4 Discussion

The clinical benefit from maintenance PARPis treatment according to several phase III trials has come to the

foreground, but the high price is a barrier to its wide applications. Owing to the national policy, the price of PARPis have greatly reduced in China, even by more than 80%, which extremely reduces the threshold for the application of PARPis to cover more OC patients. Previous studies conducted by Wolford et al. (2020) and Leung et al. (2021) reported similar results for olaparib and niraparib, that olaparib was estimated to be more affordable and effective for patients with OC whether platinum-resistant or platinum-sensitive. While, Guy et al. (2019) and Zhong et al. (2018) reported that niraparib was more effective than olaparib in OC patients. Due to the particularity of the methodology itself, the results of pharmacoeconomic evaluation have poor transferability among different countries. To our best knowledge, this is an unprecedented study to evaluate the CE outcomes of fuzuloparib compared to RS, olaparib and niraparib for patients with germline BRCA1/2 mutation and platinum-sensitive recurrent OC from the perspective of the Chinese healthcare systems.

Based on our model, olaparib costs $31992.69, $17710.65 and $32589.34 per additional QALY gained compared with RS, olaparib and niraparib when only the health benefits in the PFS were taken into account. The PSA suggested a high probability up to 99.9% that fuzuloparib would be considered cost-effective at a WTP threshold of $50000 per QALY. Findings of the one-way sensitivity analysis showed that PFS of fuzuloparib was the most sensitive parameter compared to RS, this result indicated that patients gained more benefits with longer PFS. The cost of PARPis were also found to be a major driver of economic results. When the price of fuzuloparib decreased by 30%, the ICER for maintenance fuzuloparib decreased to a lower level than olaparib and niraparib in those people. On balance, the variables in the model are unlikely to affect the final outcome.

Currently, China implements drug pricing negotiation policy to help dynamically manage the national reimbursement drug list (NRDL) in order to alleviate the economic burden of patients and improve the affordability of drugs. Pharmacoeconomics provides an important reference in this process. And on the basis of the latest results of the drug pricing negotiations in 2021, fuzuloparib, olaparib and niraparib have successfully incorporated in NRDL, significantly increasing the availability and affordability of those drugs for patients. Drug treatment is still the main means in Chinese medical institutions at the moment. Diagnosis related groups (DRGs) payment is implemented in medical institutions and drug selection was paid more focus on the cost performance of drugs. Thereby, pharmacoeconomics is of great significance in hospital pharmacy.

Whereas, there are several limitations needing to be noted in our study. First, except for fuzuloparib, most of the people included were non-Chinese population or a small number of Chinese populations. Second, four PARPis have been approved in China at present, since the results of phase III clinical study of pamiparib has not been published, this study only included other three PARPis (fuzuloparib, olaparib and niraparib). Third, the utility values came from ENGOT-OV16/NOVA without Chinese population, instead of FZOCUS-2 including Chinese population (Mirza et al., 2016). Although health-related quality of life according to EQ-5D-5L were also assessed, the data have not been reported clearly in FZOCUS-2, so it is difficult to provide an accurate value, and the utility value reduced by adverse reactions was not taken into account. Fourth, the model adopts the simple model commonly used in the study of tumor pharmacoeconomics, without detailed classification of subgroups. Therefore, it seems to be difficult to accurately describe the disease progress. Finally, PFS was employed to measure QALY because the overall survival data on niraparib and fuzuloparib were not available during this study. Regardless of these limitations, however, the variables in the study didn't affect the final outcome.

5 Conclusion

These estimates indicate that at a WTP threshold of $12551.50–37654.50/QALY, fuzuloparib was less cost-effective for patients with germline BRCA1/2 mutation and platinum-sensitive recurrent OC compared to olaparib, but was superior to niraparib from Chinese healthcare systems perspective. These findings may help clinicians to make optimal treatment decisions for those patients. Because of the great majority of data in this study from literatures, more high-quality clinical and Chinese economic real-world data are needed. Besides, mature OS data is also required to validate these results.

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

JW and JN conceived the study idea and devised the study methodology. HW, LS, and YD participated in the design and coordination of the study. JN, HW, and LS did the statistical analysis and interpretation of the results. JN and YL completed the drafting of manuscript. All authors contributed to improving the manuscript, read and approved the version of the manuscript to be published. All authors take responsibility of appropriate content.

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.2022.987337/full#supplementary-material

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Toripalimab plus chemotherapy vs. chemotherapy in patients with advanced non-small-cell lung cancer: A cost-effectiveness analysis

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Background: The potency and safety of toripalimab combination with chemotherapy (TC) as the first-line therapy for advanced non-small cell lung cancer (NSCLC) have been demonstrated in the CHOICE-01 study. Our research explored whether TC was cost-effective compared to chemotherapy alone from the Chinese payer perspective.

Materials and methods: Clinical parameters were obtained from a randomized, multicenter, registrational, placebo-controlled, double-blind, phase III trial. Standard fee databases and previously published literature were used to determine costs and utilities. A Markov model with three mutually exclusive health statuses (progression-free survival (PFS), disease progression, and death) was used to predict the disease course. The costs and utilities were discounted at 5% per annum. The main endpoints of the model included cost, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). Univariate and probabilistic sensitivity analyses were performed to investigate the uncertainty. Subgroup analyses were performed to verify the cost-effectiveness of TC in patients with squamous and non-squamous cancer.

Results: TC combination therapy yielded an incremental 0.54 QALYs with an incremental cost of $11,777, compared to chemotherapy, giving rise to ICERs of $21,811.76/QALY. Probabilistic sensitivity analysis revealed that TC was not favorable at 1 time GDP *per capita*. With a prespecified willingness-to-pay threshold (WTP) of three times the GDP *per capita*, combined treatment had a 100% probability of being cost-effective and had substantial cost-effectiveness in advanced NSCLC. Probabilistic sensitivity analyses showed that TC was more likely to be accepted with a WTP threshold higher than $22,195 in NSCLC. Univariate sensitivity analysis showed that the utility of PFS state, crossover proportions of the chemotherapy arm, cost per cycle of pemetrexed treatment, and discount rate were the dominant influencing factors. Subgroup analyses found that in patients with squamous NSCLC, the ICER was $14,966.09/QALY. In the non-squamous NSCLC, ICER raised to $23,836.27/QALY. ICERs were sensitive to the variance of the PFS state utility. TC was more likely to be accepted when WTP increases exceeded $14,908 in the squamous NSCLC subgroup and $23,409 in the non-squamous NSCLC subgroup.

Conclusion: From the perspective of the Chinese healthcare system, TC may be cost-effective in individuals with previously untreated advanced NSCLC at the prespecified WTP threshold compared to chemotherapy, and more significant in individuals with squamous NSCLC, which will provide evidence for clinicians to make the best decisions in general clinical practice.

KEYWORDS

toripalimab, cost-effectiveness, NSCLC, CHOICE-01, markov model

Introduction

Lung cancer developing from the bronchial mucosal epithelium and alveoli is still one of the most malignant neoplastic diseases, with the highest mortality and incidence (Bray et al., 2018; Miller et al., 2018). Non-small cell lung cancer (NSCLC) accounts for about 83% of lung cancer cases (Siegel et al., 2020). In fact, only 6% of patients with advanced NSCLC are alive 5 years after diagnosis (Topalian et al., 2019), the design of new treatment methods to improve survival is urgently needed. The treatment of lung cancer mainly includes surgical, radiotherapy and systemic drug therapy. The development of therapeutic drugs has experienced three eras, including the era of cytotoxic chemotherapy drugs, anti-angiogenic drugs, targeted drugs, and immunotherapy drugs emerging in recent years (Fisher and D'Orazio, 2000; Fukuoka et al., 2011; Brahmer et al., 2015; Garon et al., 2015; Sharma and Allison, 2015; Soria et al., 2018; Ramalingam et al., 2020). At present, the immune checkpoint inhibitors (ICIs) including programmed cell death protein 1 (PD-1) or its ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have been approved for certain types of cancer (Miller et al., 2019).

Toripalimab, a monoclonal antibody targeting PD-1 developed in China, was approved by the China Food and Drug Administration as the second-line therapy for unresectable or metastatic melanoma, locally advanced or metastatic urothelial cancer, and recurrent or metastatic nasopharyngeal cancer. In addition, it was approved as the first-line treatment for unresectable locally advanced or relapsed/metastatic esophageal squamous cell cancer, non-operable locally advanced or metastatic without epidermal growth factor receptor gene mutation (EGFR) and anaplastic lymphoma kinase gene fusions (ALK) non-squamous NSCLC, locally relapsed or metastatic nasopharyngeal cancer (Keam, 2019; Wang et al., 2020; Yang et al., 2020; Zhang et al., 2021). Some researches have indicated that chemotherapy could enhance the antitumor effect of the immune system, thereby enhancing immunotherapy activity and improving clinical efficacy (Bracci et al., 2014; Peng et al., 2015; Leonetti et al., 2019; Judd and Borghaei, 2020). Recently, the CHOICE-01 study evaluated the clinical benefit of toripalimab plus chemotherapy (TC) *versus* chemotherapy alone in advanced NSCLC (Wang et al., 2022). The findings indicated that the TC arm, compared to the chemotherapy arm, improved progression-free survival (PFS) [median 8.4 vs. 5.6 months; hazard ratio (HR), 0.49; 95%CI 0.39–0.61; $p < 0.0001$] and overall survival (OS) (median not reached (>24 months) vs. 17.1 months; HR, 0.69; 95%CI 0.53–0.92; $p = 0.0099$). The incidence of grade ≥3 treatment-related adverse events (AEs) was similar between the two arms (78.6% vs. 82.1%). Thus, adding toripalimab to chemotherapy appears to be a compelling first-line therapy for advanced NSCLC. Nevertheless, proper allocation of limited medical resources and consideration of cost-effectiveness in medical decision-making are needed by clinical decision-makers. The purpose of our research was to estimate the cost-effectiveness of TC *versus* chemotherapy alone in the first-line therapy of advanced NSCLC from the Chinese healthcare system perspective.

Materials and methods

Participants and interventions

We extracted basic clinical data from a randomized, multicenter, registrational, double-blind, placebo-controlled, phase III trial (CHOICE-01) (Wang et al., 2022). Eligible patients were untreated, without EGFR or ALK driver mutations, had locally advanced (stage IIIB or IIIC) or metastatic NSCLC, and were randomly divided (2:1) into the TC or chemotherapy arm. For non-squamous NSCLC, individuals received 4–6 cycles of pemetrexed 500 mg/m^2 IV (intravenous injection) + carboplatin AUC 5 IV q3w plus toripalimab or placebo at a dose of 240 mg IV q3w, followed by maintenance of pemetrexed + toripalimab or placebo. For squamous NSCLC, individuals received 4–6 cycles of nab-paclitaxel 100 mg/m^2 intravenously (IV) on days 1, 8, and 15 + carboplatin AUC 5 IV q3w plus toripalimab or placebo at a dose of 240 mg IV q3w, followed by toripalimab or placebo maintenance. As a result, 465 patients were randomly distributed to the TC or chemotherapy arm, stratified according to baseline demographics, with substantially balanced disease features between the two treatment arms (Wang et al., 2022). The baseline case analysis assumed that the maximum treatment time for toripalimab was 2 years. We assumed that all of the adenocarcinoma patients received first line 4 cycles of pemetrexed + carboplatin plus toripalimab or placebo, followed by maintenance of pemetrexed + toripalimab or placebo. All of the squamous cell carcinoma patients received 4 cycles of nab-paclitaxel + carboplatin plus toripalimab or placebo, followed by toripalimab or placebo maintenance. After disease progression, 51.1% of individuals in the TC arm and 83.3% of individuals in the chemotherapy alone arm received at least one subsequent treatment (Wang et al., 2022), while those in the chemotherapy alone arm were allowed to cross over to toripalimab monotherapy. Assuming that the individuals in the TC arm would no longer use other immunological drugs and switch to other chemotherapy regimens after disease progression, 4 cycles of docetaxel chemotherapy would be selected for subsequent treatment (Zhu et al., 2021). In the chemotherapy arm, we supposed that individuals who progressed would adopt docetaxel or

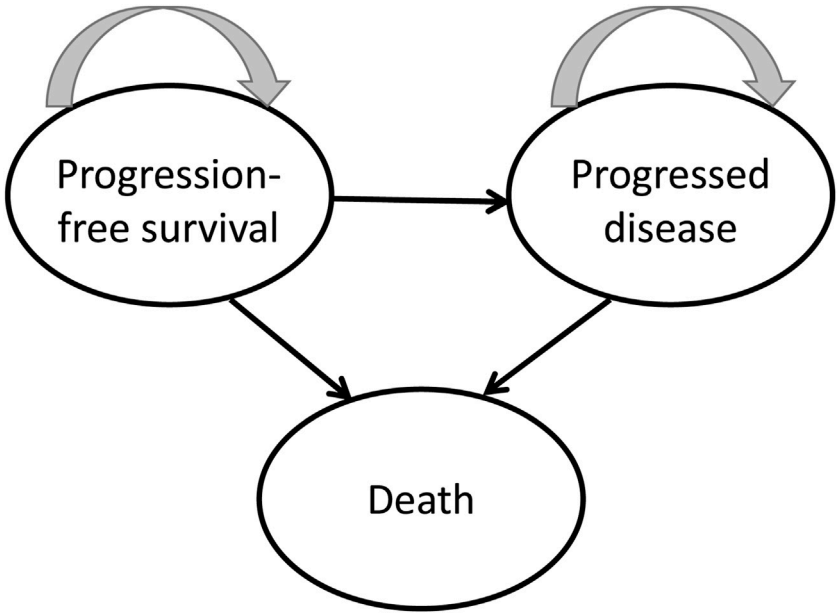

FIGURE 1
Partitioned survival model structure.

toripalimab or best supportive care (BSC), which was consistent with the guidelines and the actual situation. Computed tomography was used to evaluate the tumor once every 6 weeks.

Model framework

A mathematical Markov model was built using TreeAge Pro 2022 software to measure costs and utilities. Three mutually exclusive health states constituted the model structure: PFS, progressive disease (PD), and death (Figure 1). Almost all individuals in the two arms died after 10 years in the model simulation. Therefore, the time limit for our analysis was designed at 10 years (Cai et al., 2019; Liu et al., 2020; Weng et al., 2020). One cycle length in this model was defined as 21 days. Individuals were partitioned to each status according to the cumulative probabilities of PFS and OS and those stemming from the patient data from the CHOICE-01 study. All hypothetical individuals started out in a PFS status, receiving first-line therapy. If disease progression occurred, individuals entered PD status and received subsequent treatment until death.

Clinical data

The GetData Graph Digitizer software was utilized to extrapolate the transition probabilities over a lifetime horizon according to the PFS and OS curves for TC and chemotherapy alone from the CHOICE-01 trial (Hoyle and Henley, 2011). Survival functions such as exponential, Weibull, gamma, Gompertz, log-normal, and log-logistic distributions were fitted to the data from curves based on the Akaike and Bayesian information criterion (Kearns et al., 2019). Log-logistic distributions were selected for the PFS curve in the chemotherapy arm and OS curve in the TC arm, and log-normal distributions were selected for the PFS curve in the TC arm and OS curve in the chemotherapy alone arm (Supplementary Table S1). Based on different histological types, the distributions of parameters in the TC and chemotherapy arms were selected (Supplementary Tables S2, S3). The survival curve simulation is shown in Figure 2 and Supplementary Figures S1, S2. US life tables were used to assess the background mortality rate (Arias et al., 2017).

Costs data

Health resource use and only direct medical expenditures were regarded, including those related to drug acquisition and administration, disease management, and treatment-related adverse events (AEs) (Table 1).

Acquisition costs for toripalimab, carboplatin, nab-paclitaxel, pemetrexed, and subsequent treatments were obtained from public databases, which were all the latest in 2022 (Shao et al., 2022; YAOZH.com, 2022). The cost of drug management was equal to the cost of the chemotherapy drug preparation injection plus the cost of hospitalization. According to the published literature, the one-time cost of end-of-life care per patient who died was $2,241.18 (Rui et al., 2022), best supportivecare cost per cycle was $122.18 (Li et al., 2020). We only regarded severe AEs (grade ≥3) with an incidence of greater than 5%, involving anemia, neutropenia, leukopenia, and thrombocytopenia (Wang et al., 2022). The AEs costs were extracted from published articles (Yang et al., 2021). For each therapeutic regimen, the total expenditure per AE was calculated based on the incidence of AE and its related unit cost. It is assumed that after the occurrence of AEs, patients are treated

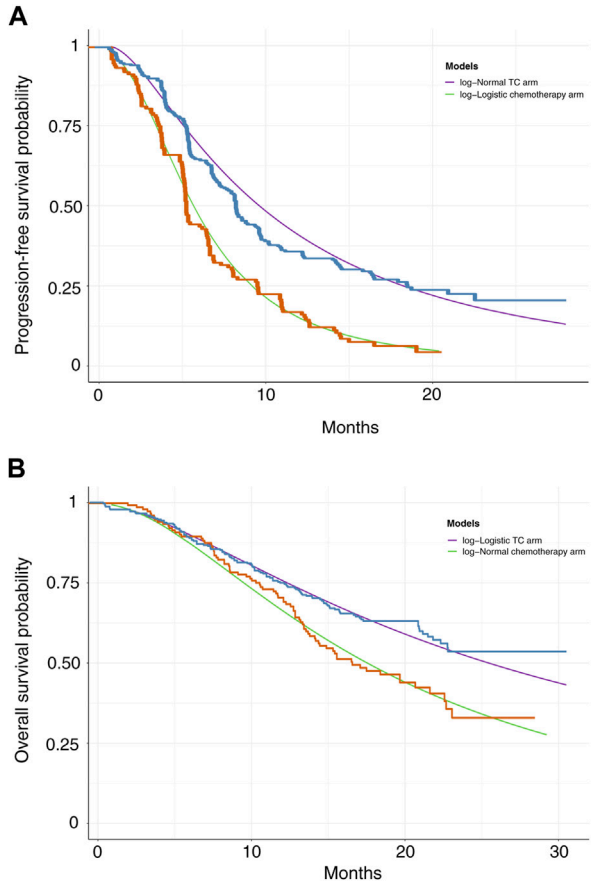

FIGURE 2
PFS **(A)** and OS **(B)** curves for the original trial and model estimated data in NSCLC.

only in the first cycle, and the cost of AE occurs only once. Drug dosage was calculated according to a body surface area of 1.72 m^2 and creatinine clearance of 70 mL/min (Goulart and Ramsey, 2011; Wu et al., 2011). Suppose that the corresponding expense is incurred at the beginning of each cycle; thus, there is no cost adjustment for the half cycle (Chen et al., 2022). From January to September 2022, the exchange rate of Chinese Yuan renminbi was 6.6 yuan per US dollar average. Total costs and quality-adjusted life-years (QALYs) were the primary outcomes, and a 5% discount rate per year was adopted in our analysis (Yang et al., 2021).

Health-state utilities

The QALYs for different therapies were assessed. The health utility scores of PFS, PD, and death status were extracted from two health status utility studies on Chinese individuals with NSCLC, with 0.80, 0.32, and 0, respectively (Nafees et al., 2008; Nafees et al., 2017). AEs resulting in disutility values were also calculated in our analysis (Tolley et al., 2013; Nafees et al., 2017; Wan et al., 2019). The decline in the overall QALY related to all AEs was applied to the first cycle of the models (Su et al., 2021). All the parameters associated with the utilities are displayed in Table 1.

Univariate sensitivity analysis and probabilistic sensitivity analysis

Sensitivity analyses were performed to examine the impact of the parameter uncertainty on the outcomes. The imported data and ranges of the sensitivity analyses are displayed in Table 1. Clinical parameters in univariate sensitivity analyses were varied over plausible ranges based on ±20% for body surface area, body weight, costs and health state utilities, with discount rate ranging from 0% to 8%, as shown in the tornado diagram. In light of real-world performance, there is no possibility that the price of toripalimab will rise; therefore, only the impact of the price slide on the incremental cost-effectiveness ratio (ICER) was conducted. Probabilistic sensitivity analysis (PSA) applied a Monte Carlo simulation of 1,000 individuals to evaluate the best strategy under various hypothetical willingness-to-pay (WTP) thresholds through simultaneous and random preset parameter variations. Scatter plots and cost-effectiveness acceptability curves (CEACs) were applied to analyze the cost-effectiveness of each option with different WTP threshold (Rabin and de Charro, 2001; Lin et al., 2020). In 2021, the Chinese *per capita* GDP was $12,269 (NBSC, 2022), so prespecified WTP was $36,807, which was three times the *per capita* GDP according to the WHO. PFS and OS parameters were obtained from the corresponding parametric survival distributions. AE disutilities and costs were derived from gamma distributions, and proportion, utility and probability from beta distributions.

Subgroup analysis

PFS and OS curve of patients with adenocarcinoma and squamous cell carcinoma were extracted from the CHOICE-01 study respectively. Therapeutic regimen and the proportion of subsequent regimens in each subgroup was the same as the baseline case analysis respectively.

Results

The median PFS and interim OS values obtained in our simulation were consistent with those in the CHOICE-01 study (Supplementary Table S4). Our model assessed median PFS of 8.4 months in the TC arm and 5.6 months in the chemotherapy arm, respectively. Based on data derived from the CHOICE-01 study, the median PFS was 8.4 months in the TC arm and 5.6 months in the chemotherapy arm. Our models assessed the interim OS analysis of not reached (>24 months) and 17.2 months for the TC and chemotherapy arms, respectively. It compared with OS of not reached (>24 months) and 17.1 months in the TC and chemotherapy arms, respectively based on the CHOICE-01 study. For different histological types, the median PFS values and interim OS analysis values for the TC and the chemotherapy arm are shown in Supplementary Tables S5, S6.

Baseline analyses

Within a 10-year time horizon based on the Markov model, the total costs were $27,971 and $16,194 for the TC and placebo

TABLE 1 Model parameters and distribution.

Variable	Baseline value (reference)	Range		Distribution
		Minimum	Maximum	
Log-normal PFS survival model with toripalimab + chemotherapy	Meanlog = 2.262; sdlog = 0.950	-	-	-
Log-logistic PFS survival model with placebo + chemotherapy	Shape = 2.489; scale = 6.089	-	-	-
Log-logistic OS survival model with toripalimab + chemotherapy	Shape = 1.510; scale = 25.348	-	-	-
Log-normal OS survival model with placebo + chemotherapy	Meanlog = 2.897; sdlog = 0.791	-	-	-
Subsequent chemotherapy proportions of toripalimab + chemotherapy arm	0.511 (Wang et al., 2022)	0.409	0.613	Beta
BSC in toripalimab + chemotherapy arm	0.489 estimated	0.3912	0.5868	Beta
Crossover proportions of chemotherapy arm	0.538 (Wang et al., 2022)	0.4304	0.6456	Beta
Subsequent chemotherapy proportions of chemotherapy arm	0.295 (Wang et al., 2022)	0.236	0.354	Beta
BSC in chemotherapy arm	0.167 estimated	0.1336	0.2004	Beta
Grade ≥3 AEs incidence in toripalimab + chemotherapy				
Anemia	0.299 (Wang et al., 2022)	0.2392	0.3588	Beta
Leukopenia	0.357 (Wang et al., 2022)	0.2856	0.4284	Beta
Neutropenia	0.555 (Wang et al., 2022)	0.444	0.666	Beta
Thrombocytopenia	0.172 (Wang et al., 2022)	0.1376	0.2064	Beta
Grade ≥3 AEs incidence in placebo + chemotherapy				
Anemia	0.359 (Wang et al., 2022)	0.2872	0.4308	Beta
Leukopenia	0.417 (Wang et al., 2022)	0.3336	0.5004	Beta
Neutropenia	0.538 (Wang et al., 2022)	0.4304	0.6456	Beta
Thrombocytopenia	0.179 (Wang et al., 2022)	0.1432	0.2148	Beta
Utility				
Progression-free disease	0.80 (Nafees et al., 2017)	0.64	0.96	Beta
Progressed disease	0.32 (Nafees et al., 2017)	0.26	0.38	Beta
AEs disutility				
Anemia	0.07 (Yang et al., 2021)	0.058	0.088	Beta
Leukopenia	0.20 (Yang et al., 2021)	0.112	0.168	Beta
Neutropenia	0.20 (Yang et al., 2021)	0.16	0.24	Beta
Thrombocytopenia	0.11 (Yang et al., 2021)	0.086	0.130	Beta
Drug cost, US$				
Toripalimab/cycle	375 (YAOZH.com, 2022)	300	375	Fixed in PSA
Carboplatin/cycle	55.18 (YAOZH.com, 2022)	44.15	66.22	Gamma
Nab-paclitaxel/cycle	122.73 (YAOZH.com, 2022)	98.182	147.273	Gamma
Pemetrexed/cycle	841.48 (YAOZH.com, 2022)	673.18	1009.78	Gamma
Docetaxel/cycle	31.60 (YAOZH.com, 2022)	25.28	37.93	Gamma
AEs cost, US$				
Anemia per event	571.98 (Yang et al., 2021)	457.58	686.38	Gamma
Leukopenia per event	451.11 (Yang et al., 2021)	360.89	541.33	Gamma
Neutropenia per event	496.46 (Yang et al., 2021)	397.17	595.75	Gamma
Thrombocytopenia per event	3820.77 (Yang et al., 2021)	3056.62	4584.92	Gamma
Administration cost, US$				
Cost of CT examination/1 time	56.05 (Shao et al., 2022)	44.84	67.27	Gamma
Cost of blood biochemical examination/1 time	45.34 (Shao et al., 2022)	36.27	54.41	Gamma
Cost of blood test/1 time	3.03 (Shao et al., 2022)	2.42	3.63	Gamma
Cost of urinalysis/1 time	0.61 (Shao et al., 2022)	0.49	0.73	Gamma
Physician Fee/1 day	3.03 (Shao et al., 2022)	2.42	3.63	Gamma
Cost of intravenous injection/1 day	1.67 (Shao et al., 2022)	1.33	2.00	Gamma
Cost of care/1 day	3.63 (Shao et al., 2022)	2.91	4.36	Gamma
Cost of bed/1 day	6.36 (Shao et al., 2022)	5.09	7.63	Gamma

(Continued on following page)

TABLE 1 (*Continued*) Model parameters and distribution.

Variable	Baseline value (reference)	Range		Distribution
		Minimum	Maximum	
Cost of terminal care per patient	2241.18 (Rui et al., 2022)	1792.94	2689.41	Gamma
BSC/cycle	122.18 (Li et al., 2020)	97.74	146.62	Gamma
Follow-up visit	77.01 (Shao et al., 2022)	61.61	92.41	Gamma
Patients' body surface area, m^2	1.72 (Yang et al., 2021)	1.38	2.06	Normal
Discount rate (%)	5 (Yang et al., 2021)	0	8	Fixed in PSA

BSC, best supportive care; PFS, progression-free survival; OS, overall survival; AEs, adverse effects; CT, computed tomography.

TABLE 2 Base-case results of the model.

Patients	Arm	Costs, US$	△Costs, US$	QALYs	△QALYs	ICER US$/QALY
Overall	Placebo + Chemotherapy	16,194	-	0.90	-	-
	Toripalimab + Chemotherapy	27,971	11,777	1.44	0.54	21,811.76
Squamous	Placebo + Chemotherapy	11,278	-	0.82	-	-
	Toripalimab + Chemotherapy	16,817	5,539	1.19	0.37	14,966.09
non-squamous	Placebo + Chemotherapy	20,513	-	0.90	-	-
	Toripalimab + Chemotherapy	42,397	21,884	1.82	0.92	23,836.27

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-years.

plus chemotherapy arms, respectively. The TC therapy yielded 1.44 QALYs and the chemotherapy yielded 0.90 QALYs. Therefore, individuals in the TC arm spent an additional $11,777 and produced an increase of 0.54 QALYs, giving rise to an ICER of $ 21,812 per QALY, which was higher than the one-time GDP *per capita*, but it was within the prespecified WTP threshold ($36,807/QALY), suggesting that TC therapy was economical compared to chemotherapy alone (Table 2).

Sensitivity analysis

Univariate sensitivity analyses

As the tornado diagram for patients with NSCLC in Figure 3 displays, the utility of PFS status, crossover proportions of the chemotherapy arm, cost per cycle of pemetrexed treatment, and discount rate were the dominant influencing factors in this research. Nevertheless, there is no intersection between the generated ICER and WTP when all parameters vary within the corresponding ranges, indicating that the model is generally robust.

Probabilistic sensitivity analysis

A Monte Carlo simulation of 1,000 patients showed that the scatter points were located in the first quadrant of the coordinate axis, indicating that TC may produce more QALYs but at a higher cost. When WTP was set at one-time GDP *per capita*, all of the scatter points of ICER are located above the WTP line. When WTP was set at three times the GDP *per capita*, all scatter points were located below the WTP line (Figure 4). As shown in Figure 5, the CEACs indicated that TC had a 100% probability of being cost-effective when the designated WTP threshold was $36,807 per QALY compared to placebo plus chemotherapy. TC was unfavorable when the WTP thresholds is below $22,195.

Subgroup analysis

Among the subgroups of individuals with squamous NSCLC, the cumulative costs and effectiveness were $16,817 and 1.19 QALYs in TC arm, and $11,278 and 0.82 QALYs in the placebo plus chemotherapy arm, respectively, and the ICER was $14,966.09/QALY (Table 2). ICERs were most sensitive to the variations of the utility of PFS status, crossover proportions of chemotherapy arm, discount rate and cost of toripalimab per cycle (Supplementary Figure S3). Among the subgroup of individuals with non-squamous NSCLC, the cumulative costs and effectiveness were $42,397 and 1.82 QALYs in the TC arm, and $20,513 and 0.90 QALYs in the placebo plus chemotherapy arm, and the ICER was $23,836.27/QALY (Table 2). ICERs were the most sensitive to variations in the utility of PFS status, cost of pemetrexed per cycle, utility of PD status, and discount rate (Supplementary Figure S4). PSA revealed that TC was more likely to be accepted with a WTP threshold higher than $14,908 in squamous NSCLC subgroup and higher than $23,409 in the non-squamous NSCLC subgroup. TC had a cost-effectiveness probability of 16% and 0% in squamous and non-squamous NSCLC, respectively, when the WTP threshold was set at one-time GDP *per capita*. With a WTP of three times the GDP *per capita*, TC therapy had substantial cost-effectiveness (Supplementary Figures S5–S8). A subgroup analysis

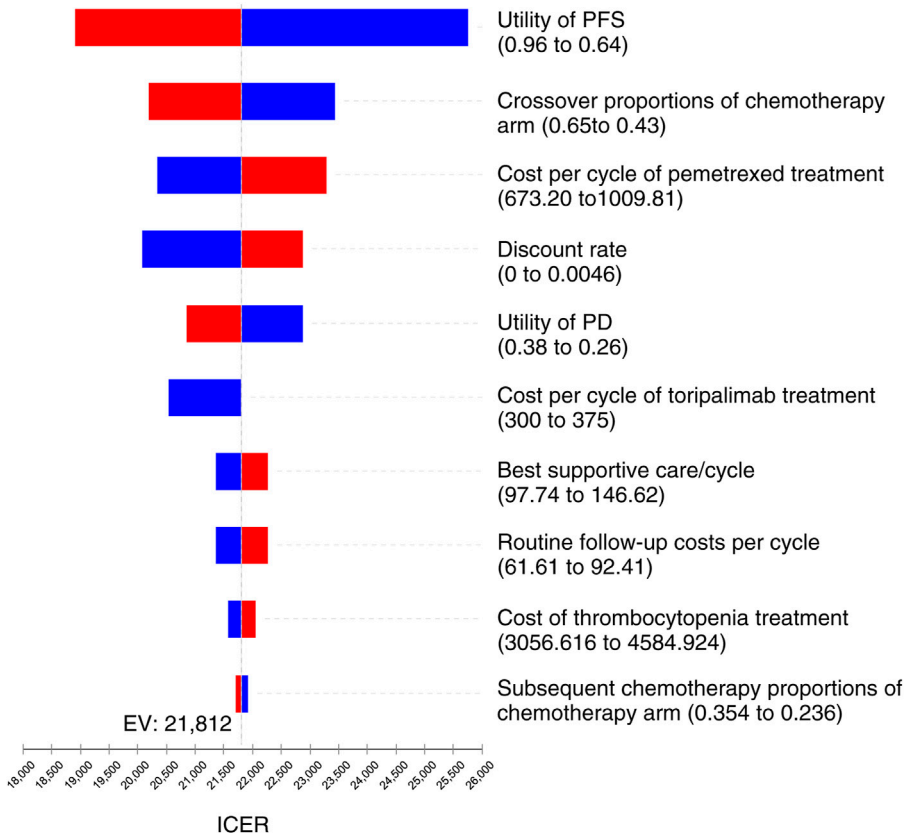

FIGURE 3
Tornado diagram for univariate sensitivity analyses in NSCLC. It summarized the results of one-way sensitivity analysis, which listed influential parameters in descending order according to their effect on the ICER over the variation of each parameter value.

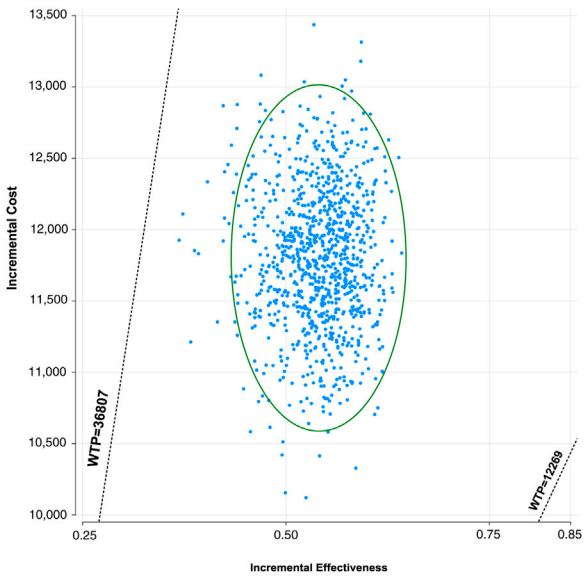

FIGURE 4
Incremental cost-effectiveness scatter plot diagram for toripalimab in combination with chemotherapy vs. chemotherapy alone in NSCLC. Each dot represents the ICER for 1 simulation. An ellipse means 95% confidence interval.

based on histological type revealed that TC was more cost-effective in individuals with squamous NSCLC.

Discussion

To our knowledge, this study is the first to synthesize the latest evidence to estimate the economic results of toripalimab in NSCLC using an economic modeling method. Currently, drug development with favorable curative potency and few adverse effects is the principal focus of research and development. The report on the clinical benefits of limited course immunotherapy plus chemotherapy in CHOICE-01 trial was of great interest to the oncologists and patients (Wang et al., 2022). Nevertheless, the pricing of antineoplastic drugs must be both effective and affordable. We assessed the cost-effectiveness of TC in advanced NSCLC as a first-line therapy due to the increasing interest and enormous unmet demand in the economic evaluation of new drugs (Uyl-de Groot and Löwenberg, 2018).

Based on our base-case analysis results, our analysis indicated that TC cost more ($27,971 *versus* $16,194) and produced more health outcomes than placebo plus chemotherapy (1.44 *versus* 0.90 QALYs), giving rise to ICERs of $21,811.76/QALY. Thus, TC was not favorable with a WTP threshold of $12,269 per QALY *versus* chemotherapy alone. While WTP threshold increased to $36,807 per QALY, TC had a probability of 100% to be cost-effectiveness. It spelled that the combination therapy may be a

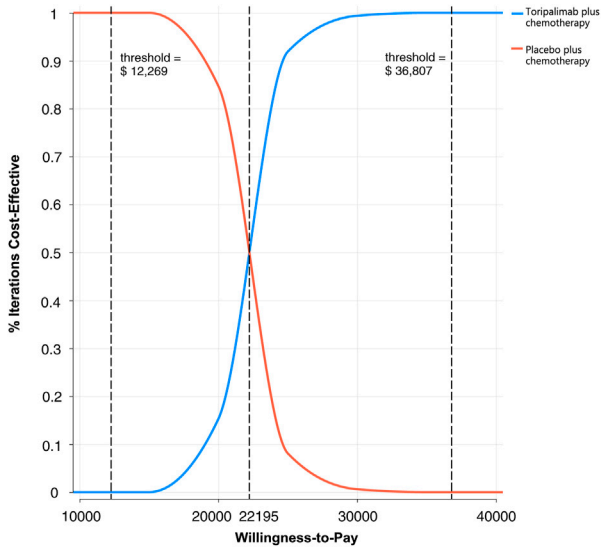

FIGURE 5
The cost-effectiveness acceptability curves for probabilistic sensitivity analyses in NSCLC.

possibly effective and cost-effective choice for NSCLC individual with a higher WTP. Univariate sensitivity analysis and PSA both suggested that these results were robust. We also found that TC was equally cost-effective in individuals with different histological types, due to favorable ICERs ($14,966.09/QALY for squamous NSCLC; $23,836.27/QALY for non-squamous NSCLC) in our subgroup analysis.

The utility of PFS state, crossover proportions of the chemotherapy arm, cost per cycle of pemetrexed treatment, and discount rate were the dominant influencing factors in our analysis. With the extensive changes of these parameters, the TC therapy still has substantial cost-effectiveness when the WTP threshold is three times of GDP *per capita*. In the subsequent therapy after disease progression, we hypothesized that individuals in the TC arm were cross-treated with chemotherapy, and those in the chemotherapy arm were cross-treated with toripalimab. According to the CHOICE-01 trial, crossover proportions of the chemotherapy arm had a considerable influence because this parameter could affect the total cost of disease progression. In addition, the high cost of pemetrexed per cycle also has a substantial impact on the sensitivity analysis, which might be associated with the longer duration of the progression-free status in terms of the OS of individuals, as we know, pemetrexed are needed to apply for both first-line and maintenance therapy in individuals with non-squamous NSCLC, thus decreasing the price of pemetrexed may be an effective strategy to reduce ICER.

Several cost-effectiveness studies on the combination of immunotherapy and chemotherapy as the first-line therapy of NSCLC have been carried out (Zeng et al., 2019; Ding et al., 2020; Lin et al., 2020; Wu and Lu, 2020). An economic evaluation from China based on the CameL-sq trial showed similar results that camrelizumab, another anti-PD-1 humanized monoclonal drug, combined with chemotherapy in previously untreated squamous NSCLC, produced additional 0.47 QALYs and the accompanying incremental costs of $6,347.81 giving rise to an ICER of $13,571.68/QALY *versus* chemotherapy alone, and was significantly cost-effective at a WTP threshold of $38,184 per QALY (Shao et al., 2022). Although the combination of immunotherapy and chemotherapy as first-line in the CameL-sq was different from the CHOICE-01 trial, both of the two PD-1 inhibitors were indicated similar clinical benefits and pricing. The conclusion was consistent and comparable with our results ($14,966.09/QALY). Adding immunotherapy on the basis of limited course of chemotherapy could quickly control the condition of illness and avoid serious chemical toxicity at the same time, which has become a new treatment choice for advanced NSCLC. Reasonable economic assessment has been an indispensable part of the allocation of cancer treatment resources, and useful and helpful in the clinical management of the disease.

Toripalimab might open up opportunities for individuals with advance NSCLC to realize OS benefit. The price of toripalimab is lower than that of imported immunotherapy drugs because of the lower transportation costs, therefore, which is more readily available and widely used in Chinese patients. Our analysis provides evidence of cost-effectiveness that could have important policy and practical significance for reducing the medical burden, providing new ideas on how to increase the affordability of great-value innovative medicines. However, economic development in China's provinces is uneven, and the WTP of a region needs to be considered when evaluating the cost-effectiveness of TC therapy. TC was favorable when 1 time GDP *per capita* was set as the WTP in Macao and Hongkong Special Administrative Region, Taiwan district, Beijing, and Shanghai. But not favorable when 3 times GDP *per capita* was set as the WTP in Heilongjiang and Gansu province. In addition, each country has different healthcare systems, costs, and modeling methods, and the conclusions summarized from one country may not be suited to another (Goldstein et al., 2015). Second, the results of our analysis were robust, as the sensitivity analysis displayed. The conclusions were more accurate than the standard survival model because of the flexible parametric modelings used to fit and extrapolate the survival data. It might be useful for patients, physicians, and policymakers to make treatment decisions based on the economic information from our subgroup analysis. Therefore, our cost-effectiveness finding gives a valuable and compelling reference for the selection of first-line therapy options for NSCLC.

This analysis has some limitations. First, it is inevitable to extrapolate the survival curve to acquire complete survival results owing to the short follow-up time of the CHOICE-01 study. The results of the actual survival curves could not be fitted entirely by the reconstructed survival curves. Nevertheless, the objective of adjusting the transition probability is to approach the real results as closely as possible. Second, the results concerning TC might have been exaggerated because grade 1 or 2 AEs were not considered and if the same AE occurs multiple times for the same patient, assumed that patient is counted only once when calculating the number of adverse events in our analysis. From our univariate sensitivity analyses, the disutilities and costs related to AEs were minor; nevertheless, these AEs could not be neglected in our general clinical practice. Third, generalizability might be affected because the costs and WTP thresholds varied between different countries and medical centers. The results were still robust as varying parameters within the range of ±20% by sensitivity analysis. Moreover, the research simulated findings were originated from a randomized clinical trial but not from prospective real world study. The more mature the available data, the more stable the model. Future work needs to be conducted to illustrate

whether our model-based and trial-based outcomes can be simulated with long follow-up in real-world settings.

In summary, our analysis estimated the cost-effectiveness of TC compared with chemotherapy alone in previously untreated individuals with advanced NSCLC and indicated that TC is a cost-effective choice for a Chinese-payer perspective. Furthermore, subgroup analysis based on histological type showed that TC was more cost-effective in individuals with squamous NSCLC, which could be regarded in the decision-making process to propose treatment suggestions for individuals with advanced NSCLC. However, due to some limitations of this article, further long term follow-up outcomes and real-world data are demanded.

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

Conception and design: PC and GH; Collection and assembly of data: GH and WL; Data analysis and interpretation: WL and SK; Manuscript writing: GH and WL; Final approval of manuscript: All authors.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1131219/full#supplementary-material

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Severe cutaneous adverse reactions to drugs: A real-world pharmacovigilance study using the FDA Adverse Event Reporting System database

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Background: Sound drug safety information is important to optimize patient management, but the widely recognized comprehensive landscape of culprit-drugs that cause severe cutaneous adverse reactions (SCARs) is currently lacking.

Objective: The main aim of the study is to provide a comprehensive landscape of culprit-drugs for SCARs to guide clinical practice.

Methods: We analyzed reports associated with SCARs in the FDA Adverse Event Reporting System database between 1 January 2004 and 31 December 2021 and compiled a list of drugs with potentially serious skin toxicity. According to this list, we summarized the reporting proportions of different drugs and drug classes and conducted disproportionality analysis for all the drugs. In addition, the risk characteristic of SCARs due to different drugs and drug classes was summarized by the positive–negative distribution based on the results of the disproportionality analysis.

Results: A total of 77,789 reports in the FDA Adverse Event Reporting System database were considered SCAR-related, of which lamotrigine (6.2%) was the most reported single drug followed by acetaminophen (5.8%) and allopurinol (5.8%) and antibacterials (20.6%) was the most reported drug class followed by antiepileptics (16.7%) and antineoplastics (11.3%). A total of 1,219 drugs were reported as culprit-drugs causing SCARs in those reports, and the largest number of drugs belonged to antineoplastics. In disproportionality analysis, 776 drugs showed at least one positive pharmacovigilance signal. Drugs with the most positive signals were lamotrigine, acetaminophen, furosemide, and sulfamethoxazole/trimethoprim.

Conclusion: Our study provided a real-world overview of SCARs to drugs, and the investigation of SCAR positive–negative distribution across different drugs revealed its risk characteristics, which may help optimize patient management.

KEYWORDS

severe cutaneous adverse reactions, FDA Adverse Event Reporting System, culprit-drug, disproportionality analysis, pharmacovigilance

1 Introduction

Severe cutaneous adverse reactions (SCARs) are relatively uncommon but life-threatening adverse skin reactions, which are caused by an immunologically mediated inflammatory reaction with a prominent phenotype in the skin (Hoetzenecker et al., 2016; Ardern-Jones and Mockenhaupt, 2019; Bellon, 2019). Drug reaction with eosinophilia and systemic symptoms (DRESS), Steven–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) are among the most commonly recognized SCARs (Duong et al., 2017). Although SCAR cases are rare, the mortality is relatively high. It is reported that the mortality of all SCARs accounts for 4% for AGEP, 2%–6% for DRESS, and up to 48% for TEN (Owen and Jones, 2021). Due to the very high mortality, the management of SCARs is significantly challenging.

Culprit-drug identification and its early withdrawal are the first mandatory steps for SCAR patients (Paulmann and Mockenhaupt, 2016; Duong et al., 2017; Owen and Jones, 2021; Zhang et al., 2021) because it may decrease mortality (Garcia-Doval et al., 2000; Valeyrie-Allanore et al., 2007). An evidence-based and comprehensive list of causative drugs may aid in the identification and early withdrawal of a culprit-drug, but related work is currently focused on specific drug class, regions, or SCAR subclasses (Kardaun et al., 2013; Oshikoya et al., 2020; Chung et al., 2021; Shukla et al., 2021), which may limit the application of research findings. Therefore, there is an urgent need for studies on the causative drug covering a wide spectrum of drugs in large populations.

Pharmacovigilance is scientific and data gathering activity relating to the detection, monitoring, understanding, and prevention of adverse events (AEs) for a medicine, which is a key component of drug safety regulatory processes and principally involves the identification and evaluation of safety signals associated with the use of a medicinal product (Lucas et al., 2022). Medicine safety monitoring is a continuous and dynamic process throughout all the phases of the life cycle of a drug because although drug safety evaluation is very rigorous and thorough in a pre-clinical trial, these studies are conducted on limited numbers of patients that are selected based on strict eligibility criteria, meaning they do not fully represent real-world populations in limited duration, and it is difficult to detect rare and long-term adverse

TABLE 1 Eighteen narrow-scope PTs in SMQ classification of SCARs.

PT	MedDRA code
Acute generalized exanthematous pustulosis	10048799
Bullous hemorrhagic dermatosis	10083809
Cutaneous vasculitis	10011686
Dermatitis bullous	10012441
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalized	10012456
Drug reaction with eosinophilia and systemic symptoms	10073508
Epidermal necrosis	10059284
Erythema multiforme	10015218
Erythrodermic atopic dermatitis	10082985
Exfoliative rash	10064579
Oculomucocutaneous syndrome	10030081
SJS–TEN overlap	10083164
Skin necrosis	10040893
Stevens–Johnson syndrome	10042033
Target skin lesion	10081998
Toxic epidermal necrolysis	10044223
Toxic skin eruption	10057970
Severe cutaneous adverse reactions (SMQ)[a]	20000020

[a]This is an SMQ-level term which includes all 18 narrow-scope PTs.
PT, preferred term; MedDRA, Medical Dictionary for Drug Regulatory Activities; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; SMQ, Standardized MedDRA Query.

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

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

AE, adverse event.

reactions (ADRs) (Trifirò and Crisafulli, 2022). Therefore, pharmacovigilance is significant in detecting drug ADRs and ensuring medicine safety because it breaks the intrinsic limitations in pre-marketing clinical trials and allows to exhaustively evaluate the drug safety profile by using post-marketing real-world data that are collected during routine clinical care.

Many different approaches are currently applied to achieve medicine safety monitoring in modern pharmacovigilance practice, including spontaneous reporting databases, electronic health record monitoring and research frameworks, social media surveillance, and the use of digital devices (Lavertu et al., 2021). Among those methods, spontaneous reporting database is a kind of well-established platform that is widely used to perform real-world post-marketing studies and provides a real-time overview of major toxicities, thus informing clinical practice for proactive monitoring (Lavertu et al., 2021; Raschi et al., 2021). In this regard, the FDA Adverse Event Reporting System (FAERS) database is a publicly available drug ADR data resource covering the entire population and a wide range of drugs worldwide, with the added advantage of being able to discover these kinds of rare but serious ADRs cost-effectively. Therefore, the FAERS opens a new window for understanding the real-world causative drug of SCARs and provides an unprecedented opportunity to complete the possible causative drug list and risk assessment.

In practice, By probing for disproportionality between drug use and AE occurrence in the FAERS, these real-world AE data can be used to identify the potential culprit-drugs of specific AEs, optimize drug selection for individual patients, and explore drug–drug interaction (Kass-Hout et al., 2016). The present study evaluates the relationship between drugs and SCARs in FAERS using a well-established adverse reaction signal monitoring approach, exploring and summarizing the relationship between drugs and SCARs from the

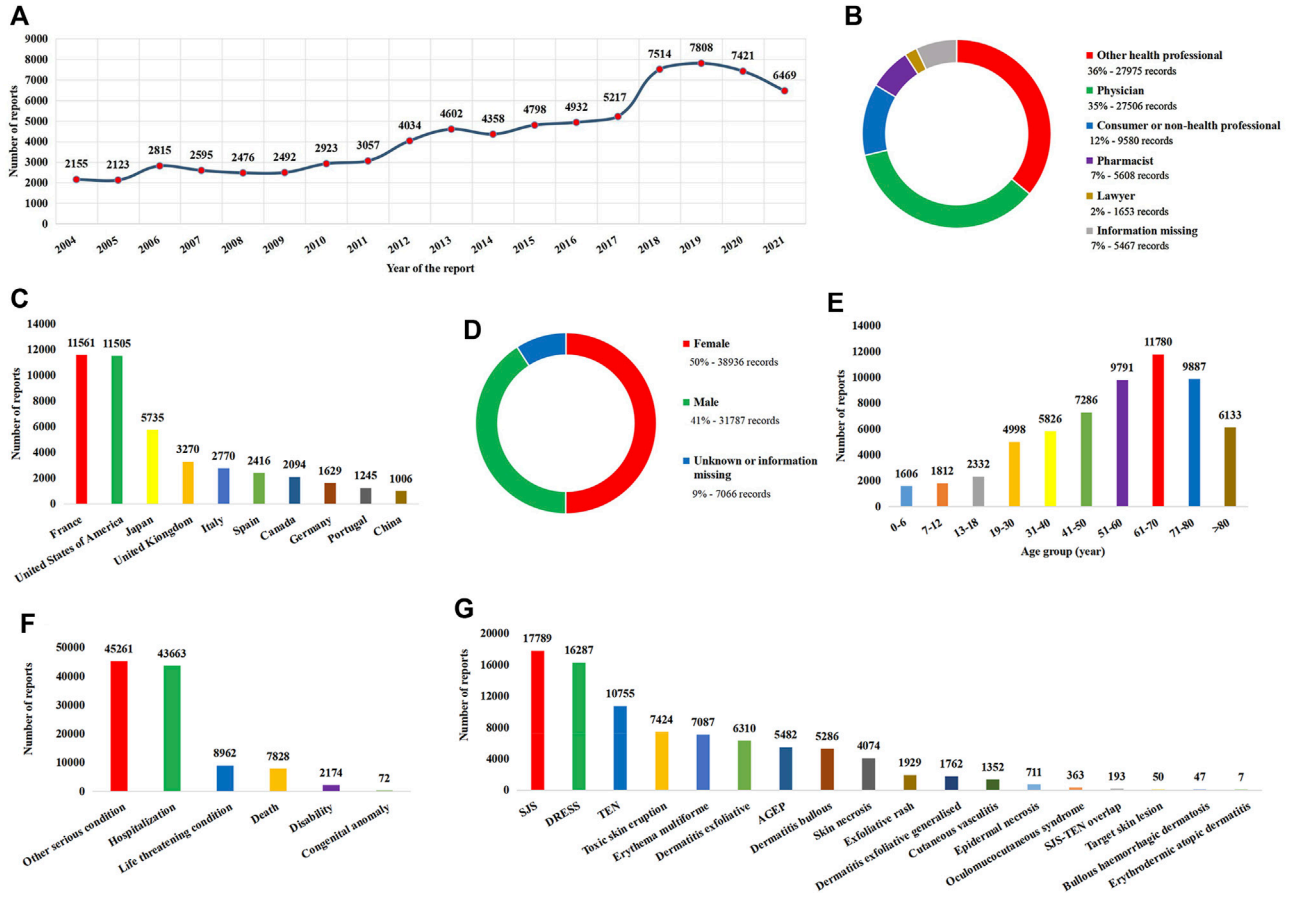

FIGURE 1
Basic information and patient characteristics according to the report. **(A)** Distribution of the reporting year. **(B)** Distribution of the reporter. **(C)** Top 10 countries with the most sources of reports. **(D)** Distribution of patient gender. **(E)** Distribution of patient age. **(F)** Distribution of the patient outcome. **(G)** Distribution of adverse reactions of preferred terms. AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

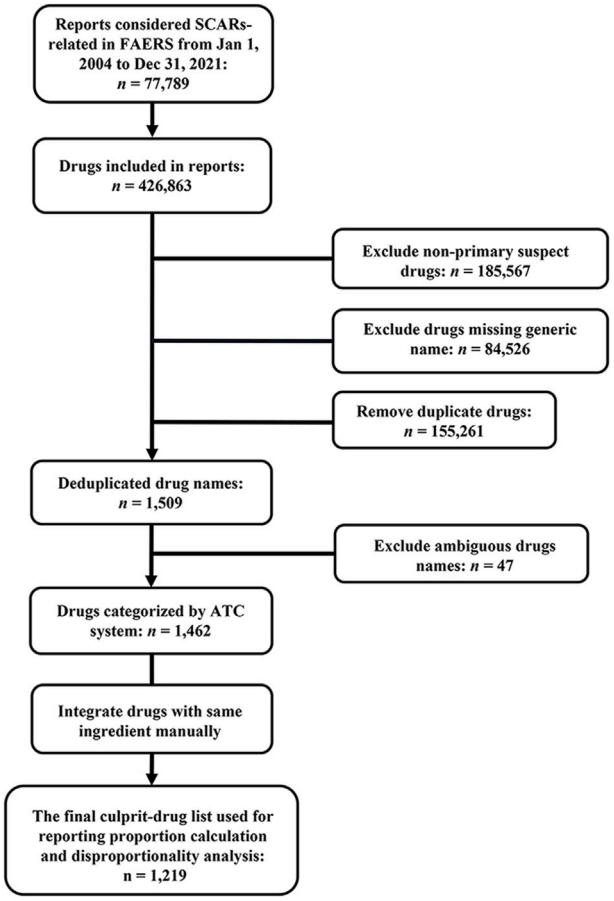

FIGURE 2
Flowchart for data acquisition and processing. ATC, Anatomical Therapeutic Chemical; FAERS, FDA Adverse Event Reporting System; SCARs, severe cutaneous adverse reactions.

pharmacovigilance perspective and providing a reference for clinical decision-making.

2 Methods

2.1 Data source

FAERS is a drug adverse reaction information release platform established by using the preferred terms (PTs) of the Medical Dictionary for Drug Regulatory Activities (MedDRA) to code AEs. It currently opens all adverse reaction reports since 2004 in openFDA with more than 10,000,000 patient adverse reaction report data available for public retrieval and downloads and is updated quarterly. These reports include information on patient demographics, medication use, AEs, indications, outcomes, and report sources. By constructing a reasonable query request, the query, screening, statistics, and download of the target adverse reaction report data can be realized through the application programming interface (API) (Kass-Hout et al., 2016). In this study, we reviewed reports on SCARs between 1 January 2004 and 31 December 2021.

2.2 Definition of the SCAR report in FAERS

In the study, narrow-scope PTs in the Standardized MedDRA Query (SMQ) were used to identify the target report in FAERS. Within an SMQ, a PT can be classified as having a narrow or broad scope. The narrow scope identifies the PTs that are more likely to represent the condition or an area of interest, while the broad-scope PTs may end up having little to minimal interest for use in the analysis upon further investigation (Mozzicato, 2007). Searching in MedDRA 23.0, there were 18 narrow-scope PTs in the SMQ classification of SCARs (Table 1). If one of those PTs was included in the "patient.reaction.reactionmeddrapt" field of the report, we considered it SCAR-related.

2.3 Adverse reaction signal detection method

Disproportionality analysis was conducted to identify adverse reaction signals by computing the reporting odds ratio (ROR) and the corresponding 95% confidence intervals (CIs). Based on the classic two-by-two contingency table (Table 2), the ROR was calculated as the ratio of the odds of reporting SCARs *versus* all other ADRs for a given drug compared with the reporting odds for all other drugs present in FAERS (Sakaeda et al., 2013). The ROR and 95% CI can be calculated using the following formulas:

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

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

When the lower limit of the 95% CI of the ROR was >1 with at least three cases, the ROR was considered significant and regarded as a positive signal (Zhai et al., 2019), which means the drug of interest may have the potential risk to induce the AE of interest. Instead, if the lower limit of the 95% CI and the case number cannot reach the criteria mentioned previously, it means there is a weak association between AE occurrence and drug use, namely, a negative signal.

2.4 Data extraction and signal detection

The downloaded file from FAERS through openFDA API is highly structured data stored in "JSON" format. It is a collection of data containing patient demographic and administrative information, the origin of information, drug indication, previous and concurrent medications, dates of commencement and discontinuation of therapy, AEs, and drug use outcome (Altebainawi et al., 2023). By specifying specific fields, we can precisely locate the required information mentioned previously to perform analysis and gather those data into a datasheet. In this study, we used the R packages "httr" to call the API, "jsonlite" to read the downloaded file, and "dplyr" to sort out and analyze the data. The specific execution process is as follows.

First, we downloaded all SCAR-related report data between 1 January 2004 and 31 December 2021 from the FAERS database through API and extracted basic report information, including report time, report source, patient demographic information, adverse event outcomes, and the number of reports involving each PT.

TABLE 3 Number of culprit-drugs of the SMQ group and each PT subgroup.

Group	No. (%) of drugs among 1,219 culprit-drugs
Stevens–Johnson syndrome	981 (80.5)
Erythema multiforme	864 (70.9)
Toxic epidermal necrolysis	852 (69.9)
Dermatitis exfoliative	839 (68.8)
Dermatitis bullous	812 (66.6)
Drug reaction with eosinophilia and systemic symptoms	804 (66.0)
Toxic skin eruption	786 (64.5)
Skin necrosis	744 (61.0)
Exfoliative rash	680 (55.8)
Acute generalized exanthematous pustulosis	628 (51.5)
Dermatitis exfoliative generalized	525 (43.1)
Cutaneous vasculitis	497 (40.8)
Epidermal necrosis	375 (30.8)
Oculomucocutaneous syndrome	154 (12.6)
SJS–TEN overlap	113 (9.3)
Bullous hemorrhagic dermatosis	68 (5.6)
Target skin lesion	29 (2.4)
Erythrodermic atopic dermatitis	17 (1.4)
Severe cutaneous adverse reactions (SMQ)[a]	1,219 (100.0)

[a]This is an SMQ term which includes all 18 narrow preferred terms.
MedDRA, Medical Dictionary for Drug Regulatory Activities; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; SMQ, Standardized MedDRA Query.

Second, we extracted the drug information from the downloaded dataset. According to the reported role of the drug in the report, drugs can be divided into primary suspect drugs, concomitant drugs, and drugs interacting with the suspect drug. For the accurate collection of culprit-drugs, only primary suspect drugs ("patient.drug.drugcharacterization" field = 1) were reserved. After obtaining the primary suspect drug generic names in the "patient.drug.openfda.generic_name" field on all SCAR reports, to obtain the final culprit-drug list for the signal detection, we excluded drugs that were missing generic names, duplicated, and ambiguous.

Third, the Anatomical Therapeutic Chemical (ATC) system was used to categorize drugs into classes according to their therapeutic effects and characteristics (Skrbo et al., 2004). For drugs with the same active ingredient (e.g., different salt forms), professional pharmacists performed manual integration.

Fourth, 18 narrow-scope PTs combined with the drug were used to compute ROR and 95% CI. After that, the total ROR and 95% CI were calculated for each drug using the SMQ level, so there are 19 ROR and 95% CI values (one for the SMQ level and 18 for the PT level) for each evaluated drug.

Fifth, according to the PT subclass and SMQ level, we conducted categorical statistics on the SCAR reports in FAERS, yielding the top 10 agents and ATC drug classes (second ATC level) with the highest reporting proportions.

Finally, according to the signal detection results, the drugs were divided into positive signal and negative signal drugs. To achieve the final list of drugs closely related to SCARs, drugs with at least one of the 19 signals that met the criteria for a positive signal were screened.

In this study, R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for the data processing and analysis described previously.

3 Results

3.1 Basic information and patient characteristics according to the report

A total of 14,496,963 reports were included in FAERS between 1 January 2004 and 31 December 2021. Of these, 77,789 (0.54%) reports were considered SCAR-related. Reports on SCARs have been increasing in recent years, with 2019 being the year with the most reports (Figure 1A). In terms of report submission, health professionals (78%) were the leading reporters (Figure 1B), and France and the United States were the leading reporting countries (Figure 1C). In terms of patients, there were more female patients than male patients (Figure 1D), and the main age group was 61–70 years (Figure 1E). Furthermore, SCARs can lead to severe outcomes, accounting for 7,828 (10%) patient deaths (Figure 1F). Among the narrow-scope PTs included in SCARs, SJS was the most reported PT (Figure 1G).

PT	Proportions of the top 10 agents									
group	1	2	3	4	5	6	7	8	9	10
SJS	Lamotrigine (12.1%)	Phenytoin (6.4%)	Acetaminophen (6.1%)	Ibuprofen (4.8%)	Allopurinol (4.7%)	Carbamazepine (4.3%)	Acetylsalicylic acid (3.7%)	Furosemide (3.4%)	TMP-SMX (3.1%)	Amlodipine (2.7%)
DRESS	Allopurinol (11.8%)	Vancomycin (9.5%)	Lamotrigine (9.0%)	Carbamazepine (5.2%)	Acetaminophen (5.1%)	Levetiracetam (4.3%)	TMP-SMX (4.1%)	Pantoprazole (3.8%)	Ceftriaxone (3.7%)	Furosemide (3.5%)
TEN	Acetaminophen (11.2%)	Furosemide (8.6%)	Lamotrigine (8.2%)	Allopurinol (7.8%)	Ibuprofen (6.5%)	Vancomycin (6.0%)	Acetylsalicylic acid (5.3%)	Omeprazole (5.1%)	Ciprofloxacin (4.9%)	Prednisolone (4.6%)
TSE	Furosemide (5.7%)	Acetaminophen (5.1%)	Allopurinol (4.6%)	TMP-SMX (4.0%)	Esomeprazole (3.7%)	Lamotrigine (3.5%)	Amlodipine (3.1%)	Pantoprazole (3.1%)	Clopidogrel (3.0%)	Vancomycin (2.9%)
EM	Acetaminophen (4.9%)	Lamotrigine (4.5%)	Acetylsalicylic acid (3.8%)	Ribavirin (3.4%)	Ibuprofen (3.4%)	Omeprazole (3.2%)	Amlodipine (2.8%)	Carbamazepine (2.8%)	Allopurinol (2.8%)	Prednisolone (2.8%)
DE	Furosemide (6.2%)	Allopurinol (5.8%)	Acetylsalicylic acid (4.4%)	Acetaminophen (4.3%)	Methotrexate (3.8%)	Omeprazole (3.5%)	Clopidogrel (3.4%)	TMP-SMX (3.4%)	Amlodipine (3.3%)	Carbamazepine (3.2%)
AGEP	Acetaminophen (8.3%)	Vancomycin (6.5%)	Furosemide (5.1%)	Amoxicillin (4.8%)	Omeprazole (4.5%)	Clindamycin (4.5%)	Ceftriaxone (4.3%)	Enoxaparin (4.1%)	Metronidazole (3.9%)	Ibuprofen (3.9%)
DB	Furosemide (6.0%)	Acetaminophen (4.9%)	Omeprazole (3.7%)	Ibuprofen (3.0%)	Acetylsalicylic acid (2.9%)	Methotrexate (2.9%)	Metformin (2.8%)	Amlodipine (2.6%)	Allopurinol (2.5%)	Simvastatin (2.5%)
SN	Methotrexate (13.6%)	Prednisone (12.8%)	Adalimumab (11.7%)	Tocilizumab (10.1%)	Etanercept (10.0%)	Rituximab (9.8%)	Infliximab (9.7%)	Sulfasalazine (9.7%)	Abatacept (9.6%)	Leflunomide (9.4%)
ER	Adalimumab (10.1%)	Etanercept (5.8%)	Acetylsalicylic acid (5.4%)	Methotrexate (4.8%)	Prednisone (4.6%)	Lenalidomide (4.6%)	Levothyroxine (4.0%)	Simvastatin (3.7%)	Omeprazole (3.6%)	Furosemide (3.5%)
DEG	Allopurinol (6.8%)	Methotrexate (6.1%)	Furosemide (5.4%)	Prednisone (5.1%)	TMP-SMX (4.8%)	Adalimumab (4.4%)	Pantoprazole (3.9%)	Vancomycin (3.5%)	Dupilumab (3.5%)	Secukinumab (3.5%)
CV	Methotrexate (10.6%)	Etanercept (9.8%)	Adalimumab (9.4%)	Tocilizumab (7.0%)	Abatacept (6.5%)	Anakinra (6.0%)	Leflunomide (5.5%)	Prednisone (5.1%)	Tofacitinib (4.9%)	Amlodipine (4.1%)
EN	Methotrexate (22.4%)	Lamotrigine (9.6%)	Acetaminophen (6.2%)	Prednisone (4.2%)	Furosemide (4.2%)	Cyclophosphamide (3.7%)	Acetylsalicylic acid (3.5%)	Methylprednisolone (3.5%)	Diclofenac (3.5%)	Carbamazepine (3.4%)
OS	Lamotrigine (10.5%)	Carbamazepine (8.0%)	Diclofenac (6.3%)	Furosemide (4.4%)	Acetylsalicylic acid (3.6%)	Amlodipine (3.6%)	Lansoprazole (2.8%)	Sulfasalazine (2.5%)	Clarithromycin (2.5%)	Zonisamide (2.2%)
STO	Ibuprofen (14.0%)	Lamotrigine (10.4%)	Acetaminophen (9.3%)	Pantoprazole (5.7%)	Pegfilgrastim (5.2%)	Ceftriaxone (5.2%)	Amoxicillin (4.7%)	Linezolid (4.7%)	Carbamazepine (4.7%)	Fluconazole (4.1%)
TSL	Aripiprazole (22.0%)	Risedronate (20.0%)	Sertraline (20.0%)	Lenalidomide (18.0%)	Bortezomib (16.0%)	Omeprazole (12.0%)	Ibuprofen (8.0%)	Acetaminophen (8.0%)	Lamotrigine (6.0%)	Dexamethasone (6.0%)
BHD	Furosemide (14.9%)	Bisoprolol (12.8%)	Daratumumab (10.6%)	Metolazone (10.6%)	Eplerenone (10.6%)	Escitalopram (10.6%)	Heparin (10.6%)	Enoxaparin (8.5%)	Warfarin (8.5%)	Acetylsalicylic acid (8.5%)
EAD	Pregabalin (42.9%)	TMP-SMX (42.9%)	Lenalidomide (42.9%)	Bortezomib (42.9%)	Thiamine (42.9%)	Daratumumab (42.9%)	Rivaroxaban (42.9%)	Dexamethasone (42.9%)	V+S (14.3%)	Baricitinib (14.3%)
SMQ	Lamotrigine (6.2%)	Acetaminophen (5.8%)	Allopurinol (5.8%)	Furosemide (4.6%)	Vancomycin (4.4%)	Ibuprofen (3.3%)	Omeprazole (3.2%)	Acetylsalicylic acid (3.2%)	Carbamazepine (3.1%)	Methotrexate (2.9%)

FIGURE 3
Top 10 agents with the highest reporting proportions at the SMQ and PT levels. AGEP, acute generalised exanthematous pustulosis; BHD, bullous haemorrhagic dermatosis; CV, cutaneous vasculitis; DB, dermatitis bullous; DE, dermatitis exfoliative; DEG, dermatitis exfoliative generalized; DRESS, drug reaction with eosinophilia and systemic symptoms; EN, epidermal necrosis; EM, erythema multiforme; EAD, erythrodermic atopic dermatitis; ER, exfoliative rash; OS, oculomucocutaneous syndrome; PT, preferred term; SCARs, severe cutaneous adverse reactions; SMQ, Standardized MedDRA Queries; STO, SJS-TEN overlap; SN, skin necrosis; SJS, Stevens-Johnson syndrome; TMP-SMX, sulfamethoxazole and trimethoprim; TSL, target skin lesion; TEN, toxic epidermal necrolysis; TSE, toxic skin eruption; V+S, velpatasvir and sofosbuvir.

3.2 Identification of the culprit-drug list

As each report usually included multiple drugs, there were a total of 426,863 drugs recorded in 77,789 SCAR-related reports. Due to reporters who were mainly health professionals who had preliminarily evaluated the role of drugs in the development of SCARs, primary suspect drugs were included in the analysis as a culprit-drug in this study. After excluding non-primary suspect drugs, drugs that were missing generic names, duplicated, and ambiguous, and integrating drugs with the same active ingredient, a total of 1,219 drugs made up the final culprit-drug list, which means each drug in the list was classified as primary suspected drugs in at least one report (Figure 2). However, the number culprit-drugs varied across PTs, with the SJS group (80.5%) containing the most drugs and the EAD group (1.4%) containing the least (Table 3).

3.3 Reporting proportions of culprit-drugs

Among these 1,219 kinds of drugs, the top 10 agents with the highest reporting proportions at the SMQ and PT levels are presented in Figure 3. According to the ATC classification (second level), the top 10 drug classes with the highest reporting proportions at the SMQ and PT levels are presented in Figure 4.

3.4 Adverse reaction signal detection results

Each potential culprit-drug causing SCARs was combined with SMQ and each PT for disproportionality analysis, yielding 19 pharmacovigilance signals for each drug. Details of the disproportionality analysis results for each drug are listed in Supplementary Table S1.

For the SMQ level and each PT, the distribution of adverse drug reaction signals and drug classes is presented in Figure 5. On the whole, the number of positive signal drugs in each group was less than that of negative signal drugs. In terms of the drug class (ATC second level), antineoplastic agents, antibacterials for systemic use, and antivirals for systemic use were the top three drug categories involved in most groups. However, it is worth noting that antibacterials for systemic use showed the largest rate of positive drugs in most PT groups.

Due to the overlap and differences in positive drugs in different groups, to obtain drugs with a strong statistical association with SCARs, we integrated a positive signal number for each drug (Table 4). Of the 1,219 drugs, the number of positive signals for each drug is between 0 and 16, and 776 drugs had at least one positive signal in each group. Among these drugs, four drugs, namely, lamotrigine, acetaminophen, furosemide, and sulfamethoxazole/trimethoprim, contained the most positive signals, and each drug included 16 positive signals (Supplementary Table S1).

PT	Proportions of the top 10 chemical drug subclasses									
group	1	2	3	4	5	6	7	8	9	10
SJS	Antiepileptics N03 (27.3%)	Antibacterials J01 (17.0%)	Analgesics N02 (11.2%)	DARD A02 (9.0%)	Psycholeptics N05 (8.4%)	AAP M01 (8.3%)	Antineoplastics L01 (8.3%)	Psychoanaleptics N06 (8.0%)	Corticosteroids H02 (7.2%)	Antivirals J05 (6.1%)
DRESS	Antibacterials J01 (30.4%)	Antiepileptics N03 (22.2%)	Antigout preparations M04 (12.3%)	DARD A02 (10.9%)	Psycholeptics N05 (8.1%)	Corticosteroids H02 (8.1%)	Analgesics N02 (7.9%)	Antimycobacterials J04 (6.2%)	Antineoplastics L01 (5.8%)	Immunosuppressants L04 (5.5%)
TEN	Antibacterials J01 (28.1%)	Antiepileptics N03 (21.9%)	Analgesics N02 (17.2%)	DARD A02 (15.6%)	Corticosteroids H02 (13.5%)	Diuretics C03 (10.8%)	Antineoplastics L01 (10.6%)	AAP M01 (10.5%)	Psycholeptics N05 (9.5%)	Antigout preparations M04 (8.1%)
TSE	Antibacterials J01 (18.4%)	Antineoplastics L01 (16.3%)	DARD A02 (13.3%)	Antiepileptics N03 (10.9%)	Antithrombotics B01 (9.1%)	Immunosuppressants L04 (8.5%)	Analgesics N02 (8.3%)	Psycholeptics N05 (8.1%)	Diuretics C03 (7.5%)	Corticosteroids H02 (7.2%)
EM	Antineoplastics L01 (15.5%)	Antiepileptics N03 (13.4%)	Antibacterials J01 (12.8%)	DARD A02 (11.6%)	Analgesics N02 (9.7%)	Corticosteroids H02 (9.0%)	Immunosuppressants L04 (8.1%)	Antivirals J05 (7.8%)	Psychoanaleptics N06 (7.2%)	AAP M01 (6.8%)
DE	Antibacterials J01 (12.4%)	Immunosuppressants L04 (9.7%)	Antineoplastics L01 (9.5%)	Antiepileptics N03 (9.1%)	DARD A02 (8.3%)	Analgesics N02 (8.1%)	AARAS C09 (7.1%)	Corticosteroids H02 (6.7%)	Diuretics C03 (6.3%)	Lipid modifying agents C10 (5.9%)
AGEP	Antibacterials J01 (33.0%)	DARD A02 (11.9%)	Analgesics N02 (11.6%)	Antiepileptics N03 (8.8%)	AAP M01 (8.1%)	Corticosteroids H02 (7.8%)	Diuretics C03 (7.1%)	Antithrombotics B01 (6.8%)	Psycholeptics N05 (6.8%)	Psychoanaleptics N06 (5.6%)
DB	Antibacterials J01 (13.6%)	Antineoplastics L01 (12.8%)	DARD A02 (10.9%)	Immunosuppressants L04 (10.8%)	Antiepileptics N03 (10.0%)	Analgesics N02 (9.6%)	Diuretics C03 (8.3%)	Antithrombotics B01 (7.9%)	Corticosteroids H02 (7.6%)	AARAS C09 (7.3%)
SN	Antineoplastics L01 (24.3%)	Immunosuppressants L04 (23.0%)	Corticosteroids H02 (20.8%)	Antithrombotics B01 (16.0%)	Analgesics N02 (11.6%)	AIAA A07 (10.3%)	DARD A02 (10.2%)	DTBD M05 (10.1%)	Antineoplastics L01 (9.3%)	AAP M01 (8.1%)
ER	Immunosuppressants L04 (31.5%)	Antineoplastics L01 (16.9%)	Analgesics N02 (11.1%)	DARD A02 (10.5%)	AARAS C09 (9.4%)	Antibacterials J01 (9.4%)	Lipid modifying agents C10 (9.2%)	Corticosteroids H02 (8.9%)	Antiepileptics N03 (8.0%)	Psychoanaleptics N06 (7.6%)
DEG	Immunosuppressants L04 (21.5%)	Antiepileptics J01 (20.6%)	Antineoplastics L01 (19.4%)	Corticosteroids H02 (11.5%)	DARD A02 (11.5%)	Psycholeptics N05 (7.9%)	Antiepileptics N03 (7.7%)	Antigout preparations M04 (6.9%)	Antithrombotics B01 (6.8%)	Diuretics C03 (6.5%)
CV	Immunosuppressants L04 (33.2%)	Corticosteroids H02 (13.8%)	Antineoplastics L01 (11.8%)	Antibacterials J01 (10.9%)	DARD A02 (9.9%)	Antithrombotics B01 (8.9%)	Analgesics N02 (8.7%)	AARAS C09 (8.7%)	Diuretics C03 (8.6%)	Beta blocking agents C07 (8.1%)
EN	Immunosuppressants L04 (28.6%)	Antiepileptics N03 (18.6%)	Antibacterials J01 (14.2%)	Antineoplastics L01 (14.2%)	Corticosteroids H02 (13.2%)	Analgesics N02 (10.5%)	DARD A02 (7.3%)	Psycholeptics N05 (6.5%)	AAP M01 (6.3%)	Diuretics C03 (5.8%)
OS	Antiepileptics N03 (21.8%)	DARD A02 (8.3%)	Antibacterials J01 (8.3%)	AAP M01 (7.7%)	Psycholeptics N05 (6.3%)	Drugs used in diabetes A10 (5.0%)	Antineoplastics L01 (5.0%)	Diuretics C03 (4.7%)	Analgesics N02 (4.7%)	CCB C08 (4.4%)
STO	Antiepileptics N03 (22.3%)	Antibacterials J01 (20.7%)	AAP M01 (18.1%)	Analgesics N02 (10.4%)	DARD A02 (8.8%)	Corticosteroids H02 (6.7%)	Antimycotics J02 (6.7%)	Drugs used in diabetes A10 (6.2%)	Antineoplastics L01 (6.2%)	Beta blocking agents C07 (5.7%)
TSL	DTBD M05 (22.0%)	Psycholeptics N05 (22.0%)	Antineoplastics L01 (20.0%)	Immunosuppressants L04 (20.0%)	Psychoanaleptics N06 (20.0%)	Analgesics N02 (14.0%)	DARD A02 (12.0%)	Corticosteroids H02 (12.0%)	AAP M01 (10.0%)	Antibacterials J01 (6.0%)
BHD	Antithrombotics B01 (31.9%)	Diuretics C03 (23.4%)	Antineoplastics L01 (19.1%)	Analgesics N02 (17.0%)	Beta blocking agents C07 (14.9%)	Vasoprotectives C05 (12.8%)	Corticosteroids H02 (12.8%)	Antibacterials J01 (10.6%)	Psychoanaleptics N06 (10.6%)	CCB C08 (6.4%)
EAD	Antithrombotics B01 (57.1%)	Antibacterials J01 (57.1%)	Immunosuppressants L04 (57.1%)	Vitamins A11 (42.9%)	Corticosteroids H02 (42.9%)	Antineoplastics L01 (42.9%)	Antiepileptics N03 (42.9%)	DARD A02 (14.3%)	Beta blocking agents C07 (14.3%)	AARAS C09 (14.3%)
SMQ	Antibacterials J01 (20.6%)	Antiepileptics N03 (16.7%)	Antineoplastics L01 (11.3%)	DARD A02 (11.2%)	Analgesics N02 (10.4%)	Immunosuppressants L04 (9.6%)	Corticosteroids H02 (9.4%)	Psycholeptics N05 (7.5%)	Diuretics C03 (6.5%)	AAP M01 (6.5%)

FIGURE 4
Top 10 drug classes with the highest reporting proportions at the SMQ and PT levels. AAP, antiinflammatory and antirheumatic products; AARAS, agents acting on the renin-angiotensin system; AIAA, antidiarrheals or intestinal antiinflammatory/antiinfective agents; AGEP, acute generalised exanthematous pustulosis; BHD, bullous haemorrhagic dermatosis; CCB, calcium channel blockers; CV, cutaneous vasculitis; DARD, drugs for acid related disorders; DB, dermatitis bullous; DE, dermatitis exfoliative; DEG, dermatitis exfoliative generalized; DRESS, drug reaction with eosinophilia and systemic symptoms; DTBD, drugs for treatment of bone diseases; EN, epidermal necrosis; EM, erythema multiforme; EAD, erythrodermic atopic dermatitis; ER, exfoliative rash; OS, oculomucocutaneous syndrome; PT, preferred term; SCARs, severe cutaneous adverse reactions; SMQ, Standardized MedDRA Queries; STO, SJS-TEN overlap; SN, skin necrosis; SJS, Stevens-Johnson syndrome; TSL, target skin lesion; TEN, toxic epidermal necrolysis; TSE, toxic skin eruption.

4 Discussion

SCARs is an interdisciplinary clinical problem that has received extensive attention from both dermatologists and pharmacists. In this study, we provided a comprehensive overview of drugs causing SCARs from the pharmacovigilance perspective, summarized a list of 1,219 drugs that were reported as culprit-drugs causing SCARs in FAERS between 2004 and 2021, and described the reporting proportions of different drugs and drug classes. At the same time, we further detected the risk signals of the aforementioned drugs and evaluated the risk association between the occurrence of SCARs and drugs. To our knowledge, this study provides, for the first time, a comprehensive list of SCAR-causing drugs and shows a novel strategy to gain a comprehensive understanding of SCAR-causing drugs. Although the intrinsic nature of spontaneous reporting databases leads to unavoidable limitations in the application of our results, if we use those results properly, it can help to some extent in the rapid and evidence-based identification of culprit-drugs causing SCARs in the clinical setting.

In this study, we offered a multi-dimensional evaluation perspective. First, we presented the top 10 agents and drug classes with the highest reporting proportions at the SMQ and PT levels, respectively. Through this result, we can understand the drugs and drug classes that commonly cause SCAR in the clinic and can further locate specific subtypes of SCARs, such as SJS, TEN, DRESS, or AGEP. In our study, lamotrigine (SMQ level) was the agent with the highest reporting proportion followed by acetaminophen and allopurinol, while antibacterials (SMQ level) were the drug class with the highest reporting proportions followed by antiepileptics and antineoplastic agents. However, our results are not consistent with previous studies in reporting the proportion rank (Kardaun et al., 2013; Su and Aw, 2014; Zhao et al., 2019; Oshikoya et al., 2020; Ambe et al., 2021). Reporting on the proportions of drugs or drug classes may vary according to the region, study design, sample size, and patient inclusion and exclusion criteria, but our larger sample and global perspective make our results on reporting proportions more reliable, giving more precise guidance on which drugs to focus on. However, we also noted that higher reporting proportions do not necessarily mean a higher risk of SCARs because differences in the frequency of drug use may also lead to a higher reporting proportion.

For the aforementioned reason, in this study, we introduced the pharmacovigilance method as a more uniform metric for risk assessments to evaluate the ADR signals of each drug at the SMQ and PT levels. Although there have been studies using signal mining methods to assess the risk of drugs causing SCARs, the scope of the research is limited to specific drug classes or SCAR subclasses (Xu et al., 2021; Zhu et al., 2021; Bomze et al., 2022), so that the risk comparison between drugs can only be achieved within a limited range. In this study, we extended this scope to all reported culprit-drugs to date, allowing for cross-drug class, cross-PT risk

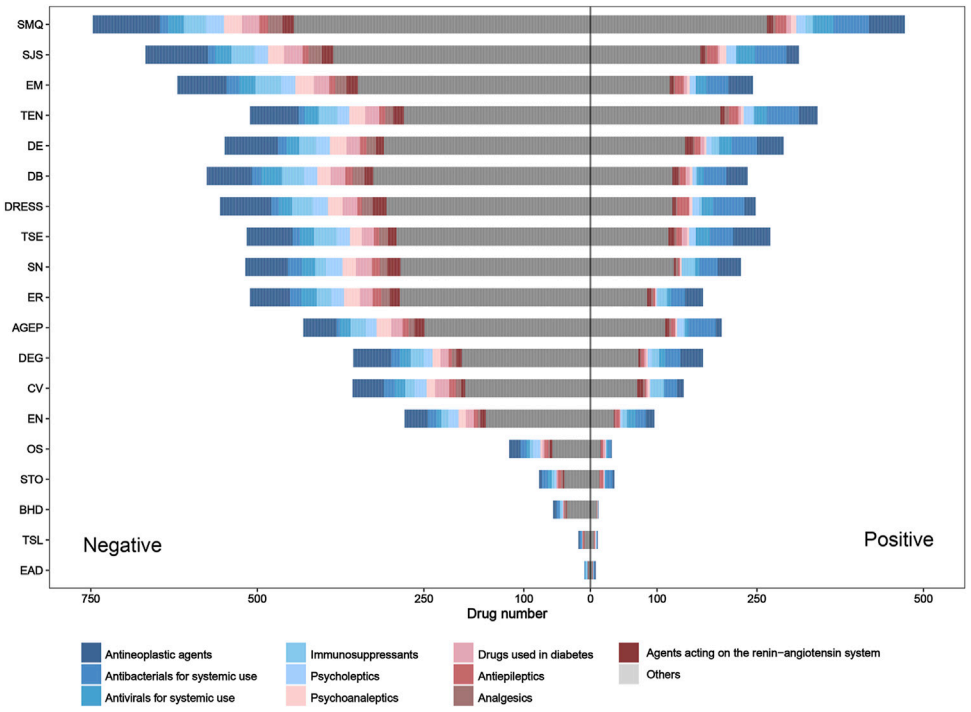

FIGURE 5
Pharmacovigilance signal distribution and drug class distribution of reported culprit-drugs at the SMQ and PT levels. AGEP, acute generalized exanthematous pustulosis; BHD, bullous hemorrhagic dermatosis; CV, cutaneous vasculitis; DB, dermatitis bullous; DE, dermatitis exfoliative; DEG, dermatitis exfoliative generalized; DRESS, drug reaction with eosinophilia and systemic symptoms; EN, epidermal necrosis; EM, erythema multiforme; EAD, erythrodermic atopic dermatitis; ER, exfoliative rash; OS, oculomucocutaneous syndrome; PT, preferred term; SMQ, Standardized MedDRA Query; STO, SJS–TEN overlap; SN, skin necrosis; SJS, Stevens–Johnson syndrome; TSL, target skin lesion; TEN, toxic epidermal necrolysis; TSE, toxic skin eruption.

assessment (Supplementary Table S1), which is more applicable to rapidly assess the risk of drugs causing SCARs in clinical practice. In addition, we summarized the distribution of pharmacovigilance signals, with 776 of the 1,219 drugs showing at least one positive signal, suggesting that those drugs need more attention in clinical use, especially drugs that exhibit multiple positive signals, such as lamotrigine, acetaminophen, furosemide, and sulfamethoxazole/trimethoprim. If we apply these results rationally, it will help optimize culprit-drug identification and the early withdrawal of them from treatment.

In addition, it is noteworthy that, of the 1,219 drugs, antineoplastics were the drug class containing the largest number of drugs and the drug class with the third highest reporting proportion (SMQ level) in FAERS. In previous studies, antineoplastics were not a common culprit-drug causing SCARs (Kardaun et al., 2013; Su and Aw, 2014; Zhao et al., 2019; Oshikoya et al., 2020), but our results suggested that anti-tumor drugs play an important role in the occurrence of SCARs. We believe that the difference should be mainly attributed to the development and clinical application of novel anti-tumor drugs and widespread attention to their skin toxicity in recent years (Quach et al., 2021; Nikolaou et al., 2022). In real-world scenarios, pharmacovigilance can be a handy tool for detecting and validating the potential skin toxicity of drugs, and several studies using the pharmacovigilance method have reported a risk of SCARs caused by some targeted antineoplastic drugs (Yang et al., 2021; Zhu et al., 2021), and some of the results were verified in clinical practice (Birmingham et al., 2022; Oya et al., 2022). Our results are consistent with their data mining findings, which illustrates the reliability of our results, more importantly; however, we captured that the main causative drugs of SCARs have changed in recent years, and antineoplastics have become an important drug class leading to SCARs. Capturing such changes will help find drugs with a focus on the original basis, which may optimize the management of SCARs. In this regard, our study provides an opportunity and strategy to capture such changes.

The present study also has some unavoidable limitations. First, due to the voluntary nature of reporting to FAERS, the fact that some data was not peer-reviewed may bias the results. A high number of reported cases for SCARs in the FAERS database were from healthcare providers (78%), which may improve the quality of reporting. Second, the actual incidence of SCARs due to drugs cannot be determined, as the total number of patients using these medications is unknown. Third, the signal detection results only suggest that there is a statistical association, and the question of whether there is a real causal relationship still needs further evaluation. Fourth, we cannot eliminate the potential influence of the presence of concomitant therapeutic drugs and (or) comorbidities on the occurrence of SCARs, which may bias our signal detection results. Fifth, underreporting, Weber effect, and

TABLE 4 Distribution of the number of positive adverse drug reaction signals.

Positive ADR signal number	No. (%) of culprit-drugs
16	4 (0.3)
15	9 (0.7)
14	9 (0.7)
13	9 (0.7)
12	21 (1.7)
11	14 (1.1)
10	26 (2.1)
9	21 (1.7)
8	36 (3.0)
7	48 (3.9)
6	47 (3.9)
5	63 (5.2)
4	75 (6.2)
3	90 (7.4)
2	118 (9.7)
1	186 (15.3)
0	443 (36.3)
Total	1,219 (100.0)

ADR, adverse drug reaction.

notoriety bias may exist in some drugs or drug classes, and may lead to a biased result, but recent studies have shown that these factors have relatively little effect on FAERS (Hoffman et al., 2014; Neha et al., 2021). In this study, we did not evaluate the influence of these factors on our research results, so their influence on our results is still unknown. Finally, our study can only provide a reference for the culprit-drug identification of SCARs and cannot replace the professional opinions of dermatologists.

5 Conclusion

The large population, wide geographic coverage, and publicly available accessibility of FAERS have qualified this spontaneous ADR reporting data source as an important resource in the study of the culprit-drug landscape of SCARs. As the largest study of its kind, we provided a whole picture of SCARs in a worldwide landscape. Our study provides evidence that can help to quickly identify the culprit-drugs that might cause SCARs. It may be relevant to many interested parties, including regulators, medical personnel, and others involved in drug management and use. Meanwhile, our work provides a powerful strategy to mine for information on drugs related to SCARs in the future and provides a real-world window for developing a pharmacovigilance strategy for drug-related injuries. However, it is particularly noteworthy that our studies, as a pharmacovigilance study using FAERS, can only provide a signal of possible associations between drugs and ADRs, so it is still necessary to conduct further investigation through appropriate research to verify the true relationship between drugs and ADRs.

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

QD and SL planned the project. DL, JG, QD, and SL designed the detail of the study. DL, JG, JZ, TZ, FL, DZ, LD, WL, QL, and CQ contributed to data collection and analysis. SL, QD, JG, and DL contributed to writing and editing of the manuscript. DL generated the figures for the manuscript. All authors corrected 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1117391/full#supplementary-material

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Relationships between beliefs about statins and non-adherence in inpatients from Northwestern China: a cross-sectional survey

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Background: Studies have identified patients' beliefs about medicines as an important determinant of non-adherence. However, scant data are available on the possible association between patients' beliefs and statin non-adherence among adult patients in China. The objectives of this study are to assess the prevalence of statin non-adherence, and to identify the factors associated with statin non-adherence, especially the association between inpatients' beliefs about statins and non-adherence in a tertiary hospital in the Northwestern China.

Methods: A cross-sectional questionnaire-based survey was carried out in the department of cardiology and neurology between February and June 2022. The Beliefs about Medicine Questionnaire (BMQ) was used to assess patients' beliefs about statins. The Adherence to Refills and Medications Scale (ARMS) was used to assess statin adherence. Logistic regression analyses were performed to identify the factors associated with statin non-adherence. Receiver operator characteristic (ROC) was conducted to assess the performance of the logistic regression model in predicting statin non-adherence.

Results: A total of 524 inpatients participated and finished the questionnaire, 426 (81.3%) inpatients were non-adherent to statin, and 229 (43.7%) inpatients expressed strong beliefs about the stain treatment necessity, while 246 (47.0%) inpatients expressed strong concerns about the potential negative effects. We found that the low necessity beliefs about statin (adjusted odds ratio [OR] and 95% confidence interval [CI], 1.607 [1.019, 2.532]; p = 0.041), prescribed rosuvastatin (adjusted OR 1.820 [1.124, 2.948]; p = 0.015) and ex-drinker (adjusted OR 0.254 [0.104, 0.620]; p = 0.003) were independent determinants of statin non-adherence.

Conclusion: Statin adherence was poor in this study. The findings indicated a significant association between inpatients' lower necessity beliefs and statin non-adherence. More attention should be focused on statin non-adherence in China. Nurses and pharmacists could play an important role in patient education and patient counseling in order to improve medication adherence.

KEYWORDS

medication adherence, statin, beliefs about medicine, nurses, pharmacists, China

Introduction

Cardiovascular disease remains the top cause of death in China (Liu et al., 2019). Statins, as a class of medications, have a critical role in the prevention and treatment of cardiovascular diseases. However, it was indicated that only about 1.4% of 0.5 million participants reported current use of statins for the secondary prevention of cardiovascular disease in China (Chen et al., 2014). Although the beneficial effects of statin therapy had been documented in the past 30 years, statin adherence remained suboptimal in clinical practice (Gomez Sandoval et al., 2011; Rodriguez et al., 2019). Around 40%–75% patients discontinued their statin therapy within 1 year after initiation (Banach et al., 2016). Poor adherence limited the efficacy of statin therapy (Xu et al., 2017). Non-adherence or discontinuation of statin therapy was associated with increased risk for cardiovascular and cerebrovascular morbidity, events, and mortality, which significantly increased medical costs (Gomez Sandoval et al., 2011; Li and Huang, 2015; Xu et al., 2017; Rodriguez et al., 2019). Statin adherence was also suboptimal in China. It was reported that 59.2% of patients were of poor statin adherence in Taiwan (Li and Huang, 2015), only 5.4% of 99,655 patients were deemed adherent among new statins users for primary prevention of cardiovascular disease during the initial 12-month follow-up period in Tianjin (Zhao et al., 2020).

Adherence to medications is defined as the process by which patients take their medications as prescribed. Non-adherence to medications can thus occur in the following situations or combinations thereof: late or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen or early discontinuation of the treatment (Vrijens et al., 2012). Many factors may affect medication adherence. Patients' beliefs and attitude regarding medications were known to be common cause of medication non-adherence (Horne and Weinman, 1999; Horne et al., 2013). The Beliefs about Medicines Questionnaire (BMQ) is a useful tool to identify patients at risk of non-adherence (Horne and Weinman, 1999; Wei et al., 2017). We derive two testable hypotheses for our empirical study. The first one is that statin adherence is poor in the Northwestern China. The second is that patients who have doubts about the necessity of statin and concerns about the potential adverse consequences of statin is more likely to be non-adherent.

Medication adherence is particularly important for positive health outcomes. However, adherence patterns among statin users have not been comprehensively reviewed in the Northwestern China. Scant data are available on the possible association between patients' beliefs and statin non-adherence among adult Chinese patients. Barriers to medication adherence have to be understood to establish strategies to achieve therapeutic goals (Brown and Bussell, 2011). The objectives of this study are to assess the prevalence of statin non-adherence, and to identify the factors associated with statin non-adherence, especially the associations between inpatients' beliefs about statins and non-adherence.

Materials and methods

Study design and setting

A questionnaire was constructed and conceptualized based on a literature review. This cross-sectional survey was carried out in the department of cardiology and neurology of Xi'an People's Hospital (Xi'an Fourth Hospital) between February and June 2022. This tertiary hospital is located in Shaanxi Province of Northwestern China. It has around 1,300 beds in all and covers two districts, including 60-bed cardiology unit and 90-bed neurology unit. All the investigators had received standardized training on survey procedures and communication skills.

Study population and sample size

The inclusion criteria for participants were inpatients who 1) aged ≥18 years; 2) were diagnosed with hyperlipidemia, atherosclerosis, coronary atherosclerotic heart disease, acute coronary syndrome or prior stroke; 3) were prescribed statins (atorvastatin, simvastatin or rosuvastatin); 4) agreed to participate in the survey. It should be noted that the study population comprised not only patients who were started statin treatment during hospitalization but also those who might had been on statin treatment prior to being admitted to the hospital, regardless of when this treatment was initiated. Patients were excluded if they were too ill to participate. The exclusion criteria were inpatients who 1) had been admitted to the ICU or transferred from or to the ICU halfway; 2) experienced adverse clinical outcomes including myocardial infarction, acute cerebral infarction or death during hospitalization; 3) could not communicate due to physical or mental problems.

The minimum number of participants was calculated by using the following formula: $n = z^2p(1\text{-}p)/d^2$, where n was the sample size, z was coefficient of confidence interval (1.96), p was prevalence rate, and d was type I error level of 0.05. Adherence to long-term therapy for chronic conditions was assumed to be 50% based on previous study (Brown and Bussell, 2011; Nieuwlaat et al., 2014). A minimum sample size of 384 inpatients were required based on the above assumptions. Finally, 524 inpatients were recruited in our study.

Survey procedures

Content and validity of the original version of the questionnaire was established by an expert panel of the multidisciplinary research team (three experienced clinical pharmacists, one director of a hospital pharmacy, one professor majoring in cardiology, one professor majoring in neurology and one epidemiologist). A pilot study involving 30 participants was also conducted. The questionnaire was revised as necessary after gaining the feedback of experts, as a few questions which were hard to understand were modified or removed. Inpatients were approached by investigators in the medical wards. The purpose and content of the study were explained to eligible inpatients and written informed consents were obtained prior to being enrolled in the study. Face-to-face interviews were conducted individually, using paper-and-pencil method lasting approximately 15–20 min. Inpatients completed the questionnaire either by themselves or with help from the investigators. For the illiterate subjects, the investigators explained the meaning of the items of the questionnaire and recorded their responses. Participants returned their questionnaires to investigators immediately after completion in the wards. Investigators checked carefully for any missing information.

Measurement instruments

Two validated instruments were used: the Adherence to Refills and Medications Scale (ARMS) was used to assess statin adherence. The BMQ-Specific Scale was used to assess patients' beliefs about statins. The Chinese versions of the ARMS and BMQ-Specific scales were adapted for use in our study after we obtained authorization from the developers of the scales.

Beliefs about medicines questionnaire-specific (BMQ-specific)

The BMQ-Specific developed by Horne and Weinman (1999) was used to assess patients' beliefs about the medication prescribed for a particular illness. In brief, it comprised two scales: 1) a five-item treatment necessity scale Specific-Necessity that assessed the patients' beliefs about the necessity of taking the medication to maintain or improve their health, and 2) a six-item treatment concern scale Specific-Concerns that focused on beliefs about the treatment's potential adverse consequences (Horne and Weinman, 1999; Horne, Weinman, Hankins, 1999). Respondents must indicate their degree of agreement with each individual statement of the 11 questions on a five-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The total necessity scores were divided by 5 and the total concerns scores were divided by 6, respectively, to give a scale score ranging from 1 to 5. Higher score indicated stronger beliefs. Participants were categorized into four groups (high/low necessity and high/low concerns) based on whether they scored above or below the scale midpoint for the Specific-Necessity and Specific-Concerns scales (Horne and Weinman, 1999; Wei et al., 2017). The previous study suggested that the Chinese version of the BMQ-Specific could serve as a reliable and valid tool for assessing medication beliefs in Chinese patients (Nie et al., 2019). The internal consistency reliability of the BMQ-Specific scale was evaluated using Cronbach's α coefficient in Chinese population, which indicated a high level of reliability, with α values of 0.784 for necessity and 0.698 for concern subscales, respectively. In addition, the test-retest reliability of the BMQ-Specific scale was evaluated using the intraclass correlation coefficient (ICC), which demonstrated satisfactory reliability and stability (ICC = 0.759). Furthermore, the ratio of χ^2 to degrees of freedom (df) was 2.231, and the Goodness of Fit Index (GFI) was 0.928, while the Standardized Root Mean Square Residual (SRMR) and Root Mean Square Error of Approximation (RMSEA) were 0.074 and 0.075, respectively, indicating a good validity (Cai et al., 2020). The BMQ-Specific scale was provided as a supplementary file (see Supplementary File S1).

Medication adherence

The ARMS was developed to evaluate self-reported adherence to taking and refilling medications among patients with chronic disease (Kripalani et al., 2009; Kripalani et al., 2015). The ARMS scale comprised two subscales: eight items designed to assess adherence to taking medications and four items designed to refill prescriptions, respectively. A 4-point Likert-type scale was used to score responses as "none," "some of the time," "most of the time," and "all of the time," assuming the values from 1 to 4, respectively. Lower score, ranging from 12 to 48, represented better adherence. According to the published literature (Kripalani et al., 2009; Polanski et al., 2020), participants were classified into two groups based on their total adherence score: <16 points (adherence group) and ≥16 points (non-adherence group), respectively. The Chinese version of the ARMS scale was found to be reliable and valid for assessing medication adherence of Chinese patients with chronic disease. The internal consistency of the ARMS scale was evaluated using Cronbach's α coefficient, which indicated a high level of reliability ($\alpha = 0.731$). The test-retest reliability of the ARMS scale was assessed using Spearman's rho, which indicated satisfactory reproducibility and stability (rho = 0.871). Moreover, the criterion validity of the ARMS scale was assessed using Spearman's rho, which demonstrated satisfactory validity (rho = 0.711) (Wu et al., 2021). The ARMS scale was provided as a supplementary file (see Supplementary File S2).

Data collection

The designed questionnaire included sociodemographic, clinical data, the ARMS scale, the BMQ-Specific scale, and other information. Sociodemographic characteristics included age, gender, body height, body weight, smoking status, alcohol consumption, occupational status, place of residence, marital status, and education level. Information about diagnosis at admission, comorbidity conditions, health insurance, statin prescribed, and co-medications potentially influencing patients' adherence to statin were collected from the electronic medical records. Co-medications included anticoagulants, antiplatelets, antihypertensives, hypoglycemics and lipid-lowing agents (except statins). To assess patient-related factors associated with statin non-adherence, we collected the duration of statin treatment, patients' awareness of the primary reason for prescription of statins, regular review, and regular exercise per week. The questionnaire adopted in our study was provided as a supplementary file (see Supplementary File S3). Three branded and generic statin preparations including atorvastatin, rosuvastatin and simvastatin were available in our hospital when this study was conducted.

Outcome measurements

The primary outcome was the prevalence of statin non-adherence. Factors associated with statin non-adherence were investigated as the second outcome in our study, and the association between inpatients' beliefs about statins and non-adherence.

Statistical analysis

Basic characteristics were presented using frequencies (percentages) for categorical variables. Differences in demographic and clinical characteristics between adherent and non-adherent inpatients were evaluated using the Chi-square test

TABLE 1 Demographic and clinical characteristics of the study subjects.

Characteristics	Overall population (*n* = 524, %)	Adherent (*n* = 98, %)	Non-adherent (*n* = 426, %)	*p-value*
Age (years)				0.544
≤44	39	4(10.3)	35(89.7)	
45–54	81	17(21.0)	64(79.0)	
55–64	162	31(19.1)	131(80.9)	
65–74	148	31(20.9)	117(79.1)	
≥75	94	15(16.0)	79(84.0)	
BMI(kg/m^2)				0.986
<18.5	17	3(17.6)	14(82.4)	
18.5–23.9	173	31(17.9)	142(82.1)	
24–27.9	243	47(19.3)	196(80.7)	
≥28	91	17(18.7)	74(81.3)	
Gender				0.542
Female	185	32(17.3)	153(82.7)	
Male	339	66(19.5)	273(80.5)	
Smoking status				0.818
Non-smoker	308	59(19.2)	249(80.8)	
Current smoker	188	35(18.6)	153(81.4)	
Ex-smoker	28	4(14.3)	24(85.7)	
Alcohol consumption				**0.003***
Non-drinker	421	71(16.9)	350(83.1)	
Current drinker	81	17(21.0)	64(79.0)	
Ex-drinker	22	10(45.5)	12(54.5)	
Diagnosis				
Hyperlipidemia	28	5(17.9)	23(82.1)	0.906
Atherosclerosis	3	2(66.7)	1(33.3)	0.091
Coronary atherosclerotic heart disease	381	68(17.8)	313(82.2)	0.413
Acute coronary syndrome	141	33(23.4)	108(76.6)	0.094
Prior stroke	47	5(10.6)	42(89.4)	0.137
Duration of statin treatment				0.526
<1 year	307	57(18.6)	250(81.4)	
1–5 years	151	29(19.2)	122(80.8)	
6–9 years	35	4(11.4)	31(88.6)	
≥10 years	31	8(25.8)	23(74.2)	
Occupational status				0.797
Employed	296	55(18.6)	241(81.4)	
Unemployed	7	2(28.6)	5(71.4)	
Retired	221	41(18.6)	180(81.4)	
Residence				0.809

(Continued on following page)

TABLE 1 (*Continued*) Demographic and clinical characteristics of the study subjects.

Characteristics	Overall population (*n* = 524, %)	Adherent (*n* = 98, %)	Non-adherent (*n* = 426, %)	*p-value*
Rural	241	44(18.3)	197(81.7)	
Urban	283	54(19.1)	229(80.9)	
Health insurance				0.923
Uninsured	137	26(19.0)	111(81.0)	
Insured	387	72(18.6)	315(81.4)	
Marital status				0.798
Single/Unmarried	3	1(33.3)	2(66.7)	
Married and living with a partner	489	90(18.4)	399(81.6)	
Divorced or widowed	32	7(21.9)	25(78.1)	
Education level				0.412
≤High school graduation	423	82(19.4)	341(80.6)	
≥University (college) graduation	101	16(15.8)	85(84.2)	
Comorbidity conditions				
Hypertension	266	49(18.4)	217(81.6)	0.911
Diabetes mellitus	117	17(14.5)	100(85.5)	0.226
Atrial fibrillation	91	15(16.5)	76(83.5)	0.561
Statin prescribed				**0.023***
Atorvastatin	276	63(22.8)	213(77.2)	
Rosuvastatin	231	31(13.4)	200(86.6)	
Simvastatin	17	4(23.5)	13(76.5)	
Concurrent used drugs				
Anticoagulants	36	7(19.4)	29(80.6)	0.906
Antiplatelets	479	91(19.0)	388(81.0)	0.571
Antihypertensives	138	25(18.1)	113(81.9)	0.837
Hypoglycemics	103	14(13.6)	89(86.4)	0.138
Lipid-lowering agents (except statins)	17	3(17.6)	14(82.4)	0.910
Patients' awareness of the primary reason for prescription of statins				0.722
No	233	42(18.0)	191(82.0)	
Yes	291	56(19.2)	235(80.8)	
Necessity beliefs				**0.038***
Low	295	46(15.6)	249(84.4)	
High	229	52(22.7)	177(77.3)	
Concerns beliefs				0.261
Low	278	57(20.5)	221(79.5)	
High	246	41(16.7)	205(83.3)	
Regular review				0.920
No	281	53(18.9)	228(81.1)	
Yes	243	45(18.5)	198(81.5)	

(Continued on following page)

TABLE 1 (*Continued*) Demographic and clinical characteristics of the study subjects.

Characteristics	Overall population (*n* = 524, %)	Adherent (*n* = 98, %)	Non-adherent (*n* = 426, %)	*p-value*
Regular exercise per week				**0.043***
<3 times	246	37(15.0)	209(85.0)	
≥3 times	278	61(21.9)	217(78.1)	

The data are presented as numbers (proportions). Bold values indicate a *p*-value <0.05. BMI, body mass index.

for categorical variables, the Mann-Whitney test for skew continuous variables, and the independent sample *t*-test for normal continuous variables. Variables found to be significant at *p*-value < 0.1 from the univariable logistic regression were included in multivariable logistic regression model to characterize the independent factors associated with statin non-adherence. Receiver operator characteristic (ROC) analysis was conducted to assess the performance of the logistic regression model in predicting statin non-adherent. All analysis were performed by using the SPSS V25.0 Statistical Software Package for Windows. A *p*-value < 0.05 was considered statistically significant for all analyses.

Results

A total of 550 respondents agreed to participate in the survey. Twelve participants did not return the questionnaire and 14 questionnaires were uncompleted, 524 (95.3%) respondents were included in our study.

The mean age of the 524 participants was 63.0 ± 12.3 years, and the majority (64.7%) were male. The demographic and clinical characteristics of the study subjects were presented in Table 1. A total of 426 (81.3%) patients were non-adherent to statin. All inpatients were prescribed statin monotherapy during the study period. Atorvastatin was taken by 52.7%, rosuvastatin by 44.1% and simvastatin by 3.2% of the study population. Of the 524 inpatients, 229 (43.7%) inpatients expressed strong beliefs about the treatment necessity, while 246 (47.0%) inpatients expressed strong concerns about the potential negative effects.

Univariable and multivariable logistic regression analysis of factors associated with statin non-adherence were provided in Table 2.

In the univariable analysis, four factors were significantly associated with statin non-adherence: necessity beliefs (p = 0.039), statin prescribed (p = 0.007), alcohol consumption (p = 0.002), regular exercise per week (p = 0.044). Patients reported low necessity beliefs about statins were less likely to be adherent compared with those reported high necessity beliefs (unadjusted OR 1.590 [1.023–2.472]). Patients who were prescribed rosuvastatin were less likely to be adherent compared with those prescribed atorvastatin (unadjusted OR 1.908 [1.191–3.057]). Ex-drinkers indicated higher odds of statin adherence compared with non-drinkers (unadjusted OR 0.243 [0.101–0.585]). Patients who exercised more than 3 times regularly per week were more likely to be adherent to statin therapy compared with patients who exercised less than three times (unadjusted OR 0.630 [0.401, 0.988]).

In the multivariable logistic regression analysis (adjusted by alcohol consumption, atherosclerosis, atherosclerosis, statin prescribed, patients' necessity beliefs about statins, regular exercise per week), patients' low necessity beliefs about statins (adjusted odds ratio [OR] and 95% confidence interval [CI], 1.607 [1.019, 2.532]; p = 0.041) and prescribed rosuvastatin (adjusted OR 1.820 [1.124, 2.948]; p = 0.015) were associated with lower odds of statin adherence while ex-drinker (adjusted OR 0.254 [0.104, 0.620]; p = 0.003) was associated with higher odds of statin adherence.

The ROC curve for logistic regression model predicting statin non-adherent was shown in Figure 1. The model provided an area under the curve (AUC) for the ROC curve of 0.72 (95% CI = 0.66–0.77).

Discussion

Medication adherence has been defined as the extent to which a patient takes medications as prescribed by their healthcare providers (Osterberg and Blaschke, 2005). Based on previously published studies, medication adherence varies between 32% and 79% for statins users (Huiskes et al., 2021). A total of 426 (81.3%) patients were non-adherent to statin in our study, therefore, the adherent rate was only 18.7%. Statin adherence in our study was substantially lower than the results found in developed countries such as Netherlands (Huiskes et al., 2021), Republic of Korea (Chung et al., 2018), Finland (Rannanheimo et al., 2015) and United States (Chan et al., 2010), as well as other regions of China (Li and Huang, 2015; Zhang et al., 2022). It was reported that only 5.4% of 99,655 patients were deemed adherent among new statin users for primary prevention of cardiovascular disease during the initial 12-month follow-up period in Tianjin, which showed lower adherence level than our study (Zhao et al., 2020). It was unexpected that statin adherence was so poor in our study. The reasons may include that there was no recognized gold-standard method to measure adherence. Different definitions and measures of medication adherence contributed to the variations of adherence level among studies and population groups (Chung et al., 2018). The variable medication adherence levels among countries might also be due to different healthcare delivery systems (Osterberg and Blaschke, 2005; Bushnell et al., 2011). Literature had indicated patients with adequate medication literacy were more likely to be adherent (Zheng et al., 2020). However, the level of medication literacy among patients with coronary heart disease was suboptimal in China and needed to be improved (Zheng et al., 2020).

TABLE 2 Univariable and multivariable logistic regression analysis of factors associated with statin non-adherence.

Characteristics	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Age (years)				
≤44	1.000(Reference)			
45–54	0.430(0.134–1.379)	0.156		
55–64	0.483(0.160–1.460)	0.197		
65–74	0.431(0.142–1.306)	0.137		
≥75	0.602(0.186–1.944)	0.396		
BMI(kg/m^2)				
18.5–23.9	1.000(Reference)			
<18.5	1.019(0.276–3.761)	0.978		
24–27.9	0.910(0.551–1.504)	0.714		
≥28	0.950(0.494–1.829)	0.879		
Gender				
Female	1.000(Reference)			
Male	0.865(0.543–1.379)	0.543		
Smoking status				
Non-smoker	1.000(Reference)			
Current smoker	1.036(0.651–1.648)	0.882		
Ex-smoker	1.422(0.475–4.253)	0.529		
Alcohol consumption				
Non-drinker	1.000(Reference)		1.000(Reference)	
Current drinker	0.764(0.422–1.381)	0.373	0.773(0.420–1.421)	0.407
Ex-drinker	0.243(0.101–0.585)	**0.002***	0.254(0.104–0.620)	**0.003***
Diagnosis				
Hyperlipidemia	1.223(0.403–3.714)	0.722		
Atherosclerosis	0.094(0.008–1.171)	0.066	0.135 (0.012–1.567)	0.109
Coronary atherosclerotic heart disease	0.741(0.329–1.669)	0.469		
Acute coronary syndrome	0.530(0.239–1.177)	0.119		
Prior stroke	1.854(0.709–4.852)	0.208		
Duration of statin treatment				
<1 year	1.000(Reference)			
1–5 years	0.959(0.584–1.576)	0.869		
6–9 years	1.767(0.600–5.205)	0.302		
≥10 years	0.656(0.279–1.540)	0.333		
Occupational status				
Employed	1.000(Reference)			
Unemployed	0.571(0.108–3.018)	0.509		
Retired	1.002(0.640–1.568)	0.993		
Residence				

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TABLE 2 (*Continued*) Univariable and multivariable logistic regression analysis of factors associated with statin non-adherence.

Characteristics	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Rural	1.000(Reference)			
Urban	0.947(0.609–1.473)	0.809		
Health insurance				
Uninsured	1.000(Reference)			
Insured	1.025(0.623–1.686)	0.923		
Marital status				
Married and living with a partner	1.000(Reference)			
Single/Unmarried	0.451 (0.040–5.030)	0.518		
Divorced or widowed	0.806(0.338–1.920)	0.626		
Education level				
≤High school graduation	1.000(Reference)			
≥University (college) graduation	1.277(0.711–2.295)	0.413		
Comorbidity conditions				
Hypertension	0.967(0.617–1.515)	0.882		
Diabetes mellitus	1.500(0.838–2.685)	0.172		
Atrial fibrillation	1.249(0.681–2.291)	0.473		
Statin prescribed				
Atorvastatin	1.000(Reference)		1.000(Reference)	
Rosuvastatin	1.908(1.191–3.057)	**0.007***	1.820(1.124–2.948)	**0.015***
Simvastatin	0.961(0.303–3.052)	0.947	0.975(0.280–3.397)	0.968
Concurrent used drugs				
Anticoagulants	0.639(0.194–2.106)	0.461		
Antiplatelets	0.551(0.171–1.776)	0.318		
Antihypertensives	0.956(0.567–1.612)	0.867		
Hypoglycemics	1.642(0.876–3.077)	0.122		
Lipid-lowing agents (except statins)	1.008(0.276–3.687)	0.990		
Patients' awareness of the primary reason for prescription of statins				
No	1.000(Reference)			
Yes	0.923(0.592–1.438)	0.722		
Necessity beliefs				
High	1.000(Reference)		1.000(Reference)	
Low	1.590(1.023–2.472)	**0.039***	1.607(1.019–2.532)	**0.041***
Concerns beliefs				
High	1.000(Reference)			
Low	0.775(0.497–1.209)	0.262		
Regular review				
No	1.000(Reference)			
Yes	1.023(0.658–1.589)	0.920		

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TABLE 2 (*Continued*) Univariable and multivariable logistic regression analysis of factors associated with statin non-adherence.

Characteristics	Unadjusted OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Regular exercise per week				
<3 times	1.000(Reference)		1.000(Reference)	
≥3 times	0.630(0.401–0.988)	**0.044***	0.665(0.418–1.059)	0.085

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

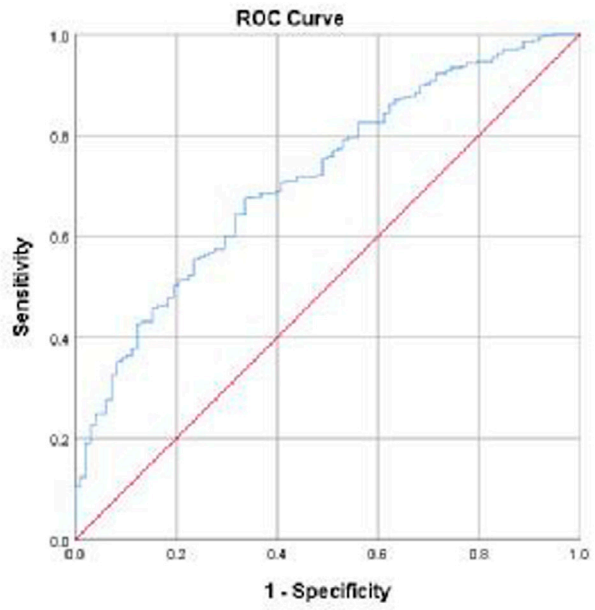

FIGURE 1
Receiver Operating Characteristic (ROC) curve for logistic regression model predicting statin non-adherent: AUC of ROC curve = 0.716 (95% CI = 0.663–0.770). The ROC curve was produced in SPSS.

Furthermore, new statin users were more likely to be non-adherent compared with previous users (Kopjar et al., 2003). It was reported that the first 180 days of follow-up was the most critical period when many patients became non-adherent or discontinued treatment (Ofori-Asenso et al., 2018). It appeared that 48.2% of the patients were non-adherent among new statin users, and 23.9% discontinued within the first treatment year (Ofori-Asenso et al., 2018). A total of 307 (58.6%) inpatients in our study commenced statin therapy in the past year, which might contribute to poor statin adherence in our study as well.

Both unadjusted and adjusted results revealed that low necessity beliefs were significantly associated with non-adherence. Our findings were consistent with previous findings that the odds of non-adherence were significantly increased when patients reported low necessity beliefs (Horne and Weinman, 1999; Horne et al., 2013; Foot et al., 2016; Huiskes et al., 2021). Study had mentioned that illness perception was an underlying factor for beliefs about the treatment necessity (Horne, Weinman, Hankins, 1999). The higher perception of illness was associated with increased likelihood of stronger agreement on the necessity of treatment, as well as better adherence to the therapy (Chung et al., 2018; Cai et al., 2020). Stronger beliefs in the necessity of the medication occurred in patients who believed their illness to be lasting or experienced more symptoms (Horne, Weinman, Hankins, 1999). Patients with asymptomatic diseases who did not realize the need to take medicine were more likely to be non-adherent (Xu et al., 2020). Low adherence may be a choice between patients' assessment of their personal treatment needs and their concerns about the potential adverse consequences of taking medicine (Cai et al., 2020). Our analysis found Specific-Concerns was not associated with non-adherence. Patients' awareness of the primary reason of statin therapy was also not found to be associated with non-adherence in our study. Further investigation is required to measure the association between patients' beliefs and their adherence.

Atorvastatin was the most frequently prescribed statin in our study, which was consistent with previous study (Hsieh et al., 2017). Inpatients who took rosuvastatin during the study period had lower adherence than atorvastatin. Limited literature had revealed direct association between types of statins and adherence. One study revealed that patients were more adherent to atorvastatin compared with other statin preparations (Xie et al., 2022), which was in accordance with our study. Another study found that patients prescribed atorvastatin or rosuvastatin indicated higher odds of statin adherence compared with those prescribed simvastatin (Morotti et al., 2019). It was also reported that the persistence was higher with atorvastatin compared with simvastatin (Huser et al., 2005). Higher likelihood of adherence to atorvastatin might be due to its better tolerability, efficacy and safety (Xie et al., 2022).

There were conflicting data regarding the association between alcohol consumption and medication adherence. It was reported that alcohol consumption was associated with increased risk for medication non-adherence (Bryson et al., 2008). However, a study in Republic of Korea revealed that ex-drinkers were less adherent to statins than drinkers (Chung et al., 2018). Our study suggested that ex-drinkers indicated higher odds of statin adherence compared with non-drinkers. In the univariable analysis, patients who exercised more than three times regularly per week were more likely to be adherent to statin therapy compared with patients who exercised less than three times. The finding in our study was contrary to previous study, which revealed that regular exercise per week was not associated with adherence (Chung et al., 2018). These findings might be explained by the fact that patients with healthy lifestyle might adherent because they were more likely to seek for healthier behaviors (Brookhart et al., 2007).

Poor adherence limited the efficacy of statin therapy, which might trigger risk of cardiovascular and cerebrovascular adverse events (Gomez Sandoval et al., 2011; Xu et al., 2017). A variety of

effective interventions were recommended to improve medication adherence (Bates et al., 2009; Gatwood and Bailey, 2014). Compared with the demographic and clinical factors associated with non-adherence, patients' beliefs were more readily modifiable (Clifford et al., 2006). Optimal adherence to medications could be supported by taking account of patients' necessity beliefs and concerns (Horne et al., 2013). More effective communication with patients is crucial to emphasize the importance of continuous statins therapy even under the conditions of asymptomatic, and make them aware of the potential risk of adverse health outcomes (Maningat et al., 2013; Banach et al., 2016; Kruger et al., 2018; Tan et al., 2019). However, clinicians were required to meet more patients in less time, which made it was difficult to perform enough communication with patients (Nieuwlaat et al., 2014). Study have revealed insufficient communication between patients and their doctors regarding the prescription, and 32% overall and 24% of patients with 3 or more chronic conditions reported no dialogue with their doctor about all their medicines in the last 12 months (Wilson et al., 2007). The lack of adequate explanation about the diseases as well as the benefits and potential side effects of medication provided by the clinicians were acknowledged as strong contributors to non-adherence (Devaraj et al., 2017; Brinton, 2018). Many patients discontinued statin use because of uncertainty about the benefits of statins and concerns about adverse effects (Fung et al., 2010). Considering that clinicians have limited time, nurses or pharmacists-led education programs and reminder systems have been shown to be active interventions to improve statin adherence (De Geest and Sabate, 2003; Bates et al., 2009; Marzec and Maddox, 2013; Gatwood and Bailey, 2014; Nieuwlaat et al., 2014). A better assessment of the patients' needs and barriers to medication adherence could be performed through face-to-face education. Education augments the health literacy of patients and improves medication adherence by increasing the knowledge of their conditions, complications and management (Tan et al., 2019). Pharmacist-led counseling program on medication adherence for patients helped establishing a routine of daily self-medication and potentially improved their long-term clinical outcomes (Taitel et al., 2012).

Strengths and limitations

This is the first study to assess patients' adherence to statins and explore the association between beliefs about medicines and self-reported adherence in the Northwestern China. A better understanding of the prevalence of statin non-adherence and barriers to statins adherence is critical for designing effective interventions to improve adherence. We believe that this study will help healthcare providers understand that non-adherence to statins is a serious problem for patients. Inpatients who had stronger doubts about their personal need for statins were significantly more likely to be non-adherent. Our findings provide a basis for future accessible and systematic interventions to improve medication adherence in China. Our study has several limitations. First, it was conducted in one hospital, which could not represent the general situation in China. Prospective designs in a wide range of settings are necessary for a thorough assessment of the role of beliefs in predicting non-adherence. The second one is that adherence was only measured by a self-reported questionnaire in this study. Although the ARMS Scale has been validated as a measure of general behavior in chronic diseases, self-reported adherence may not be the best measurement for medicine adherence because of subjective and sensitive to social desirability bias (Huiskes et al., 2021). Third, the majority of patients in our study were elder people with multiple comorbidities. As potential factors affecting medication adherence, polypharmacy, health literacy, drug side effects and the price or out-of-pocket to obtain statins were not investigated in the current study, these could be the reasons for poor adherence in our study. In addition, there were differences in adherence to statin therapy between new users and previous users. Inpatients were not stratified according to the duration of statin treatment, which might lead to bias. Further prospective research is required to confirm the factors associated with statin adherence.

Conclusion and implications

Statin adherence was poor in the Northwestern China. This study indicated a significant association between patients' lower necessity beliefs and statin non-adherence. More attention should be focused on statin non-adherence in China. In addition, our results also suggested that groups of individuals who were prescribed rosuvastatin were less adherent, and patients who were ex-drinker might adherent. Nurses and pharmacists could play an important role in patient education and patient counseling in order to improve medication adherence.

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 the Ethical Committee of Xi'an People's Hospital (Xi'an Fourth Hospital) (No: 20220087). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: HL, YlZ, and HW. Data collection: HL, HM, and YYZ. Methodology and software: HL, HM, and XJ. Supervision: YlZ and HW. Original draft: HL. Critical revision of the manuscript: YlZ, HW, and XJ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

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Outpatient depression current care expenditure changes in Liaoning Province from 2015 to 2020: a study based on the "system of health accounts 2011"

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Introduction: Depression is the leading cause of disability worldwide and has become a health issue of global concern. Based on the "System of Health Accounts 2011" (SHA 2011) for patients with depression, this paper studies the changes in the current curative expenditure (CCE) of outpatient depression in Liaoning Province, China, and provides policy recommendations.

Method: A stratified multistage random sample of 56,994 patients with depression included from 1,227 healthcare facilities in Liaoning Province were included. The significance of differences in variables within groups was analyzed by univariate analysis (including descriptive statistics analysis, Mann-Whitney U test and Kruskal–Wallis H test), and factors influencing depression outpatient CCE were analyzed by multiple linear regression analysis and constructing structural equation models (SEM).

Results: The CCE of outpatient depression was ranging from CNY 75.57 million to CNY 100.53 million in 2015–2020, with the highest of CNY 100.53 million in 2018, CNY 103.28 million in 2019. Medical expenditures are mainly concentrated in general hospitals and provincial healthcare institutions, accounting for about 90% of all provincial scope expenditures. The multiple regression results show that provincial healthcare institutions, purchase of drug, select medical treatment for depression, general hospitals and urban employees' health insurance are the main influencing factors for depression outpatient CCE. The results of SEM show that insurance status negative impact outpatient expenditure.

Conclusion: Health insurance is an important factor in equitable access to healthcare resources for patients, and medication expenditure is the influential factor affecting the high expenditure of outpatient clinics. It is of great importance to reduce the medical burden of patients by increasing the coverage of medical

insurance, increasing the proportion of bills that are eligible for reimbursement, and improving the system by guaranteeing the supply of psychotropic medication.

KEYWORDS

depression, outpatient expenditure, CCE, SHA 2011, burden of disease

1 Introduction

Depression has four indicators of alarm: high prevalence, high relapse rate, high disability rate and high suicide rate. Depression has been a leading cause of disability globally for decades (Collaborators, 2018), accounting for 1.8% of global disability-adjusted life years (DALYs) and is the second leading cause of death after cancer (Wu et al., 2010). According to the World Health Organization (Lepine and Briley, 2011; Organization, 2012), 280 million people globally suffered from depression in 2019, and depression is the leading causative factor for mental illness in the next decade. Depression affects approximately 3.8% of the global population (Institute for Health Metrics and Evaluation, 2019), with prevalence rates ranging from 3.9% to 6.0% (2.63–5.45 million people) in European countries (including the United Kingdom, Russia, Germany, Italy, and Spain), 4.9% (15.29 million people) in the United States, and 2.7% (3.26 million people) in Japan (Institute for Health Metrics and Evaluation, 2019). In the UK, 1.7 billion, £203.5 billion is spent annually on depression treatment, medication purchases (National Institute for Clinical Excellence, 2009; Health and Social Care Information Centre, 2017). Globally, depression and anxiety disorders cost the world up to $1 trillion per year (World Health Organization, 2017). In addition to causing death, depression reduces worker productivity and increases the risk of absenteeism. Even with aggressive cognitive-behavioral therapy and medication, all depressive symptoms are rarely eliminated, and the risk of persistence and relapse is high. As China's economy grows, the number of people with depression has gradually increased, reaching 5,005.5 million in 2019, accounting for 3.7% of China's total population (Institute for Health Metrics and Evaluation, 2019), and is one of the main contributors to the number of disability-adjusted life years in China in 2010 (Yang et al., 2013). The prevalence of depression and DALYs are higher in northeastern China (Ren et al., 2020). Due to the high disability and prevalence of depression, depression is mainly treated through medication and counseling, which is a long and costly treatment cycle. As a result, costs associated with the treatment of depression are likely to account for a significant proportion of healthcare costs.

One study used econometric modeling to examine healthcare costs associated with depression and depressive symptoms, estimating projected healthcare costs for depression and depressive disorders based on a two-step approach with a two-part model and four-part model coefficients (Hsieh and Qin, 2018) and analyzing antidepressant use and expenditures based on evidence from urban claims data in China (Ding et al., 2022). Patient and self-medication visits (Jin et al., 2022), as well as the economic burden of hypertension and depression (Wu et al., 2021). Were assessed based on data from the China Health and Retirement Longitudinal Study (CHARLS) database and using a zero-inflated Poisson regression model, including a Logit model predicting multiple zeros and a Poisson count model. Previous studies have analyzed and estimated healthcare expenditures for depression in China based on information from different databases, but it is likely that each study used a different estimation model, which is less informative for assessing overall expenditures for depression in China. Currently, a study in Shandong Province analyzed hospitalization costs for childhood depression (Guo et al., 2019), but to our knowledge, no studies have been found that provide a systematic accounting framework for subnational depression costs, and the lack of analysis of the costs of different dimensions, such as the extent and type of depression healthcare institutions, financing structure, and disease type, reduces the accuracy of the measurements and the different countries' Comparability.

There is a need to determine how to estimate the economic burden of depression in a highly accurate and recognized way. The current highly recognized and widely used methodology for measuring healthcare costs is SHA2011. SHA2011 was revised by the Organization for Economic Cooperation and Development, Eurostat (EUROSTAT), and the World Health Organization, which jointly organized a group of experts on health costing to follow the System of National Accounts (SNA) and the Principles of Health Cost Accounting (PNA). This led to the establishment of an international health costing classification and statistical reporting system that reflects the sources of health financing. The separate allocation and use of health funds makes health costs measured using this system more relevant, feasible and sustainable.

Therefore, based on the SHA2011 accounting framework and using sample data from Liaoning Province, this study measured the outpatient costs of depression in Liaoning Province and further assessed the relationship between outpatient services in terms of healthcare institutions, degree and type of disease, financing structure, beneficiary populations, and economic burden of depression, which can lead to a more meaningful analysis of healthcare resources, cost containment, and control strategies, and provide policy recommendations for the province of Liaoning, and even for China Provide policy recommendations for depression cost control.

2 Materials and methods

2.1 Data sources

Four sources contributed to the research data. The Statistical Yearbook of Health and Family Planning of Liaoning Province (2015–2020), the Liaoning Provincial Health Financial Annual Report (2015–2020), the Liaoning Provincial Government Health Investment Monitoring Data (2015–2020), and the Liaoning Provincial Statistical Yearbook, are the statistical data from the health and related administrative departments that represent the total cost of treatment services in Liaoning Province (2015–2020). Sample data from the multistage stratified probabilities-proportional

random sampling approach was used to collect patient healthcare costs, population data and clinical information about healthcare facilities (Ma et al., 2020; Fang et al., 2021). Dalian, Fushun, Jinzhou, Panjin and Tieling cities were selected to conduct random, multistage spot checks in the first analytic phase, including the following variables GDP, national income, national income *per capita* and population density. In the second phase, the quality of data collection and the accuracy of health information systems (medical insurance system, patient consultation information record system, and medical and health cost details) were included from one district and two counties were selected in each sample city totaling 15 district and county sample sites identified. In the third phase, the medical and health institutions in the 15 sample districts and counties were selected according to the type and level of medical institutions, including 83 public health institutions (disease prevention and control institutions, maternal and child health institutions, health education institutions, emergency centers, blood centers, family planning guidance institutions, health supervision institutions and specialized disease control institutions), 83 medical institutions (public hospitals and private hospitals), 1061 grassroots institutions (community health service institutions, health centers, outpatient clinics, clinics, and village health offices), totaling 1,227 medical and health institutions. Through the health information system, the medical records of outpatients and inpatients from various institutions were gathered and a database was created with data on gender, age, region, date of consultation, initial diagnosis, disease name, type of medical institution, total cost, cost details and insurance type (Zhai et al., 2015). The sample data were cleaned and checked using the ICD-10 disease classification code to determine the severity of diseases. Only incident depression diagnoses were chosen for the sample data and additional diagnoses were not taken into account. To find, recode or delete ICD-10 data that does not adhere to the standard, we used Excel's VLOOKUP function. We also cleaned and coded gender, age, cost, institution type, institution level and insurance type following the export template for outpatient and inpatient expenses of the health information system.

2.2 Study samples

The study sample included patients with depression who were initially diagnosed by a professional clinician at a healthcare facility between 1 January 2015 and 31 December 2020. The sample inclusion criteria used the International Classification of Diseases, 10th Revision (ICD-10) to identify F32-F33 as patients with depression. Patients with depression are classified as F32-F33; 1) mild depression (F32.0, F33.0); 2) moderate depression (F32.1, F33.1); 3) major depression (F32.2, F32.3, F33.2, F33.3); 4) other depression (F32.8, F32.9, F33.8, F33.9) (Ding et al., 2022). For all diseases we treated as missing values the disease name and disease ICD-10 of the outpatient visit information submitted by the sample organizations as null values, and we had to discard such data because we could not take estimation or other replacement supplementation methods for the null values of the disease name and disease ICD-10. Liaoning province based on SHA2011 accounting for the total cost of health mental illness specialized hospitals only in Dalian Seventh People's Hospital, and part of the year in the sample pool does not have data for this institution, in view of the uniformity of the data sample institutions, so it was decided to remove the sample of depression in this institution. Among all health facilities, the cost of hospitalization was determined to be too low after screening the sample data, thus only the financial burden of outpatients diagnosed with depression was investigated (Table 1).

2.3 Quality control and data management

Sample data were collected from the total health cost accounting management system by professional clinicians at all levels and in all types of medical institutions based on disease diagnoses recorded as ICD-10 codes. Relevant personnel involved in the study received professional training from experts at the National Health Commission's Centre for Health Development Studies conducted an on-site evaluation of the effectiveness of the training, and only those who passed the assessment could participate in the formal data processing. During the data collection process, the missing, incorrect or unreasonable data provided by the agency in the total health cost accounting management system were identified, returned to the source agency, and resubmitted to the system upon change or addition. Patient personal information for the sample data was digitally coded, and names and specific identities were not disclosed, therefore the local institutional review board waived patient consent. Sample data collected were cleaned and screened according to ICD-10 disease classification codes, and only patients diagnosed with depression for the first time were selected to have multiple disorders in the sample data, regardless of other co-morbidities. The VLOOKUP function was used in Microsoft Excel (Excel 2013; Microsoft Corporation, Redmond, Washington, USA) to find, recode, or delete non-compliant ICD-10 data for gender, age, cost, facility type, facility classification and insurance types. Data were cleaned and coded according to the Health Information System outpatient and inpatient cost export templates. All processed sample data were statistically and statistically analyzed using STATA 15.0 (Stata Corp of Texas, USA).

2.4 Estimating CCE for depression in the frame of SHA 2011

SHA2011 is a standard technique for policy analysis and financial flow description that is similar globally. The distribution of beneficiaries, institutional allocation and the flow of health funding, including long-term care, rehabilitation and treatment services are all described in detail. The total outpatient revenue of various institutions at all levels was derived from the official statistical data of the Liaoning Provincial Health Statistical Yearbook and the Liaoning Provincial Financial Annual Report based on the SHA2011 theoretical framework. The Liaoning Province CCE was calculated using the outpatient diagnosis of depression based on the institution type (general hospital, traditional Chinese medicine hospitals, specialized hospitals, specialized public health institutions, maternal and child health institutions, primary medical institutions, outpatient departments), age group (5 years old as a gradient) and various disease categories. Outpatient CCE included income from outpatient treatment and subsidies for the

TABLE 1 Composition of outpatient and hospitalization expenditure in Liaoning Province, 2015–2020.

Year	Outpatient expenditure (million (%))	Hospitalization expenditure (million (%))	Total
2020	98.04 (95.93)	4.16 (4.07)	102.20 (100.00)
2019	103.28 (93.74)	6.89 (6.26)	110.17 (100.00)
2018	100.53 (92.26)	8.44 (7.74)	108.97 (100.00)
2017	97.86 (95.66)	4.43 (4.34)	102.29 (100.00)
2016	85.99 (93.94)	5.55 (6.06)	91.54 (100.00)
2015	75.57 (91.04)	7.44 (8.96)	83.01 (100.00)

basic expenses of outpatient treatment. Outpatient curative income was mainly the income obtained by medical institutions from the provision of routine medical services, the basic expenditure subsidy of outpatient clinics was the financial input subsidies provided by the government to guarantee the routine functioning of medical institutions. The formula is as follows:

$$S_{OCCE} = S_{OCI} + S_{OCBES}$$

In the above formula, S_{OCBES} indicates outpatient CCE. S_{OCI} indicates outpatient curative income, including treatment fee, drug fee, registration fee, consultation fee, check fee, surgery fee, test fee, and other fees. Outpatient curative basic expenditure subsidy included personnel expenses, and public expenses (office expenses, printing expenses, travel expenses, water and electricity expenses, postal and telecommunication expenses, vehicle expenses, special materials, conference expenses, training expenses, etc.). To calculate outpatient curative income, it is necessary to first obtain the total outpatient income of various types of medical institutions at all levels from the Liaoning Provincial Statistical Yearbook and the Liaoning Provincial Financial Annual Report, and then exclude the preventive service costs of various types of institutions at all levels in the case database of the sample institutions. The formula is:

$$S_{OCI} = S_{TOI} \times \left(1 - \frac{\alpha_p}{\alpha}\right)$$

The above formula S_{TOI} represents the total outpatient revenue of Liaoning Province, α_p represents the revenue from outpatient preventive services of representative sample institutions, α represents the total outpatient revenue of sample institutions, $\frac{\alpha_p}{\alpha}$ represents the proportion of preventive service revenue of representative sample institutions to total outpatient revenue, $1 - \frac{\alpha_p}{\alpha}$ represents the proportion of outpatient treatment service revenue of representative sample institutions to total outpatient revenue.

The formula for calculating the actual outpatient treatment income represented by the cases in the sample institutions is as follows:

$$S_{iOCI} = S_{OCI} \times \frac{\alpha_i}{\alpha - \alpha_p}$$

In the above formula, α_i indicates the total EXP for cases in sample institutions, $\frac{\alpha_i}{\alpha - \alpha_p}$ represents the ratio of the total EXP of a case to the sum of the total EXP of all cases in the current sample institution, and S_{iOCI} refers to the value of the actual outpatient treatment income that a case represents.

After calculating the real value of outpatient treatment income represented by cases, the income from outpatient treatment in different dimensions was obtained by adding the age groups and disease types. The age group was based on a gradient of 5 years old, and the disease type was based on four categories of the global burden of disease (GBD) and 22 categories of ICD_10 outpatient treatment income from different perspectives. The formula is as follows:

$$S_{nOCI} = \sum_{i=1}^{n}\left(S_{OCI} \times \frac{\alpha_i}{\alpha - \alpha_p}\right)$$

The outpatient curative basic expenditure subsidy was obtained from the financial basic appropriation income of various medical institutions at all levels from the Liaoning Provincial Statistical Yearbook and the Liaoning Provincial Financial Annual Report, as the total outpatient curative basic expenditure subsidy, and the service volume selects the general emergency of various medical institutions at all levels, including the number of visits and total hospital bed days. The basic expenditure subsidy was calculated based on workload and did not include the proportion of outpatient preventive services in the sample institutions as a proportion of the total number of consultations in the sample institutions. The formula is as follows:

$$N_{OCI} = N_{TOI} \times \left(1 - \frac{N_p}{N_{OS}}\right)$$

In the above formula, N_{TOI} represents total outpatient and emergency visits, N_{OCI} represents the total number of treatment services, N_p represents the number of outpatient preventive services in sampled institutions, N_{OS} represents the total number of outpatient visits in sampled institutions, $\frac{N_p}{N}$ represents service outpatient as a percentage of the total number of visits to sampled institutions. Due to the difference between the workload of physicians' outpatient clinics and inpatient workloads, the basic expenditure subsidy for therapeutic outpatient clinics was calculated according to the service volume, and the service volume was unified. The calculation formula of the proportion of hospitalized bed days to the total service volume was as follows:

$$P_{IS} = \frac{N_{IS}}{N_{IS} + N_{OCI}{}^{*}K}$$

In the above formula, P_{IS} represents the proportion of inpatient services to total services, N_{IS} represents total hospital bed days, K is

a constant according to the recommendation of the National Health Development Research Center of China, $K = 0.1$.

To calculate the outpatient curative basic expenditure subsidy, the proportion of inpatient services in the total service volume was excluded. The calculation formula is as follows:

$$S_{OCBS} = S_{TOCBS} \times (1 - P_{IS})$$

In the above formula, S_{TOCBS} represents fiscal basic appropriation income obtained from statistical yearbooks and financial annual reports.

The formula of the actual outpatient treatment basic expenditure subsidy represented by the cases in the sample institutions is as follows:

$$S_{iOBES} = S_{OCBES} \times \frac{\alpha_i}{\alpha - \alpha_p}$$

In the above formula, S_{iOBES} represents the case represents the actual basic expenditure subsidy for outpatient treatment.

After calculating the actual outpatient treatment basic expenditure subsidy represented by the case, the outpatient treatment basic expenditure subsidy of different dimensions was obtained according to the age group and the type of disease. The age group was based on a gradient of 5 years old, and the disease types are subsidized for basic outpatient treatment from different perspectives in four categories of GBD and 22 categories of ICD_10. The formula is as follows:

$$S_{nOCBES} = \sum_{i=1}^{n}\left(S_{OCBES} \times \frac{\alpha_i}{\alpha - \alpha_p}\right)$$

To calculate CCE through financing plans, government plans (basic expenditure subsidies, medical assistance for urban and rural residents), social medical insurance plans (urban workers, urban residents, new rural cooperative medical system, work injury, unemployment, pension, maternity insurance), commercial medical insurance, non-profit organization financing (charitable donations), corporate financing (medical assistance for corporate employees), and household personal hygiene expenditures include residents' hygiene expenditures were included (Patel et al., 2007).

2.5 Factors influencing outpatient expenditures

We screened a total of 56,994 depression outpatient sample data from a total of 32,185,646 outpatient sample data over 6 years (5,726 outpatient patients with depression were gathered in 2015, followed by 6,462 in 2016, 5,066 in 2017, 12,220 in 2018, 10,910 in 2019 and 16,610 in 2020). Univariate analysis was used to set dummy variables for categorical variables for subsequent analysis, including descriptive statistics. Dichotomous variables included whether to purchase drug, whether to select treatment and sex, therefore, using Mann-Whitney U test yielded $p < 0.05$ as inclusion criteria for multifactorial analysis and multicategorical variables included age, insurance status, institution level, institution type and year, and the Kruskal–Wallis H test was used to derive $p < 0.05$ as inclusion criteria for multifactorial analysis. The factors influencing depression outpatient CCE were analyzed by using the logarithmically transformed depression outpatient costs as the dependent variable and including all independent variables that underwent univariate analysis by multiple linear regression analysis. We used IBM SPSS Statistics V.25.0 (IBM Corp) for univariate and multifactor analyses of depression outpatient clinics. AMOS Graphics, V24.0 (SPSS) was used to construct SEM to explore the factors influencing the cost of depression outpatient clinics.

2.6 Patient and public participation

Data for this study were obtained directly from the Total Health Cost Accounting System. Therefore without patient and public participation.

3 Results

3.1 The basic result of depression

Since 95% of depressed patients were concentrated in outpatient clinics, we studied only outpatient depressed patients with CCE. Generally speaking, from 2015–2020, the CCE of depression increased from CNY 75.57 million in 2015 to CNY 98.04 million in 2020, with the highest of CNY 100.53 million in 2018, CNY 103.28 million in 2019. In comparison to these 6 years of results, depression outpatient CCE 2015-2019 has been growing fast and then slow, with a slight drop in CCE in 2020, possibly due to the novel coronavirus affecting the normal operation of healthcare facilities, which has the same trend as CCE/GDP. However, the proportion of all disease CCE over 0.06%, was an unstable change trend. Depression treatment costs *per capita* also increased from CNY 1.72 in 2015 to CNY 2.30 in 2020 (Table 2).

3.2 Distribution of CCE among different groups

For the percentage of results of different subgroups of depression outpatient CCE, the main focus was on the choice to purchase medication, choice of treatment, female, 15-64 years, self-pay, provincial health facilities and general hospitals. The highest percentage of answering "yes" to whether to purchase drug was 97.32% in 2015. The highest value was 92.68 million CNY in 2019. The highest percentage of answering "yes"to whether to purchase drug was 67.72% in 2016, with a maximum value of 58.23 million CNY in 2016. The highest percentage of sex was 69.66% for females in 2020, with a maximum value of 68.30 million CNY. Age group share was highest at 87.39% in 2016 and maximum at 86.83 million in 2019. Insurance status share was highest at 88.02% self-pay in 2015 and maximum at 82.96 million CNY in 2020. Institutional level share was highest at 90.45% in 2017 for provincial health facilities and the maximum is 92.89 million CNY in 2019. The highest percentage of institution type is 96.93% for general hospitals in 2018 and the maximum is 97.44 million CNY in 2019 (Table 3).

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TABLE 2 Distribution of outpatient CCE for depression in the province from 2015 to 2020.

Year	Depression outpatient CCE(million)	The proportion of all diseases CCE(%)	The proportion of GDP (%)	Depression CCE *per capita* (yuan)
2015	75.57	0.072	0.003	1.72
2016	85.99	0.070	0.004	1.96
2017	97.86	0.066	0.004	2.24
2018	100.53	0.067	0.004	2.31
2019	103.28	0.064	0.004	2.37
2020	98.04	0.061	0.004	2.30

3.3 Allocation of CCE for different types of depression

Overall, the CCE for different types of depression showed a rising and then falling trend, the changing trend of CCE for other depression was consistent, for mild depression and major depression CCE kept increasing with the year, for moderate depression CCE showed a falling trend from 2015–2018 and gradually rebounded from 2018–2020. ICD-10 mainly divided depression into four categories, other depression CCE is the highest, followed by moderate depression, then by major and mild depression. In 2019, other depression outpatient treatment costs peaked at CNY 103.28 million. The highest cost for mild depression was CNY 3.10 million in 2020 and the lowest cost was CNY 0.74 million in 2015. The highest cost of moderate depression is CNY 5.07 million in 2020 and the lowest is CNY 4.33 million in 2018. The highest cost of major depression was CNY 2.52 million in 2020 and the lowest was CNY 0.59 million in 2015 (Table 4).

3.4 Distribution of CCE by age

The CCE of depression varies greatly by age group. In general, CCE for depression starts to increase rapidly after the age of 14, peaking at CNY 14.77 million and CNY 14.60 million for the 15–19 age group in 2020 and 2019, peaking at CNY 9.58 million for the 20–24 age group in 2018, peaking at CNY 10.08 million in the 30–34 age group in 2017, the 60–64 age group peaked at CNY 9.01 million in 2016, the 50–54 age group peaked at CNY 8.25 million in 2015. The age group from 15–64 is dominant in the 2015–2020 fee and shows a wave shift for each age group. However, those below 15 years and above 64 years contribute less to depression CCE(Figure 1).

3.5 Health financing schemes

From 2015 to 2020, out-of-pocket (OOP) costs first increased by CNY 7.11 million, from CNY 30.01 million in 2015 to CNY 37.12 million in 2018, and then decreased by CNY 0.36 million, from CNY 37.12 million in 2018 to CNY 36.76 million in 2020. Meanwhile, the OOP share first decreases by 4.71%, from 39.72% in 2015 to 35.01% in 2019, then increases by 2.49% from 35.01% in 2019 to 37.50% in 2020. Between 2015 and 2020, public financing first increased by CNY 19.58 million, from CNY 38.18 million in 2015 to CNY 57.76 million in 2019, then decreased by CNY 4.77 million from CNY 57.76 million in 2019 to CNY 52.99 million in 2020. The public financing share shows an opposite trend to the OOP share, first increasing by 5.40%, from 50.52% in 2015 to 55.92% in 2019, then decreasing by 1.87% from 55.92% in 2019 to 54.05% in 2020. Overall, public financing and basic social health insurance are the main sources of funding for outpatient depression costs, with an overall OOP share of more than 35% and a smaller voluntary financing share of less than 10% (Table 5). The average cash flow from 2015 to 2020 from the "three services and one business" to four types of medical institutions: general hospitals, specialty hospitals, traditional Chinese medicine hospitals, primary healthcare institutions (community health centers, community health service stations, township health centers, health centers, village health centers, etc.) are shown in the Sankey diagram (Figure 2). The three financing schemes flow mainly to general hospitals, followed by traditional Chinese hospitals. General hospital financing is dominated by public financing and OOP.

3.6 Factors influencing outpatient expenditures

Descriptive analysis, Mann-Whitney U test and Kruskal–Wallis H test of depression outpatient costs according to the number of independent samples included in different groups showed that depression outpatient costs were significantly different ($p < 0.001$) by whether to purchase drug, whether to select treatment, sex, age, insurance status, institution level, institution type and year. (Table 6).

The influencing factors of outpatient expenditure of depression in Liaoning Province were analyzed by multiple regression in Table 7. The included independent variables include whether to purchase drug, whether to select treatment, sex, age, insurance status, institution level, institution type and year. There were multiple covariates between the independent variables and no covariates between the independent variables and the response variables, so all independent variables were included in the regression equation ($p < 0.01$) and the linear model explained 38.4% of the variation in total outpatient costs. From the standardized regression coefficients, the positive effect on depression outpatient costs was in the order of provincial healthcare institutions, purchase drug, municipal level, select treatment, 15–64 age group, etc. The negative influence on the cost of depression outpatient clinics was in the order of traditional

TABLE 3 Distribution of outpatient expenses for depression by whether to purchase drug, whether to select treatment, sex, age, insurance status, institution level and type of medical institution, 2015–2020 (million (%)).

	2015	2016	2017	2018	2019	2020
Whether to purchase drug						
Yes	73.54 (97.32)	82.59 (96.05)	93.75 (95.80)	91.92 (91.43)	92.68 (89.74)	87.59 (89.34)
No	2.03 (2.68)	3.340 (3.95)	4.11 (4.20)	8.61 (8.57)	10.60 (10.26)	10.45 (10.66)
Whether to select treatment						
Yes	49.13 (65.01)	58.23 (67.72)	52.59 (53.74)	55.38 (55.08)	53.40 (51.70)	56.85 (57.98)
No	26.44 (34.99)	27.76 (32.28)	45.27 (46.26)	45.15 (44.92)	49.88 (48.29)	41.19 (42.02)
Sex						
Female	48.84 (64.62)	55.10 (64.08)	64.53 (65.94)	67.21 (66.86)	67.43 (65.29)	68.30 (69.66)
Male	26.73 (35.38)	30.89 (35.92)	33.33 (34.06)	33.32 (33.14)	35.85 (34.71)	29.74 (30.34)
Age						
0–14	0.33 (0.43)	0.24 (0.28)	0.63 (0.64)	1.72 (1.71)	3.75 (3.63)	5.07 (5.17)
15–64	64.37 (85.18)	75.14 (87.39)	83.89 (85.72)	86.27 (85.82)	86.83 (84.07)	81.90 (83.54)
≥65	10.87 (14.39)	10.60 (12.33)	13.34 (13.63)	12.54 (12.47)	12.71 (12.30)	11.07 (11.29)
Insurance status						
Urban employees' basic medical insurance	8.43 (11.16)	10.81 (12.57)	13.94 (14.24)	13.58 (13.51)	14.97 (14.49)	14.84 (15.13)
Urban residents' basic medical insurance	0.02 (0.03)	0.24 (0.28)	2.15 (2.20)	3.30 (3.29)	6.24 (6.04)	0.18 (0.18)
New rural cooperative medical care	0.09 (0.12)	0.14 (0.16)	0.18 (0.18)	0.32 (0.32)	0.59 (0.57)	0.07 (0.07)
Self-funded	66.52 (88.02)	74.57 (86.72)	81.45 (83.23)	82.54 (82.11)	81.48 (78.89)	82.96 (84.62)
Institution level						
Provincial level	67.45 (89.25)	77.68 (90.33)	88.52 (90.45)	90.29 (89.81)	92.89 (89.93)	87.62 (89.37)
Municipal level	8.03 (10.63)	8.22 (9.56)	8.92 (9.12)	10.02 (9.97)	10.26 (9.94)	9.88 (10.08)
District level	0.07 (0.09)	0.07 (0.08)	0.36 (0.37)	0.20 (0.20)	0.11 (0.10)	0.38 (0.39)
Country level	0.02 (0.03)	0.03 (0.03)	0.06 (0.07)	0.02 (0.02)	0.03 (0.03)	0.16 (0.16)
Institution type						
General hospital	71.36 (94.43)	79.29 (92.20)	92.83 (94.86)	97.44 (96.93)	97.55 (94.45)	89.78 (91.58)
Traditional Chinese medicine hospital	4.12 (5.45)	6.44 (7.49)	4.43 (4.53)	3.07 (3.05)	5.28 (5.11)	7.87 (8.03)
Specialized hospital	0.09 (0.11)	0.27 (0.31)	0.37 (0.38)	0.00 (0.00)	0.02 (0.02)	0.31 (0.31)
Primary medical institutions	0.00 (0.00)	0.00 (0.00)	0.08 (0.08)	0.00 (0.00)	0.40 (0.39)	0.02 (0.02)
Outpatient service agencies	0.00 (0.00)	0.00 (0.00)	0.14 (0.15)	0.02 (0.02)	0.05 (0.04)	0.05 (0.06)
Total	75.57 (100.00)	85.99 (100.00)	97.86 (100.00)	100.53 (100.00)	103.28 (100.00)	98.04 (100.00)

Bold font represent the collective term for the categories.

Chinese medicine hospital, general hospital, primary medical institutions, etc.

3.7 Modeling and model estimates

We have developed a SEM to further investigate the effects of variables on outpatient expenditure (Figure 3). Variables that were unrelated to depression outpatient expenditure were excluded. Based on the fitting optimization index, the proposed SEM has a good fitting effect, $\chi^2 = 4.287$, df = 1,χ^2/df = 4.287, GFI = 1.000, AGFI = 1.000, CFI = 1.000, NFI = 0.999, RFI = 0.995, IFI = 1.000, TLI = 0.996, RMSEA = 0.008. Insurance status can affect outpatient expenditure through year (β = 0.03, $p < 0.001$), age (β = −0.09, $p < 0.001$). Year (β = 0.02, $p < 0.001$) and age (β = 0.18, $p < 0.001$) can affect outpatient expenditure through institution level. However, outpatient expenditure was affected by insurance status (β = −0.02, $p < 0.001$), year (β = −0.05, $p < 0.001$), age (β = −0.02, $p < 0.001$), institution level (β = −0.31, $p < 0.001$). In addition, the year was negatively correlated with age (β = −0.04, $p < 0.001$).

TABLE 4 CCE of different types of depression (CNY million).

Year	Total	Mild depression	Moderate depression	Major depression	Other depression
2015	75.57	0.74	4.45	0.59	69.80
2016	85.99	1.11	4.50	0.78	79.60
2017	97.86	1.83	4.57	1.02	90.44
2018	100.53	2.16	4.33	1.51	92.53
2019	103.28	2.55	4.56	2.03	94.14
2020	98.04	3.10	5.07	2.52	87.34

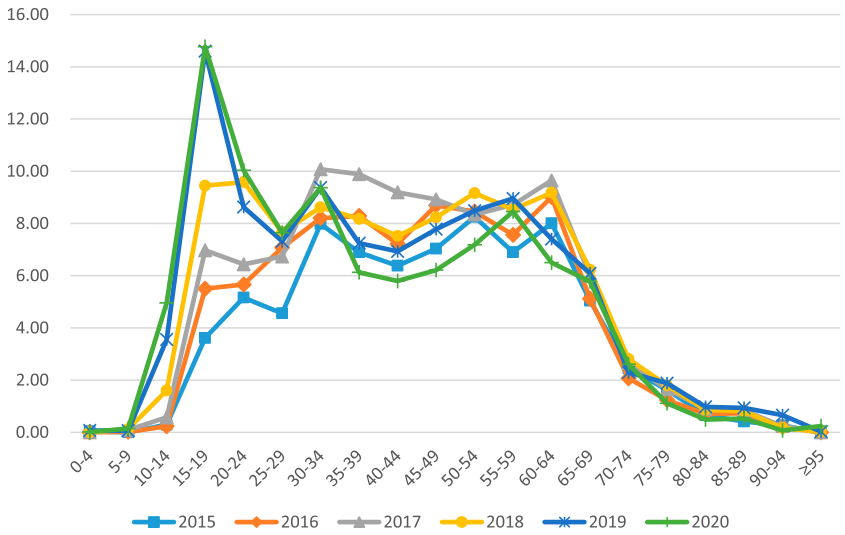

FIGURE 1
Age distribution of depression outpatients CCE 2015–2020(CNY million).

TABLE 5 Distribution of financing expenses for depression clinics in Liaoning Province from 2015 to 2020 (million (%)).

year	Public financing scheme			Voluntary financing scheme			Out-of-pocket payments	Total
	Total	Government financing scheme	Social health insurance	Total	Social donation	Enterprise financing plan		
2015	38.18 (50.52)	6.66 (8.82)	31.52 (41.70)	7.38 (9.76)	1.17 (1.55)	6.21 (8.21)	30.01 (39.72)	75.57 (100.00)
2016	44.01 (51.18)	7.96 (9.26)	36.05 (41.92)	8.84 (10.28)	1.66 (1.93)	7.19 (8.36)	33.14 (38.53)	85.99 (100.00)
2017	51.50 (52.63)	9.47 (9.67)	42.04 (42.96)	9.67 (9.88)	2.69 (2.75)	6.97 (7.13)	36.69 (37.49)	97.86 (100.00)
2018	53.59 (53.30)	9.86 (9.81)	43.72 (43.49)	9.83 (9.78)	1.95 (1.94)	7.88 (7.84)	37.12 (36.92)	100.53 (100.00)
2019	57.76 (55.92)	10.80 (10.46)	46.96 (45.46)	9.36 (9.07)	1.66 (1.61)	7.71 (7.46)	36.16 (35.01)	103.28 (100.00)
2020	52.99 (54.05)	9.50 (9.69)	43.49 (44.36)	8.28 (8.45)	1.18 (1.20)	7.10 (7.24)	36.76 (37.50)	98.04 (100.00)

FIGURE 2
Sankey diagram for the average CCE in 2015–2020 associated with depression by financing schemes and type of institutions. CCE, current curative expenditure.

4 Discussion

Although there are more studies on depression in China and abroad, there are few domestic studies on the economic burden of depression costs based on SHA 2011. Our study provides a comprehensive estimate of the size and distribution of the CCE of depression in outpatient clinics in Liaoning Province. Depression places a heavy financial burden on individuals, families and society. The financial burden varies widely among people with different types of depression and ages.

In terms of the financing structure, our findings show that the cost of outpatient depression treatment in Liaoning Province was mainly from publicly financed government financing programs (2015–2020: 31.97%–60.98%) and OOP payments (2015–2020: 31.88%–66.58%). Families of depressed patients face disproportionate catastrophic health expenditures and poverty due to high OOP costs (Patel et al., 2007). In India, the probability of incurring catastrophic health expenditures due to depression among women is 14.6%. Studies conducted in Pakistan and Ethiopia show that depression leads to increased healthcare costs and significant costs to families (Mogga et al., 2006; Hanlon et al., 2015). Similarly, it has also been shown that families with depression are households three times more likely to experience catastrophic OOP payments than those without depression (Liu et al., 2019). We believe that there is a reason for this high catastrophic cost; depression is a severely disabling disorder that can have persistent and recurrent distressing mood swings and somatic symptoms, and this intense distress results in seeking care from health professionals and taking medication, which inevitably leads to high costs, similar to the Ethiopian study (Mogga et al., 2006; Hanlon et al., 2015). Therefore, it is important to control the share of depression OOP in the total cost of depression and reduce the risk of poverty among residents due to medical care. If the proportion of OOP to total health costs can be reduced by less than 15% by using strategies such as progressive fee schedules, highly subsidized or free hospital services and providing certain medical services to the poor, few households will incur catastrophic expenditures.

In terms of institution type, our findings show that depression outpatient CCE is mainly concentrated in general hospitals, accounting for about 90%, with a wide variation in the proportion of Chinese hospitals, ranging from 3% to 19% and less than 1% in specialty hospitals and primary healthcare institutions; thus showing a serious imbalance in service provision in healthcare institutions. Because patients with depressive disorders exhibit multiple mood-related somatic symptoms, they tend to be seen repeatedly in various clinical departments, becoming high consumers of medical resources in healthcare institutions at all levels. Currently, in the People's Republic of China, there are fewer resources for mental healthcare. Most Chinese patients tend to seek depression treatment at provincial and municipal general hospitals, most of which have psychiatric or psychological clinics. In Western countries, more than half of depressed patients choose to receive treatment in primary healthcare (Oxman et al., 2002), as primary care physicians with comprehensive pharmacological knowledge and psychosocial interventions are able to provide effective treatment for depression (Gensichen et al., 2006; Gilbody et al., 2006). In China, primary care is approximately 0.8 km from most urban residents, which provides support for the somatic expression of depressive tendencies in depressed patients (Jiang et al., 2018). Depression has a long treatment period and is a highly relapsing disorder, and patients require multiple follow-up visits, systematic interventions and full involvement of community general practitioners, who therefore play an important role in relapse interventions for depression (Li Qingwei, 2016). Efforts are needed to strengthen the collaboration between primary care general practitioners and mental health professionals and the

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TABLE 6 Differences in outpatient depression expenditure by subgroup (n = 56994).

Variables	n (%)	Outpatient expenditure Median (IQR)	Z/H	*p*-Value
Whether to purchase drugs				
Yes	44377 (77.90)	444.66 (213.73–791.7425)	−101.611[a]	<0.001
No	12617 (22.10)	76.40 (19.20–278.00)		
Whether to select treatment				
Yes	20807 (36.50)	499.70 (281.60–929.66)	−75.195[a]	<0.001
No	36187 (63.50)	272.16 (68.42–551.54)		
Sex				
Female	31897 (56.00)	340.81 (127.03–658.22)	−4.933[a]	<0.001
Male	25097 (44.00)	356.25 (138.43–707.00)		
Age				
0–14	1557 (2.70)	370.40 (188.02–671.52)	187.605[b]	<0.001
15–64	47668 (83.60)	357.64 (139.61–690.57)		
≥65	7769 (13.60)	295.80 (88.56–604.17)		
Insurance status				
Urban employees' basic medical insurance	11272 (19.80)	347.92 (166.68–622.31)	191.906[b]	<0.001
Urban residents' basic medical insurance	1369 (2.40)	276.80 (75.90–523.46)		
New rural cooperative medical care	267 (0.50)	125.20 (26.00–342.00)		
Self-funded	44086 (77.40)	354.00 (125.80–704.20)		
Institution level				
Provincial level	44911 (78.80)	405.80 (181.00–766.10)	4602.559[b]	<0.001
Municipal level	10644 (18.70)	221.31 (72.84–408.24)		
District level	637 (1.10)	23.69 (3.00–66.80)		
Country level	802 (1.40)	26.00 (5.53–164.46)		
Institution type			1462.719[b]	<0.001
General hospital	53271 (93.50)	345.16 (131–669.94)		
Traditional Chinese medicine hospital	3031 (5.30)	486.79 (236.2–1044.16)		
Specialized hospital	86 (0.20)	300.99 (58.0775–533.72)		
Primary medical institutions	500 (0.90)	19.59 (3–53)		
Outpatient service agencies	106 (0.20)	41.825 (30–165)		
Year			929.699[b]	<0.001
2015	5726 (10.00)	380.14 (182.71–695.29)		
2016	6462 (11.30)	427.40 (222.48–788.58)		
2017	5066 (8.90)	345.72 (163.00–630.00)		
2018	12220 (21.40)	303.90 (89.07–588.68)		
2019	10910 (19.10)	290.10 (79.21–598.32)		
2020	16610 (29.10)	378.57 (147.64–765.03)		

[a]Stands for applying the Mann-Whitney U test (for 2 independent samples).
[b]Stands for non-parametric Kruskal–Wallis H test (for k independent samples).
IQR, means percentile level.
Bold font represent the collective term for the categories.

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TABLE 7 Multiple regression analysis of impact factors on outpatient expenditure.

	Unstandardisation coefficient		Standardisation coefficient	T	Sig
	B (95%CI)	SE	Beta		
Whether to purchase drug					
Yes	0.697 (0.687–0.707)	0.005	0.453	133.799	<0.001
No	References				
Whether to select treatment					
Yes	0.361 (0.352–0.370)	0.005	0.272	76.031	<0.001
No	References				
Sex					
Female	−0.017 (-0.025–0.008)	0.004	−0.013	−3.726	<0.001
Male	References				
Age					
0–14	0.116 (0.088–0.144)	0.014	0.030	8.16	<0.001
15–64	0.061 (0.049–0.074)	0.006	0.035	9.747	<0.001
≥65	References				
Insurance status					
Urban employees' basic medical insurance	0.061 (0.05–0.072)	0.006	0.038	11.013	<0.001
Urban residents' basic medical insurance	0.113 (0.084–0.141)	0.015	0.027	7.737	<0.001
New rural cooperative medical care	0.007 (-0.057–0.07)	0.032	0.001	0.21	0.834
Self-funded	References				
Institution level					
Provincial level	0.860 (0.823–0.896)	0.019	0.550	45.605	<0.001
Municipal level	0.599 (0.561–0.637)	0.019	0.365	31.019	<0.001
District level	−0.098 (-0.171–0.025)	0.037	−0.016	−2.635	0.008
Country level	References				
Institution type					
General hospital	−0.696 (-0.813–0.579)	0.06	−0.269	−11.673	<0.001
Traditional Chinese medicine hospital	−0.768 (-0.887–0.65)	0.06	−0.270	−12.724	<0.001
Specialized hospital	−1.001 (-1.159–0.843)	0.081	−0.061	−12.417	<0.001
Primary medical institutions	−0.918 (-1.025–0.812)	0.054	−0.134	−16.961	<0.001
Outpatient service agencies	References				
Year					
2015	−0.127 (-0.142–0.111)	0.008	−0.060	−16.008	<0.001
2016	−0.059 (-0.075–0.044)	0.008	−0.029	−7.729	<0.001
2017	−0.036 (-0.052–0.020)	0.008	−0.016	−4.306	<0.001
2018	−0.141 (-0.154–0.129)	0.006	−0.091	−21.945	<0.001
2019	−0.115 (-0.128–0.102)	0.007	−0.071	−17.317	<0.001

(Continued on following page)

TABLE 7 (*Continued*) Multiple regression analysis of impact factors on outpatient expenditure.

	Unstandardisation coefficient		Standardisation coefficient	T	Sig
	B (95%CI)	SE	Beta		
2020	References				

Note: $R^2 = 0.384$,$p < 0.001$.
B, non-standardized regression coefficient. SE, Standard Error. Beta, standardization regression coefficient. *t*, *t*-test value (t-statistic). Sig, the meaning of coefficient (*P*).
95%CI, 95% Confidence Intervals.
Taking logarithms of outpatient expenditure in multiple regression analysis.
Bold font represent the collective term for the categories.

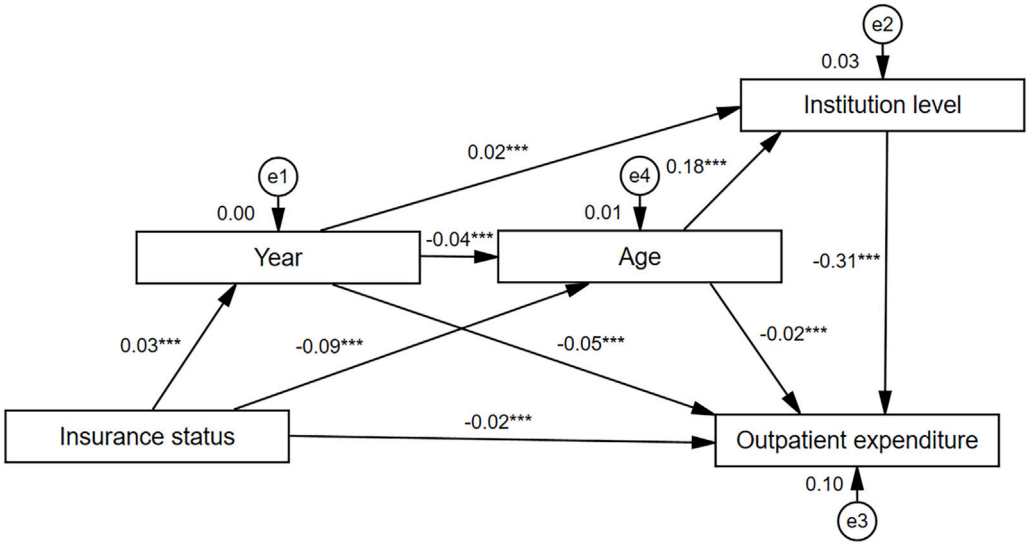

FIGURE 3
Path diagram of the structural equation model. Year contain 2015、2016、2017、2018、2019、2020. Age:0–14 = 1,15–64 = 2,≥65 = 3. Insurance status (in order of actual reimbursement ratio): Basic medical insurance for urban workers (actual reimbursement ratio = 75.60% (AdministrationNational Healthcare Security Administration, 2020))1, urban residents' basic medical insurance (59.70% (AdministrationNational Healthcare Security Administration, 2020)) = 2, new rural cooperative medical care (35.00% (Ma and Li, 2021)) = 3, self-financing (0.00%) = 4. Institution level:provincial level = 1, municipal level = 2, district level = 3, country level = 4. Taking logarithms of outpatient expense in the structural equation model.

identification and prevention of depression should be enhanced by integrating specialist and non-specialist multifaceted efforts.

Our findings show that the overall trend of depression outpatient CCE gradually increases during adolescence (0-19 years) and then decreases (19-24 years), to 25-59 years and then begins a fluctuating shift from a rapid decline after 60 years–69 years, and after≥70 years CCE slowly decreases and gradually convergence to zero. Depression cost differences are mainly related to the age of the patient. Some studies have shown that children are relatively less likely to suffer from depression (1%) compared to adults (Costello et al., 2003), but depression increases sharply during the elementary school years (5–11) (Kessler et al., 2012). This is consistent with significant age-related trends in the prevalence of depression that have been shown to increase gradually from the youngest to the higher ages and then decrease in the older age groups, with the prevalence consistently being lowest in the oldest age group (≥60) (Kessler et al., 2005). At the same time, it has been shown that the highest lifetime prevalence of lifelong illness is seen in adolescence with approximately 50% of lifetime illnesses being concomitant affective disorders, including depression (Guo et al., 2019). Among all cases of lifelong illness with psychiatric disorders, 50% start at age 14% and 75% at age 24 and in older stages, there is mostly co-morbidity of depression with other disorders (Kessler et al., 2005). The adolescent stage is a plastic turbulent period of life, depression or lifelong mental illness leading to suicide or disability at this stage has a huge cost in terms of personal growth, family burden, even social development. Therefore, it is very important to focus on screening for depression in adolescence and to prevent and control the harmful effects of depression.

Multiple linear regression analysis was used in this study to explore the factors influencing the cost of outpatient visits, the study factors explained 38.4% of the variance in depression outpatient costs. The findings of the multiple linear regression analysis showed that the drug standardized coefficient was 0.45, showing that patients' choice to take medication was associated with high outpatient costs, which indicates that medication is the main modality taken by patients in the antidepressant process and that medication plays an important role in the reducing depression (Egede et al., 2016; Lekoubou et al., 2019; Torres;Granados et al., 2023).

The three main drivers of depression healthcare expenditure are outpatient visits, medication, and the emergency room (Lurie et al., 2009). Continued outpatient visits and medication also increase the cost of depression. A study showed that antidepressant medication, although increasing short-term direct expenditures, significantly reduces the average medical expenditures of patients 12 months or even 5 years after depression diagnosis in the long run (Gu et al., 2020). This is important since the medication is effective and acceptable for treating depressed patients (Gill and Hatcher, 1999). At the same time, the higher cost of medication may be related to physicians' prescribing habits, physicians' compensation for relatively low fees for services or availability of medication to patients and the relatively low costs for patients compared to counseling (Hu, 2004). The results of our study show that, in terms of standardized coefficient B values, the impact is greater at the provincial and district levels of healthcare and less at the district level of healthcare. Also, the results of SEM showed that institution level was a significant mediating variable for the effect of year and age on the cost of depression outpatient visits. Thus, encouraging patients to go to primary care is an effective initiative to reduce the cost of outpatient visits. The standardized discourse coefficient B value of insurance status in the multiple linear regression showed that depression outpatient expenses were 0.038 and 0.027 higher than self-founded for urban workers and urban residents, indicating that medical insurance for urban workers and urban residents significantly affects depression outpatient expenses. In our SEM results, insurance status can affect outpatient expenditure through year, age. Some studies have shown that depression leads to a significant increase in commercial insurance, Medicaid, health insurance expenditures and OOP costs (Breslow et al., 2019). Depression was common among people with public insurance (Lekoubou et al., 2019). Patients with private and public insurance were prescribed more medications than those without insurance (Shao et al., 2017), patients with insurance were also more likely than uninsured patients with depression to continue antidepressant treatment for 30 days and beyond (Olfson et al., 2006). Possible reasons for these phenomena are that for patients with health insurance, medical costs are partially covered by the insurance company, which puts less financial pressure on the patient, and the patient can then be actively and sustainably treated. For patients without insurance, the high OOP costs may cause patients to abandon medication or counseling because antidepressant treatment is a very expensive treatment. Some studies have shown that people with depression have higher out-of-pocket costs on average than hypertensive patients or arthritis patients (Lurie et al., 2009), similar to those with heart disease and diabetes, which shows that the financial burden of depressed patients is quite heavy.

It is suggested that China should set up a special financial project to increase financial investment in depression, increase the number of aid patients spend on depression treatment, and increase the amount of free monthly medication subsidies for patients (Huang Fudan University, 2010). The government should improve the breadth and depth of health insurance coverage. The government should continue to reduce participation fees, especially for migrant and poor families, because many patients' families cannot effectively use medical insurance due to the process of medical treatment in different regions in China. Since depression treatment is mainly conducted in outpatient clinics and is mostly drug-based, patients have long treatment cycles and high chronicity rates, and some patients have not recovered after 5 years (Gadit, 2004). It is therefore recommended to improve the psychotropic drug supply guarantee system, increase competition among drug manufacturers, promote the use of generic drug prescriptions, and improve the transparency of drug pricing (Lekoubou et al., 2019). By including, more antidepressant drugs in the basic medical insurance, increasing the reimbursement ratio, and realizing the free supply of some basic antidepressant drugs patients may also experience reduce financial burden due to depression. A collaborative medical-mental health governance program is formed by the integration of psychiatrists, caregivers, and psychotherapists to closely monitor the clinical outcomes of patients in treatment facilities, strengthen preventive screening and testing, and adjust treatment plans according to the patient's illness to prevent recurrent depressive episodes and avoid the formation of intractable depression, which places a heavy burden on families and society. The treatment of depression mainly consists of prescription medication, which must be regulated by medical personnel to reduce the burden on patients. In the process of treatment, to avoid inducing demand and causing excessive medical treatment, accurate medical treatment is critical. Patients should actively cooperate with the treatment requirements, follow medical advice, take medication regularly and on time, and not stop medication without authorization. Because of the long treatment period of depression, many patients stop medication without authorization, resulting in recurrent depression, or even form refractory depression due to the seriousness of the situation.

The SHA2011-based accounting framework provides a good theoretical basis for explaining depression outpatient CCE in Liaoning Province. Under this theoretical framework, the type of institution, funding structure, and beneficiary population of depression outpatient CCE can be well explained. On this basis, we analyzed the distribution of costs for different disease types and explored the influencing factors of CCE as well as the direct and mediating effects on outpatient costs using structural equation modeling.

This analysis research has some limitations. First, Only outpatient costs for depression were reported in this study because outpatient costs accounted for more than 90% of the total costs in this study, which is due to the fact that the purchase of medications accounted for a larger portion of the outpatient costs, which is consistent with extant studies (Zhou et al., 2008). Also, patients with depression have a higher probability of visiting the outpatient clinic (Jia et al., 2003). Due to the number and percentage of hospitalization expenditure are too small, analysis of its internal composition and financing structure and influencing factors will be less accurate, which may have a certain degree of influence on the change of the trend of the cost of depression, while more than 90% of the extent of the outpatient expenditure of depression in this study can be speculated on the trend of the change of the total cost of the patient and the factors that influence it, and the comprehensive consideration of the results of the credibility of the choice to exclude the expenditure of hospitalization, but in the subsequent study we will continue to strengthen to ensure that the expenditure of the completeness of the study. Second, because depression is severely undertreated in medical institutions (Mitchell et al., 2009), it is likely that many residents of Liaoning Province who suffer from depression do not

seek medical treatment, therefore some cases of depression may be underreported in the dataset. However, because the proportion of hospitalization costs is really too small, so there is no further analysis of its internal composition and financing structure and influencing factors, the proportion is too small may be less accurate analysis of the distribution of costs of various dimensions, which may have some degree of influence on the change of the trend of the cost of depression, but in the follow-up study we will continue to strengthen to ensure that the cost of the completeness of the study. Then again, because depression is mainly managed by medication or combined with counseling treatment, and patients taking medication can directly purchase online medications the data on medication may also be underreported in this dataset. Furthermore, the medical burden of disease includes direct medical expenses, indirect medical expenses, and other social losses, and this study only examined direct medical expenses. Finally, this study only considered the costs of a single depression diagnosis and did not consider the costs of comorbidities. Last but not least, the missing cases of depression were mainly from the Liaoning Provincial Hospital Specializing in Mental Diseases-Dalian No. Seven People's Hospital, and the data from this institution with 2 years of data were deleted in this study due to missing data in some years. For these reasons, this study may underestimate the actual outpatient burden of depression in Liaoning Province.

In China, the medical burden of outpatient CCE for depressed patients is high, and outpatient pharmacotherapy is the most common treatment for depression. Therefore, it is recommended to improve the supply guarantee system of psychotropic drugs, enhance the competitiveness among pharmaceutical companies, promote the use of generic drugs medications and include more antidepressants in the essential drug list to achieve a free supply of some antidepressant essential drugs. Medical insurance is an important factor for patients to take aggressive treatment and adhere to it for a long time. Because patients with health insurance bear less out-of-pocket costs for treatment than those who are covered by health insurance, patients are more likely to actively cooperate with their doctors' prescribed treatment or psychological counseling therapy. Therefore, it is recommended to improve the heavy burden of depression medical costs on the state, society and families by expanding the breadth and depth of health insurance coverage, consistently lowering participation fees, and increasing reimbursement rates.

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

YM, XS, and XY contributed to conception and design of the study. YM, QW, and PC contributed to acquisition of data. XS and YZ performed the statistical analysis. YM and XS prepared the manuscript. KS and XY reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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