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Social, clinical and economic factors: Evidence-based healthcare financing and policy for cancer prevention and therapy

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Social, clinical and economic factors: Evidence-based healthcare financing and policy for cancer prevention and therapy

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Predicting Rural Women's Breast Cancer Screening Intention in China: A PLS-SEM Approach Based on the Theory of Planned Behavior

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Background: It was reported that the incidence of breast cancer (BC) was the highest among cancers worldwide. The breast cancer screening (BCS) program is regarded as an effective preventive measure. However, rural women's willingness to participate in the BCS program is relatively low. To provide measures to prevent BC, it is necessary for the government to identify the influencing factors of rural women's BCS intention.

Methods: A cross-sectional study was conducted among 3,011 rural women by a convenience sampling method through face-to-face interviews on a self-designed questionnaire based on the theory of planned behavior (TPB). The partial least square structural equation model (PLS-SEM) was conducted to determine the predictors of BCS intention, and a multi-group analysis (MGA) of age was performed to identify if there were differences in all hypotheses between different age groups.

Results: There were still rural women who have not been screened for BC in five years (41.7%). The research model of rural women's intention to accept this prevention against BC was rational. All of the hypotheses are supported. Especially, subjective norm (SN) ($\beta = 0.345$, $p < 0.001$) is found to be the strongest predictor followed by the perceived behavioral control 1 (PBC 1) (personal factors, including distance, transportation, busyness, etc.) ($\beta = 0.165$, $p < 0.001$), attitude ($\beta = 0.152$, $p < 0.001$), past behavior (PB) ($\beta = 0.150$, $p < 0.001$), knowledge ($\beta = 0.121$, $p < 0.001$), and perceived behavioral control 2 (PBC 2) (pain and cultural-social factors including embarrassment from a physician, etc.) ($\beta = 0.042$, $p < 0.05$). The advocacy and education (A&E), medical level and service attitude (ML&SA) of township health centers and village clinics can affect behavior intention (BI) *via* attitude, SN, and PBC. The results of MGA of age indicate that there are significant differences among rural women of different ages regarding the relationship between A&E and PBC 2 ($p < 0.01$) and the effect of PB on BI ($p < 0.001$).

Conclusion: The TPB with the addition of PB, knowledge, ML&SA, and A&E can provide the theoretical basis for the policy intervention that aims to enhance the rural women's BCS willingness. MGA of age is conducive to promoting the implementation of the BCS policy. The findings are of great significance to improve rural women's health levels.

Keywords: breast cancer screening intention (BCS intention), rural women, the theory of planned behavior (TPB), the partial least square structural equation model (PLS-SEM), multi-group analysis (MGA)

INTRODUCTION

The previous studies suggested that breast cancer's incidence and mortality in developed countries have decreased obviously in recent years, while the prevalence in developing countries has increased gradually (1). According to the estimates of the International Agency for Research on Cancer (IARC) on the global burden of cancer in 2020, female breast cancer (BC) was estimated to be the top of the 10 most common cancer types (2). It was considered that female breast cancer was the most commonly diagnosed cancer worldwide, which accounted for 11.7% of the total newly diagnosed cancer cases. It also showed 6.9% of the total cancer deaths, which ranked fifth (2). The statistics from the National Cancer Registry showed that the incidence of breast cancer among rural women was 79 per 100,000 in 2015 (3). The statistics from the National Health and Family Planning Commission of PRC showed that the death rate reached 6.48 per 100,000, ranking the 4th highest incidence of all cancers among rural women in China (4). The past study also demonstrated that poor women were more likely to develop BC than those with higher family income and urban residence due to the limited detection and screening facilities as well as fewer opportunities to seek better medical treatment (5). It appears that breast cancer has been a major public health problem globally, especially among the rural women who deserve more attention.

However, the etiology of breast cancer is unclear now (6, 7). But a lot of studies have confirmed that early diagnosis and treatment can reduce mortality significantly (7), and screening services play a significant role in improving the early diagnosis rate (8). According to studies in developed countries, high coverage of breast cancer screening (BCS) can effectively reduce mortality. For example, BCS was national coverage in the United Kingdom in the mid-1990s with women over 50 using breast Xray every 3 years. Thus, the mortality among patients with breast cancer aged 55∼69 decreased by 1/3 (7). In the United States, Australia, et al., the BCS program has been a national policy and continues to be promoted (7). The World Health Organization (WHO), International Union Against Cancer (UICC), and the American Cancer Society (ACS) have concluded that the BCS program is effective and is worth promoting worldwide (7).

In China, BC was considered to be one of the leading malignant tumors and the main cause of cancer death in women below 45 years old in 2015 (3), and there was also an increasingly upward trend in the rates of age-standardized incidence and mortality (3). Researchers predicted that there would be 2.5 million women aged 45–59 with BC by 2021 (9). The Chinese government always attaches great importance to BCS, and rural women's BCS has been included in the major public health services since 2009 (10). Unfortunately, even with free screening services, rural women still lacked willingness to be engaged in the screening, and the screening rate was not high (11). It was demonstrated that the rate in China rural was lower than it was in urban and far lower than it was in the developed countries. For example, the BCS rate for rural of Jilin Province only reached 9.09% in 2013 (12). Even in economically developed regions, the screening rate was not satisfying either, only reaching 38.09% of Conghua District, Guangzhou (13) and 23.3% of Wenling, Zhejiang in 2015 (14). The past research revealed that the screening rate was 38.05% in rural, while 48.09% in urban (15). As for developed countries, the BCS rate was 72.4% in the United States in 2010 and more than 70% rural women have done a screening for breast cancer and cervical cancer within 5 years in the Netherlands (16). Hence, the enthusiasm of Chinese rural women to undergo BCS urgently needs improvement.

In order to improve Chinese rural women's screening participation, the influencing factors of their BCS intention should be emphasized when designing and implementing the BCS program. However, few studies specifically focused on rural women's intention to BCS in China. Only a small number of studies examined the factors that influence BCS behavior based on socio-demographic characteristics, which are the education level, monthly income, age, etc. (17). Most studies in China did not draw on social psychological theories or behavioral theories. Whereas, with the deepening of the research, academic community has come to realize that screening is a healthy behavior that requires long-term persistence and is affected by multiple factors of the physical and social environment (7). Therefore, it is urgent to conduct empirical studies to explain and predict individual behavior of rural women's BCS in China. Subsequently, there were some studies that investigated the personal health beliefs (18) and external environmental factors (19, 20), such as the society or organizations. These studies were generally based on social psychological models, including health belief model (HBM) (18, 21) and the theory of rational behavior (TRA) (21). But the views on health HBM emphasize more about the influence of individual cognition on health behavior and consider less about the social factors. The theory of planned behavior (TPB) incorporates perceived behavioral control on the basis of TRA (22). The structural model of TPB can measure not only the internal factors but also the characterization of

Abbreviations: PB, past behavior; A&E, advocacy and education; ML&SA, medical level and service attitude.

the social environment, and it has been proved to effectively explain and predict the health prevention behavior and behavior intention (23). It is widely used in the field of health prevention behavior, including AIDS prevention (24), smoking interventions (25), cervical cancer screening (26), etc. However, only a few pieces of research evaluated breast self-examination and its effective factors (27) and the role of educational intervention in mammography screening based on TPB (28). Fewer pieces of research evaluated the rural women's breast screening intention based on TPB.

Therefore, using a PLS-SEM approach based on the TPB, this study aimed to predict the women's BCS intention and to analyze its influencing factors in rural China in order to promote women's health, and further research in this area from rural women's perspective is needed.

Theory of planned behavior is a social cognitive theory that explains how attitude toward the behavior (AB), subjective norm (SN), and perceived behavioral control (PBC) act on behavior intention (BI) and then on actual behavior as shown in **Figure 1** (29). In this model, attitude, SN, and PBC are independent and pairwise. Accurate PBC can be used as an alternative measure of actual control conditions to directly predict the possibility of behavior occurrence (as illustrated in the dashed line in **Figure 1**) (29). "Attitude toward the behavior (AB) refers to a person's general and stable tendency to perform a certain behavior (29). The tendency often contains two separable components: belief strength (b) and outcome evaluation (e), as shown in the Equation (1) (22, 30) "$AB \propto \sum b_i e_i$."

(*i means measurement project*). SN is defined as individuals' beliefs on the extent to which others would expect them to perform a behavior (29). The measurement of SN also contains two separable components, normative belief (n) and motivation to comply (m), as shown in the Equation (2) (22, 30) "$SN \propto \sum n_i m_i$" (*i means measurement project*). PBC refers to the individuals' perceptions of the controllability and ability to perform a given behavior (29). The two separable components to measure PBC are control beliefs (c) and perceived power (p), which are shown in the Equation (3) (22, 30) "$PBC \propto \sum c_i p_i$" (*i means measurement project*). Ajzen (29) proposed that the model can also accommodate any variables that effectively explain and predict the behavior and the behavior intention when studying a particular behavior in addition to three variables: attitude, SN, and PBC. That is to say, we could add new variables to this model on a reasonable basis, which could exert an impact on the behavior belief and behavior.

Combined with the existing literature, the research hypotheses and the model adopted in this study were developed based on TPB, which is shown in **Figure 2**.

According to TPB, the more positive the rural women's attitude is, the higher intention they will have (29). A previous study among rural women in Korea showed that lack of awareness may lead to the low participation rate in BCS tests (32). Additionally, Yan demonstrated that a negative attitude toward health check-ups was one of the reasons why female residents are less likely to be screened for BC in Macao (33). Considering this, we assumed that:

H1: Attitude is positively associated with the rural women's BCS intention.

Based on TPB, the rural women's discernment to be screened for BC (PBC) can directly predict the occurrence of BCS (29). Past studies demonstrated that encountered barriers, such as lack of time, long geographic distance to primary health facilities, etc., probably affect BCS (34). Therefore, the closer the distance to the township health centers or village clinics, the more convenient traffic and women's time resources, the stronger the PBC. Another stream of research revealed that it is a taboo for Asian women to show their breasts to others due to their traditional culture (35). Besides, rural women refrained from participating in BCS due to their ashamed and embarrassed reaction when exposing their breasts to male physicians (35, 36). Women also were impeded by the view that BCS is painful or uncomfortable (34). Personal fear of doctors/examiners, hospitals, and health facilities also exerted a negative impact on the women's attitudes toward BCS (19). That is to say, the less the embarrassment/fear, during the breast cancer screening, the higher the PBC score.

Based on the analysis above, we assumed that personal factors (distance, transportation, busyness, et al.) named PBC 1, pain and cultural-social factors (e.g., embarrassment) named PBC 2 both positively related to BCS for rural women.

H2a–H2b: PBC 1 and PBC 2 are positively associated with rural women's BCS intention, respectively.

According to TPB, SN has an effect on BI (29). If the SN varies, attitude and PBC will vary concordantly (29). It was evident that lack of encouragement from family members and physicians was one of the major inhibitors affecting women's decision on the BCS program (37). There was a significant correlation between lower social support and absence of BCS (19). Studies indicated that the social support network from women's colleagues in the workplace, families, and friends was important. Higher levels of social support networks lead to more positive attitude toward preventive health care (36, 38, 39). A study of 154 non-governmental organizations from 35 countries revealed that community health workers and local volunteers played a pivotal role in reducing women's discomfort and shyness while referring to breast health care (40). The multiple responsibilities undertaken by women in the workplace and at home, and the restriction of time urge the working women to postpone their own affairs for the sake of family members (37). Thus, it can be inferred that rural women will have more time to undertake BCS if they get more support and encouragement from their workplace or families. Based on the discussion above, we developed the following hypotheses:

H3a: SN is positively associated with the rural women's BCS intention.

H3b–H3d: SN also has an effect on rural women's attitude toward BCS, PBC1, and PBC2.

Many scholars have attempted to add new variables to the theoretical model of TPB in order to improve the explanatory power. The new variables included personality, behavior

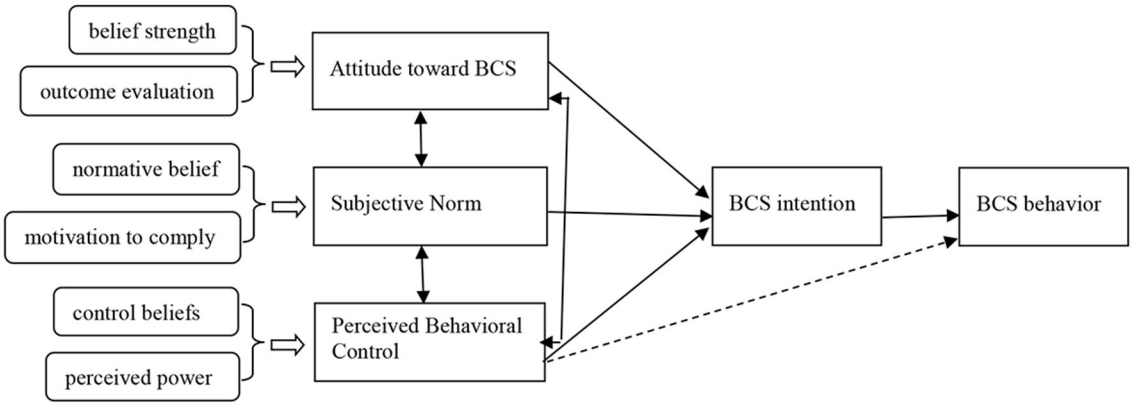

FIGURE 1 | A structural model of the theory of planned behavior (31).

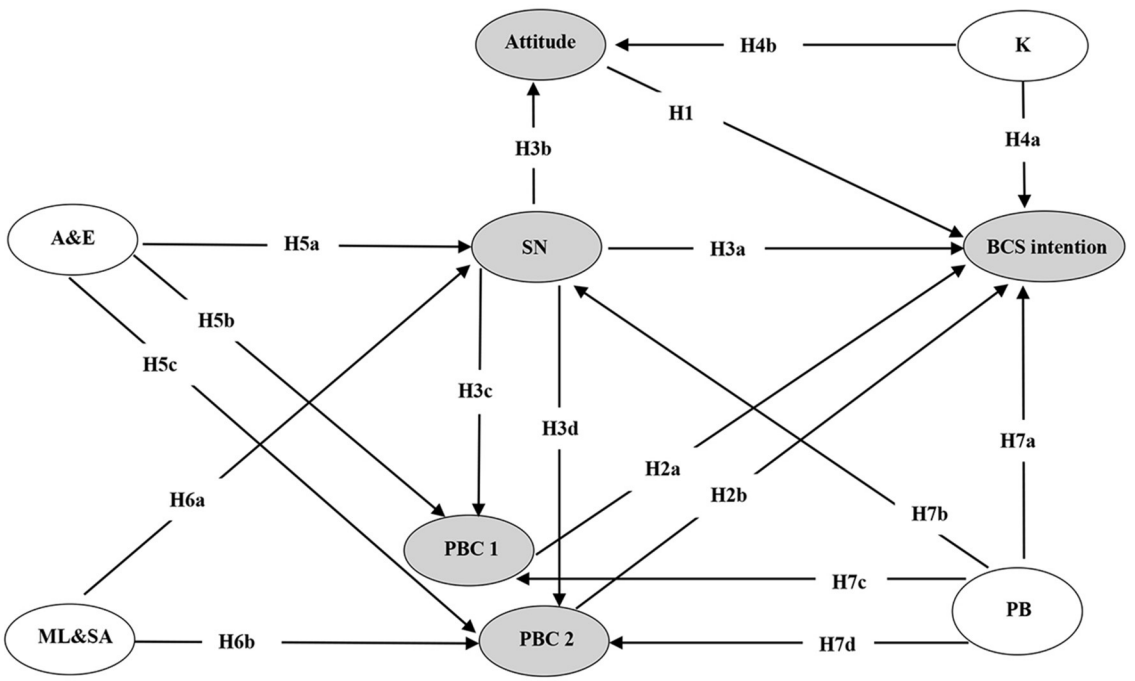

FIGURE 2 | The research hypotheses and research model. SN, subjective norm; PBC 1, perceived behavioral control 1; PBC 2, perceived behavioral control 2; BCS intention, breast cancer screening intention; K, knowledge; PB, past behavior; A&E, advocacy and education; ML&SA, the medical level and service attitude. K, PB, A&E, and ML&SA are added in the model as new variables; A&E and ML&SA belong to the supply-side factors.

experience, anticipated regret, and so on (41). According to Ajzen's view in 1991, we also added some new variables to this model.

Initially, we added the knowledge of BC and BCS. Previous studies found that cognitive and knowledge levels affected women's intention and behavior to receive BCS services (42) or mammography screening (43). Insufficient knowledge about BC made it less likely for women to engage in BCS (33). Besides, insufficient knowledge was one of the reasons for ignoring mammography (44). Therefore, we hypothesized that:

H4a–H4b: Knowledge has a positive effect on BCS intention and attitude.

Advocacy and education (A&E) also play an important role in BCS. A number of research demonstrated that health education interventions have been conducted, and health education is considered one of the most important factors affecting public health (45, 46). The study also suggested that advocates for prevention could encourage women to become role models and do advocacy for screening in their communities to build positive community sentiment and shift social norms (47). Qin also mentioned that the development of community health education

can reduce the rejection or concerns (48). As a result, we hypothesized that:

H5a–H5c: Advocacy and education (A&E) have an effect on SN, PBC 1, and PBC 2.

Medical level and service attitude (ML&SA) could influence the patients' experience and satisfaction (49, 50). The higher degree to which people satisfy with the recent medical experience, the stronger their trust in health care system will be (51). That is to say, high-level medical condition and excellent attitude could bring professional reputation and credibility; thus, women would receive more encouragement and social support from their families and friends. Additionally, patients were more likely to trust physicians who were employed by hospitals, which had better medical equipment, medical level, service, etc. (52). Therefore, we hypothesized:

H6a-H6b: The medical level and service attitude (ML&SA) of township health centers and village clinics have an effect on SN and PBC 2, respectively.

Previous research demonstrated that a bad experience in the past was one of the top three barriers to BCS (53). It means a bad experience may have a bad effect for rural women to be screened for BC. The study which was conducted in China (Wu et al.) suggested that past screening behavior could make women get more suggestions from health care providers, which promoted that SN plays an important role in the process of intention formation (54). Usually, a person who has a good habit or a good experience is more likely to perform the behavior and to comply with the recommendations from stakeholders than those who have not. The research also revealed that those who practiced breast self-examination monthly had a lower level of barriers than those who screened less frequently (55). Therefore, the study hypotheses are as follows:

H7a–H7d: The past behavior experience (PB) is positively associated with BCS intention, SN, PBC1, and PBC 2.

MATERIALS AND METHODS

Setting

A cross-sectional study was conducted in Jiangsu province. The rural women were recruited by a convenience sampling method between July and September, 2020. In the first stage, considering their different economic development levels, we selected 3 districts from 3 regions, respectively: Lianyungang, which is located in Northern Jiangsu province; Yangzhou, which is located in Central Jiangsu; and Nanjing, which is located in the southern part of the province. In the second stage, by consulting the experts, seven survey sites in rural areas were selected, covering three districts for the present study, i.e., Donghai, Haizhou, Guanyun in Lianyungang, Gaoyou, Tangwang in Yangzhou and Qixia, Jiangning in Nanjing. In the third stage, convenience sampling was used to recruit practitioners in the seven survey sites.

Participants and Data Collection

The participants were involved if they were women living in a rural area, more than 18 years old, and willing to participate in this research. Rural women with intellectual disability or language barrier who could not complete the questionnaires were excluded to ensure the validity of investigation. In order to improve the quality of the investigation, the questionnaire forms were filled out by a face-to-face interview with the help of trained and qualified investigators. Before obtaining answers, the investigators had explained to each participant who was required to fill out all the questions voluntarily and truthfully that the investigation was anonymous and the collected data would be only used in this study and kept completely confidential. The participants could get a bottle of laundry detergent as a reward. The price of it is 8 CNY.

The minimum sample size using PLS to measure models should not be <10 times the number of items of the most complex construct or the largest number of independent variables influencing the dependent variable (56). In the model of this study, the number of items of the most complex construct is 10. Besides, Raosoft was used to calculate the sample size as another way (57). According to the Sixth National Census in China, there were about 15.74 million rural women in Jiangsu, China (58). Therefore, the population size is estimated to be 15.74 million. The margin of error, confidence level, and the response distribution were, respectively set as 5%, 95%, and 50%. Then, the recommended sample size is 385.

Instruments and Measures

A self-made questionnaire was designed for data collection. A pilot survey was carried out, and the questionnaire was modified properly, which made the survey more reasonable and feasible before the formal investigation. The final formal questionnaire consisted of five parts (50 items in total). Part I: attitude and views on BCS (28 items or 14 pairs in total); Part II: BCS intention and past behavior (4 items in total); Part III: the current status of township health centers or village clinics (5 items in total); Part IV: the knowledge of BC (7 items in total); Part V: the demographic characteristics of the participants (6 items in total). Especially, 28 items of attitude and views on BCS were designed to be 14 pairs, including attitude (3 pairs or 6 items), subjective norm (5 pairs or 10 items), PBC 1 (3 pairs or 6 items), and PBC 2 (3 pairs or 6 items) to measure the two separable components of these three variables, respectively, according to Ajzen's TPB questionnaire (31). The calculation equations are as follows. (1) $AB \propto \sum b_i e_i$; (2) $SN \propto \sum n_i m_i$; (3) $PBC \propto \sum c_i p_i$ (*i* means the number of items measured) (22, 30).

The items of Part I, Part II, and Part III were scored on a five-point Likert scale. The scores range from 1 to 5 points. For example, women rated "saving cost of treatment" as the values 1 ("not at all important"), 2 ("not important"), 3 ("neutral"), 4 ("important"), and 5 ("very important"). Whereas, some items of PBC 1 (Item 3) and PBC 2 (Item 1, Item 3, and Item 5) were scored reversely. The items of Part IV were scored 1 if the choice were right, and 0 otherwise. The questionnaire was regarded as completed only if all the questions were answered. We substituted the mean of the respondents in the same unit for the missing data (59).

Data Analysis and Statistics

Data were recorded using Microsoft Excel. SPSS V.22.0 was used to conduct the descriptive statistics and calculate the scores of attitude, SN, and PBC according to Equations (1–3). Considering the interrelationship on the rural women's BCS intention and the influence factors in this research model, the hypotheses were performed by the partial least square structural equation model (PLS-SEM) using Smart PLS 3.2.8. This is because it shows a minimal restriction in sample size and residual distribution, and there is no constraint on the model specification and data distribution assumptions when it is used to analyze the complex model with latent variables (60). Especially, it integrates two methods of factor analysis and path analysis, which can be used to simultaneously measure the measurement model and the structure model and estimate the factor structure and the relationship among various factors (61).

Relevant studies have found that ages were closely related to BCS (62). It is meaningful to consider the age factor when implementing and promoting the BCS program. In recent years, the rural women's upper age limitation of participating BCS program was changed from 59 to 64 years (63). The policy poses the same effects on the rural women who are below 35 years old and who are above 64 years old. Therefore, the multi-group analysis (MGA) of Group 1 (below 35 years old or above 64 years old) and Group 2 (between 35 and 64 years old) was performed to discover the differences by using Henseler's MGA and the permutation method.

Ethics Approval

This study's ethical admission was approved by the Ethics Committee of Sir Run Run Hospital, Nanjing Medical University. The grant number is 2019-SR-017. We obtained the oral informed consent from each subject who participated in the survey.

RESULTS

About 3,200 questionnaires were distributed and 3,050 were returned. After removing the invalid questionnaire, 3,011 were usable. The valid response rate was 94.1%.

Descriptive Statistics

The demographics and relevant characteristics of the interviewers are shown in **Table 1**. The participants in Group 1(< 35 or > 64) and Group 2 (between 35–64) of BC account for 46.3% and 53.7%, respectively. The number of participants with a secondary school degree is the highest (44.3%). The majority of the participants are married or living with a common-law partner (88.7%). The number of rural women who have access to know about the BCS (68.4%) is more than those who have not (31.6%). A total of 9 approaches to know about BCS in this survey were as follows, by decreasing frequency: doctor, nurse or health staff ($n = 1{,}363$), television ($n = 989$), Wechat ($n = 935$), friends or a neighbor ($n = 707$), publicity column ($n = 600$), handbooks or leaflets ($n = 597$), newspapers or magazines ($n = 548$), family members ($n = 487$), and broadcast ($n = 309$).

The scores range from 1 to 5 points except the items of knowledge (1–7). Especially, according to the calculation equations of TPB, the overall scores of attitude, SN, PBC1, and PBC2 are on the scale of 1–25. As shown in **Table 2**, the mean score of attitude (mean score, 19.621; SD, 4.164) revealed that rural women were positive about early diagnosis and treatment (mean score, 21.027; SD, 4.965), the effect on saving cost (mean score, 19.352; SD, 5.652), and the outcome of screening (mean score, 18.485; SD, 5.011). For the construct SN, the mean score was 15.750, and the standard deviation was 4.197. The mean score of exports' effect was lowest (mean score, 12.763; SD, 6.292). The mean scores of PBC 1 (mean score, 11.809; SD, 4.062) and PBC 2 (mean score, 12.143; SD, 4.445) were not very optimistic, especially the scores of times (mean score, 9.253; SD, 4.170) and male physicians (mean score, 9.291; SD, 6.124). For A&E, the mean score was 2.967, and standard deviation was 0.886. Totally, 68.2% of rural women never/hardly/seldom received A&E on breast cancer. The mean score of ML&SA (mean score, 3.597; SD, 0.653) was also <4. As for knowledge (mean score, 4.017; SD, 2.000), 36.8% rural women scored 0–3 points. The mean score of PB was 2.394 (SD, 1.458). There were 1,256 rural women (41.7% of 3,011 participations) who were not taking part in the BCS program within the past 5 years. The mean score of rural women's behavior intention was 3.969 (SD, 0.782). There were still rural women who "strongly disagree" or "disagree" or kept "neutral" on "I plan/intend/will try to undertake BCS." The ratio reached 27%, 19.3%, and 21.8%, respectively.

Evaluation of Measurement Model

As shown in **Table 3**, all factor loadings were significant at $p < 0.001$ on its underlying construct, showing satisfactory convergent validity. Meanwhile, **Table 4** illustrated that Cronbach's $\alpha \geq 0.600$, which indicated sufficient internal consistency or reliability, and that composite reliability was adequate (64). The discriminant validity of the questionnaire was assessed. The correlation matrix for each pair of constructs is shown in **Table 4**. It is evident that the AVE square root of each construct is higher than the absolute value of its correlation (64); the cross-loadings show that all items loaded on their respective constructs are higher than those on the other constructs, and the cross-loadings differences are above the threshold of 0.10 (65). Finally, the HTMT ratio is below the threshold of 0.85 or 0.90 (66).

Evaluation of Structural Model

The model measurement results and hypothesis testing results are shown in **Figure 3**. About 40.3% of variance in the intention to BCS is explained: attitude is 25.3%, SN is 14%, PBC 1 is 19.6%, and PBC 2 is 14.9%. In particular, the values of f^2 (0.02, 0.15, and 0.35) indicate small, medium, and large effects (67). All the values of Q^2 are considerably above zero, and this finding supports the model's predictive relevance from an out-of-sample prediction perspective (68). SRMR in this model is 0.073 (i.e., below 0.08) (69), confirming the overall fit of this PLS path model.

The path coefficient (β) and t-value in **Figure 3** also demonstrate that all of the hypotheses are supported. Of all the factors affecting the intention to BCS, SN is found to be the strongest predictor.

Furthermore, we found some specific indirect effects in this model, as depicted in **Table 5**. In addition to the

TABLE 1 | Participant demographics and characteristics ($n = 3,011$).

Variable	Values	*N* (%)
Age	Group1: <35 or >64	1,393 (46.3%)
	Group2: between 35–64	1,618 (53.7%)
Education level	Illiteracy/primary school or below	562 (18.7%)
	Junior high school/ senior high school	1,333 (44.3%)
	Collegeand above	1,116 (37.1%)
Family Income (per month)	≤2,000	301 (10.0%)
	2,000–5,000	1,098 (36.5%)
	5,000–10,000	953 (31.6%)
	≥10,000	659 (21.9%)
Marital status	Never married	266 (8.8%)
	Married/ cohabitation	2,670 (88.7%)
	Divorced/separated/widowed	75 (2.5%)
The ways to know about the screening	Have	2,059 (68.4%)
	Don't have	952 (31.6%)
Total		3,011 (100%)

TABLE 2 | Mean scores for every item ($n = 3,011$).

Construct	Item	Scale	Mean ± SD	Construct	Item	Scale	Mean ± SD
Attitude		1–25	19.621 ± 4.164	A&E		1–5	2.967 ± 0.886
	A1	1–25	21.027 ± 4.965		A&E1	1–5	2.978 ± 0.985
	A2	1–25	19.352 ± 5.652		A&E2	1–5	2.955 ± 1.015
	A3	1–25	18.485 ± 5.011	ML&SA		1–5	3.597 ± 0.653
SN		1–25	15.750 ± 4.197		ML&SA1	1–5	3.507 ± 0.743
	SN1	1–25	17.082 ± 5.205		ML&SA2	1–5	3.439 ± 0.769
	SN2	1–25	16.531 ± 5.083		ML&SA3	1–5	3.845 ± 0.730
	SN3	1–25	17.112 ± 4.965	BCS intention		1–5	3.969 ± 0.782
	SN4	1–25	15.261 ± 5.425		BI1	1–5	3.895 ± 0.871
	SN5	1–25	12.763 ± 6.292		BI2	1–5	4.031 ± 0.791
PBC 1		1–25	11.809 ± 4.062		BI3	1–5	3.981 ± 0.819
	PBC1-1	1–25	12.761 ± 5.431				
	PBC1-2	1–25	9.253 ± 4.170	Knowledge		1–7	4.017 ± 2.000
	PBC1-3	1–25	13.414 ± 5.348				
PBC 2		1–25	12.143 ± 4.445	PB		1–5	2.394 ± 1.458
	PBC2-1	1–25	11.617 ± 5.437				
	PBC2-2	1–25	9.291 ± 6.124				
	PBC2-3	1–25	15.521 ± 5.968				

SD, standard deviation; A1–A3, denote the three paired items used to measure the respondents' attitudes; SN1–SN5, the five paired items used to measure the respondents' SN; PBC1-1–PBC1-3, the three paired items used to measure the respondents' PBC 1; PBC2-1–PBC2-3, the three paired items used to measure the respondents' PBC 2; A&E1–A&E3, the three items used to measure the respondents' views on A&E; ML&SA1-ML&SA3, the three items used to measure the respondents' views on ML&SA; BI1-BI3, the three items used to measure the respondents' BCS intention; PB, the past behavior within 5 years.

hypothesis put forward, we also found that SN, attitude, PBC 1, and PBC 2 all played an intermediary role in the model.

Meanwhile, we assessed the group difference in the multi-group analysis (MGA) of age in **Table 6**. Both Henseler's MGA and permutation method confirmed the significance or non-significance of the differences in all results, which strengthened the findings of this research. The output of MAG reveals that there are significant differences between the two age groups in regard to the effect of A&E on PBC2 (H5c) ($p < 0.01$) and PB on BI (H7a) ($p < 0.001$). However, there is no difference in other hypotheses according to the GMA results. In the group of women whose age are between 35 and 64, PBC 2 have a positively effect on BI (H2b) ($p < 0.05$), while there is no significant influence of H2b in the group of women whose age is below 35 or above 64 ($p > 0.05$). Similar results of H7b within these two groups are also obtained.

TABLE 3 | Factor loadings ($n = 3,011$).

Variables	Items	Factor loadings	*p*-Value	Variables	Items	Factor loadings	*p*-Value
Attitude	A1	0.815	0.000	PBC 2	PBC2-1	0.821	0.000
	A2	0.773	0.000		PBC2-2	0.717	0.000
	A3	0.807	0.000		PBC2-3	0.733	0.000
SN	SN1	0.814	0.000	A&E	A&E1	0.896	0.000
	SN2	0.872	0.000		A&E2	0.875	0.000
	SN3	0.881	0.000	ML&SA	ML&SA1	0.882	0.000
	SN4	0.776	0.000		ML&SA2	0.872	0.000
	SN5	0.571	0.000		ML&SA3	0.866	0.000
PBC 1	PBC1-1	0.875	0.000	BCS intention	BI1	0.938	0.000
	PBC1-2	0.604	0.000		BI2	0.954	0.000
	PBC1-3	0.907	0.000		BI3	0.946	0.000

A1–A3, denote the three paired items used to measure the respondents' attitudes; SN1–SN5, the five paired items used to measure the respondents' SN; PBC1-1–PBC1-3, the three paired items used to measure the respondents' PBC 1; PBC2-1–PBC2-3, the three paired items used to measure the respondents' PBC 2; A&E1–A&E3, the three items used to measure the respondents' views on A&E; ML&SA1-ML&SA3, the three items used to measure the respondents' views on ML&SA; BI1–BI3, the three items used to measure the respondents' BCS intention.

TABLE 4 | Correlations among variables ($n = 3,011$).

	α	CR	AVE	Attitude	BI	ML&SA	PBC1	PBC2	A&E	SN
Attitude	0.719	0.729	0.637	*0.798*	0.487	0.231	0.291	0.328	0.179	0.642
BI	0.941	0.942	0.895	0.408	*0.946*	0.302	0.467	0.374	0.378	0.615
ML&SA	0.846	0.906	0.763	0.184	0.270	*0.873*	0.414	0.322	0.466	0.399
PBC1	0.731	0.845	0.651	0.243	0.403	0.346	*0.807*	0.596	0.334	0.438
PBC2	0.636	0.802	0.575	0.234	0.298	0.241	0.412	*0.759*	0.180	0.397
A&E	0.725	0.879	0.784	0.129	0.310	0.365	0.265	0.117	*0.885*	0.340
SN	0.844	0.891	0.626	0.498	0.545	0.338	0.372	0.307	0.256	*0.791*

BI, BCS intention; PBC1, perceived behavioral control 1; PBC2, perceived behavioral control 2; SN, subjective norm; ML&SA, the medical level and service attitude; A&E, advocacy and education; CR, composite reliability; AVE, average variance extracted. The square roots of the AVE are shown on the diagonal and italicized elements in gray shade, above which are the HTMT values and below which are the correlations between the construct's values.

DISCUSSION

In this study, we added four exogenous variables to the TPB model, such as knowledge, past behavior, and supply-side factors (A&E and ML&SA). The data are well in accordance with the theoretical predications. Firstly, the addition of variables strengthened the explanatory power of the TPB model and further demonstrated the utility of TPB for prediction. Secondly, health policy makers and interveners could get more information in the decision-making and in the intervention process and improve the intervention effect. Finally, extending variables into the TPB model, the findings in this paper demonstrate that the original TPB model can be further developed and applicable to other areas, particularly to those related to public health.

Although BC has the highest cancer incidence rate in the world and BCS can prevent it effectively, most rural women in China, even in the economically well-developed area, had a lower willingness to be screened for BC (13–15). Our study supported this result. Our findings indicated that it is significant to explore the influencing factors of BI to BCS in rural China, especially the differences between the Group 1 and Group 2.

This study revealed how various psychosocial factors, including attitude, SN, PBC, and other external factors, such as knowledge, past behavior, and supplier factors (A&E and ML&SA), impact on BCS intention. It also provided evidence that TPB could well-explain and predict rural women's BCS intention. As hypotheses, attitude, SN, PBC 1, PBC 2, knowledge, and PB were positively related to the BCS intention, and they also played an intermediary role between the relationship of A&E and BI, ML&SA and BI. Besides, in the MGA of age, we found some significant differences between the two groups.

The finding of this research confirmed the positive relationship between attitude and rural women's BSC intention, which is consistent with the results of the similar studies on rural women in Korea (32) and female residents in Macao (33). Attitude also links other variables. Therefore, in order to improve willingness, we should constantly improve the attitude of rural women toward BCS. It cannot be overemphasized that BCS is beneficial for the early diagnosis and treatment of cancer. Therefore, health institutions can provide lectures on successful cases to rural women to make them realize the importance of screening and early diagnosis. Meanwhile, the government could give the preferential policies to

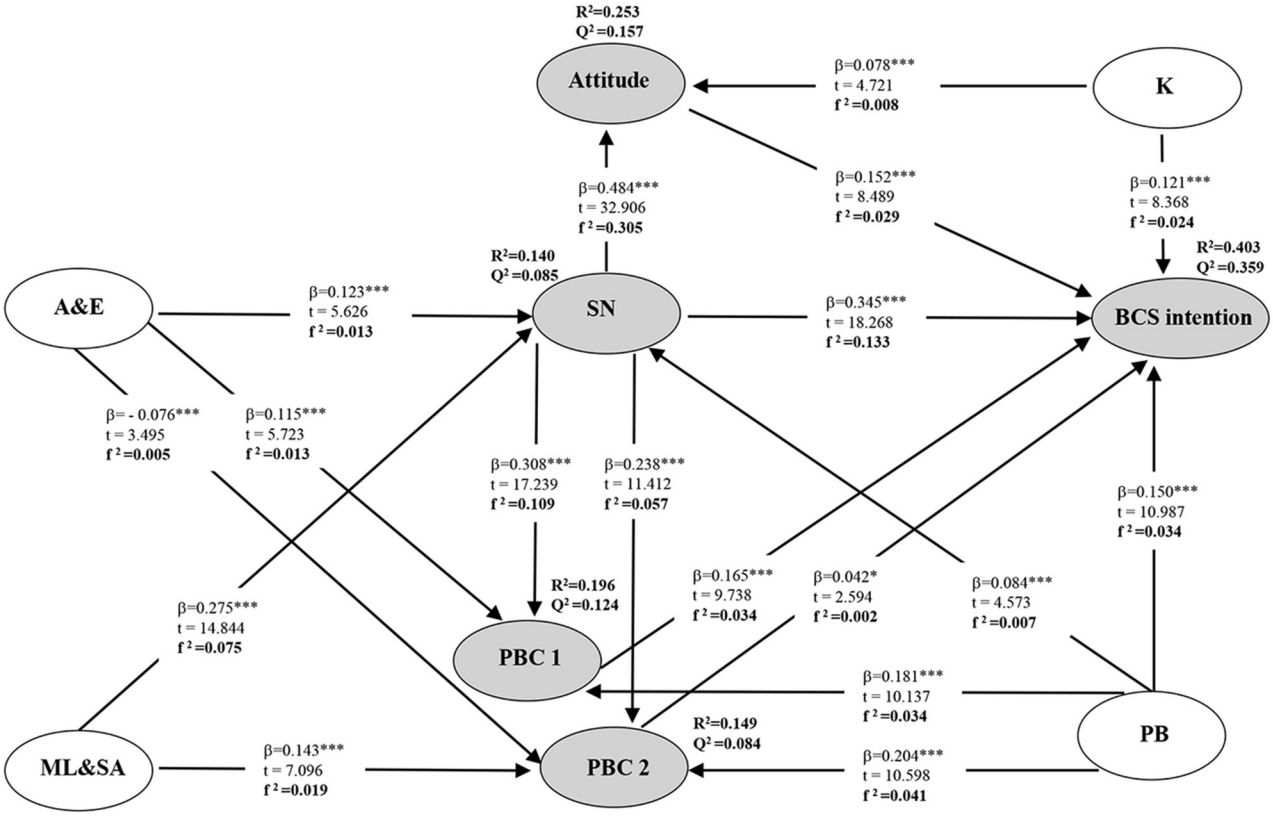

FIGURE 3 | A path diagram for the research model. β, path coefficient; *** $p < 0.001$, * $p < 0.05$; *t*, *t*-value; R^2, coefficient of determination, which represents the amount of explained variance of each endogenous latent variable; f^2, effect size; Q^2, predictive relevance; PB, past behavior; BI, behavior intention; PBC1, perceived behavioral control 1; PBC2, perceived behavioral control 2; SN, subjective norm; K, knowledge; ML&SA, the medical level and service attitude; A&E, advocacy and education; BCS intention, breast cancer screening intention.

conduct free screening for age-appropriate women, which can improve the attitude toward BCS and further enhance the behavioral intention.

In line with the results of Saudi (34), Korea (35), and Hong Kong (36), lack of time, long geographic distance, painful and uncomfortable experience during the examination, and other factors are obstacles that rural women encountered. This result can be possibly ascribed to the limited detection and screening facilities in some areas (5). It is common for rural women in China to hold a relatively conservative attitude toward their bodies. Shang's research held the opinion that examining bodies by oneself or by others was regarded as inappropriate behavior (70). These conservative social norms may help explain why Chinese rural women's feelings of embarrassment or shyness become the key barriers to be screened for BC in this study, and the result is also consistent with the past results of Im's (35). As a result, rural women must overcome some difficulties when they participate in BCS. Besides, the same thing as attitude is that PBC also is linked to other variables. Therefore, in order to improve women's BCS intention, we need to reduce the hindering factors and facilitate the promoting factors of BCS intention in rural women. Firstly, rural women could be organized to go to the hospitals or clinics for BCS. It is, maybe, a good way to implement an appointment system to reduce transportation and time costs. Next, in order to decrease bad feelings, we could show the screening process and the use of equipment in the form of an animated short film to improve rural women's understanding. Besides, it may be useful to increase the number of female physicians in order to reduce the embarrassment of being examined. Furthermore, we could conduct psychological counseling on embarrassment and fear.

At the same time, when designing various interventions to reduce embarrassment and fear and to increase a BCS rate, ML&SA, which is a positive influence factor of PBC, is closely related to the patient feelings and also needs to be considered. In this study, ML&SA can positively affect SN and PBC 2, and it can also influence BI through attitude, SN, and PBC 1. The following suggestions could be referred: (I) The health authority should make a regular screening training for physicians in the health center to improve their screening ability. The better the screening level of medical staff is, the fewer feelings of fear and pain. (II) The government could cooperate with social institutions to increase the funding of primary healthcare

TABLE 5 | Specific indirect effects (n = 3,011).

	Path	Path coefficient (β)	*t*-Value	p
1	ML&SA -> SN -> A -> BI	0.02	7.132	0.000
2	K -> A -> BI	0.012	4.042	0.000
3	A&E -> SN -> A	0.059	5.596	0.000
4	A&E -> SN -> BI	0.042	5.254	0.000
5	PB -> SN -> PBC2 -> BI	0.001	2.186	0.029
6	A&E -> SN -> PBC2 -> BI	0.001	2.293	0.022
7	SN -> PBC1 -> BI	0.051	8.287	0.000
8	ML&SA -> SN -> PBC2 -> BI	0.003	2.522	0.012
9	SN -> A -> BI	0.074	8.089	0.000
10	ML&SA -> SN -> PBC1	0.085	10.202	0.000
11	A&E -> SN -> A -> BI	0.009	4.657	0.000
12	PB -> PBC1 -> BI	0.03	6.995	0.000
13	ML&SA -> SN -> PBC2	0.065	9.182	0.000
14	PB -> SN -> BI	0.029	4.483	0.000
15	A&E -> PBC2 -> BI	−0.003	2.132	0.033
16	ML&SA -> PBC2 -> BI	0.006	2.419	0.016
17	ML&SA -> SN -> A	0.133	13.062	0.000
18	ML&SA -> SN -> PBC1 -> BI	0.014	6.905	0.000
19	PB -> SN -> PBC1 -> BI	0.004	4.031	0.000
20	ML&SA -> SN -> BI	0.095	11.251	0.000
21	PB -> SN -> PBC1	0.026	4.424	0.000
22	PB -> PBC2 -> BI	0.009	2.517	0.012
23	PB -> SN -> PBC2	0.02	4.221	0.000
24	A&E -> SN -> PBC1 -> BI	0.006	4.675	0.000
25	SN -> PBC2 -> BI	0.01	2.556	0.011
26	A&E -> SN -> PBC2	0.029	5.073	0.000
27	A&E -> SN -> PBC1	0.038	5.406	0.000
28	PB -> SN -> A	0.041	4.52	0.000
29	PB -> SN -> A -> BI	0.006	3.965	0.000
30	A&E -> PBC1 -> BI	0.019	4.804	0.000

PB, past behavior; BI, BCS intention; PBC1, perceived behavioral control 1; PBC2, perceived behavioral control 2; SN, subjective norm; A, attitude; K, knowledge; ML&SA, the medical level and service attitude; A&E, advocacy and education.

infrastructure. They should further improve the software and hardware and promote the upgrading of village clinics' screening facilities. (III) All healthcare physicians should respect and protect women's privacy during BCS. In turn, the rural women will show less embarrassment.

Mass media, relatives, friends, and healthcare providers are the main primary information sources in China (71), and are the widely used approaches for rural women to know about BCS in this study. The results of this study show that A&E, one of the supply-side factors, has positive effects on SN and PBC 1, which means that A&E plays an important role in obtaining social support and reducing the obstacles of the distance, transportation, busyness, etc. Furthermore, it can affect BI through attitude, SN, PBC 1, and PBC 2. However, 68.2% of rural women selected "never" or "hardly" or "seldom" with regard to the item "How often do you receive A&E on breast cancer." A systematic review of cancer screening interventions among Asian women had the view that it was ineffective to perform the print materials and media campaigns alone (72). Therefore, given our research findings, more intervention approaches should be taken to improve the efficacy of A&E, such as television, WeChat, publicity columns, brochures or leaflets, newspapers or magazines, and broadcast. This result also shows that A&E has negative effects on PBC 2, and this is not exactly unexpected. A&E might publicize the harm of breast cancer and increase rural women's screening intention, but it could also increase the exposure of the screening process. Thus, they may feel more embarrassed, especially with the male physician's involvement. Hence, A&E should provide positive psychological support and improve the education system. Privacy protection deserves a special attention. Besides, in this study, 66.7% of rural women "never" or "hardly" or "seldom" are advised to participate in the BCS by the physicians, which demonstrates again that healthcare physicians do not play a crucial part in the A&E. Considering that, it is necessary to collaborate with SN, e.g., healthcare providers, healthcare physicians, relatives or friends, to expand the influence of A&E.

TABLE 6 | Assessment of group difference in age ($n = 3,011$).

Hypotheses	Path coefficient (β)		*t*-Value		Path coefficient differences	p		Supported
	Group 1: <35/>64	Group 2: between 35–64	Group 1: <35/>64	Group 2: between 35–64		Henseler MGA	Permutation	
H1	0.177***	0.128***	6.641	5.244	0.049	0.174	0.189	No/No
H2a	0.172***	0.164***	6.879	7.187	0.008	0.821	0.833	No/No
H2b	0.051	0.045*	1.955	2.211	0.005	0.876	0.873	No/No
H3a	0.354***	0.334***	13.204	12.577	0.02	0.606	0.612	No/No
H3b	0.461***	0.51***	21.298	27.307	−0.049	0.086	0.097	No/No
H3c	0.296***	0.331***	11.678	13.129	−0.035	0.333	0.336	No/No
H3d	0.23***	0.271***	7.159	10.19	−0.041	0.321	0.324	No/No
H4a	0.094***	0.125***	4.151	6.695	−0.03	0.305	0.296	No/No
H4b	0.091***	0.061**	3.842	2.776	0.031	0.341	0.358	No/No
H5a	0.130***	0.114***	4.182	3.830	0.016	0.712	0.732	No/No
H5b	0.155***	0.089**	5.198	3.225	0.066	0.106	0.108	No/No
H5c	0.005**	−0.127***	0.158	4.338	0.132	0.002	0.003	Yes/Yes
H6a	0.271***	0.277***	9.317	11.591	−0.006	0.874	0.865	No/No
H6b	0.127***	0.127***	4.183	4.684	0.000	0.997	0.996	No/No
H7a	0.097***	0.200***	4.704	10.857	−0.103	0.000	0.000	Yes/Yes
H7b	0.051	0.119***	1.950	4.760	−0.068	0.06	0.073	No/No
H7c	0.141***	0.134***	5.358	5.435	0.007	0.852	0.846	No/No
H7d	0.181***	0.147***	6.075	5.905	0.033	0.388	0.387	No/No

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

In this study, SN is the strongest predictor of rural women's screening intention. SN is positively related to the rural women's BCS intention, which is similar to the existing research results of Parsa (37) and Jensen (19). Besides, it also has positive effects on rural women's attitude toward BCS, PBC 1, and PBC 2, which are consistent with the TPB model and similar to previous studies (36, 38, 39). Hence, it is necessary for the government to encourage the stakeholders to fully support rural women to conduct BCS. Family members and good friends should give psychological comfort and support to reduce the obstruction of PBC. Primary care physicians in the clinic and experts could introduce the relevant knowledge and importance of BCS to rural women. Beyond that, as a hub in the research model, SN combines other influencing factors (e.g., A&E, ML&SA, PB) and plays an intermediary role. Therefore, it is useful that rural women who have been screened in the past talk about their experience in the A&E program. For rural women who have never participated in screening, it is also beneficial for them to be familiar with the screening process. These ways can make rural women aware of the necessity for screening and follow the doctor's advice for timely screening.

The result in this study shows that having sufficient knowledge about breast cancer has a positive effect on rural women's BCS intention and attitudes toward BCS, which is consistent with the studies of Ana (44), Coyne (42), Berry (43), and Yan (33). Knowledge also influences BCS intention through attitude. The past research reported that lack of knowledge may prevent women from identifying the main symptoms of the disease and consequently lead to the neglect of the disease, which can result in a delay of detection (5, 73). Moreover, 44% of participants who get a score of 0 in the item "Which preventive measures can early detect breast cancer lesions." This result indicates that rural women's knowledge is insufficient and the prevention awareness of BC is unsatisfying. The relevant study also revealed that poor knowledge about BCS contributes to a negative attitude (54). In a certain sense, many rural women do not believe that they are at risk of BC. Authorities should strengthen the popularization of knowledge about BCS, such as lectures and videos, to help rural women learn breast examination methods. We should also encourage rural women to accept regular physical examination, including breast self-examination and physical diagnosis by physicians or professional nurses every year. Breast examination of different age groups should be taken additionally.

Past behavior is also positively associated with BCS intention. We also found that PB has a positive effect on SN, PBC 1, and PBC2 directly. It also indirectly affects BCS intention through SN, PBC 1, and PBC 2. A recent review has reported that women who have been screened for BC have more opportunities to get suggestions about the prevention of breast cancer from the physicians (54). Enhanced communication between doctors and rural women can encourage rural women to follow the doctor's advice and get screened. Rural women who have done screening are also better aware of the screening process, which can reduce their fear. This study reported that 41.7% of 3,011 participations were not taking part in the BCS program within the past 5 years. As a result, we should give more

encouragement to those rural women who had never been screened for BC.

The output of MAG reveals that there are significant differences between Group 1 (<35 or >64) and Group 2 (between 35–64) in regard to the relationship between A&E and PBC2. Especially, the effects of both groups are significant, but signs of the path coefficients are opposite: "+" for Group 1; "-" for Group 2. We figured out a possible reason. As A&E about BC-free screening program mainly targeted on rural women between 35 and 64 years old, they believe that A&E might lead to more and more people knowing that they will attend the screening, which would make them apprehensive and embarrassed. The MGA results also reveal that there is a significant difference between the two groups in the effect of PB on BCS intention, and the path coefficient of Group 2 is higher than that of Group 1. Besides, PB has a positive effect on SN for the rural women who are in Group 2, but it has no significant impact for the rural women who are in the Group 1. According to the results of MGA, in Group 2, PBC 2 has a positive effect on BI, despite little significant influence in the other group. It can be deduced that the respondents who were in Group 2 were more sensitive than those women who were in Group 1 on embarrassment, fear, and pain. In summary, the rural women in Group 2 were more susceptible to the practical behavior and practical experience from themselves or primary care physicians, while those rural women in Group 1 were more susceptible to advocacy and education. Therefore, the differences in the different stages of age could be considered in designing policy inventions. We should pay special attention to Group 2. For instance, township health centers and village clinics should schedule more female physicians and improve the healthcare physicians' screening experience. Medical institutions should publicize cancer screening among rural women through lectures or other ways for the rural women in Group 1, while, for the rural women in Group 2, the past experience and behavior of participating in screening should be emphasized, and their privacy should also be protected.

In this study, by multi-stage stratified sample method, we are concerned with the influencing factors of BCS intention of these women who are living in rural areas with different economic development levels in Jiangsu, China. Therefore, the participants of this study were representatives of rural women groups. Considering differences in economic development levels, our study results can be generalized to other rural areas across China. We have to acknowledge that there are still some limitations to this study. First, this study collected information in the form of a self-filled questionnaire. Therefore, an inaccurate estimation of BCS and recall bias were unavoidable. Second, our data came from a sample of rural women of some areas in Jiangsu Province, limiting generalizability to the urban area. Third, we could not judge causal inferences between TPB factors and actual screening behavior due to the cross-sectional study method, which did not control all possible confounding variables. Future studies should test the causal relationship by a research design of prospective control.

CONCLUSION

In this study, we investigated the influencing factors of Chinese rural women's BCS intention by a PLS-SEM approach based on TPB and proposed some intervention measures. Among all the factors affecting the intention to BCS, SN is found to be the strongest predictor, followed by PBC 1, attitude, PB, knowledge, and PBC 2. A&E and ML&SA can affect BI through attitude, SN, and PBC. The results of MGA of age indicated that there are significant differences in different path coefficients. The findings of this study provided a theoretical basis for the implementation of intervention measures to enhance rural women's BCS willingness, which is of great significance to improve rural women's health levels.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study's ethical admission was approved by the Ethics Committee of Sir Run Run Hospital, Nanjing Medical University. The grant number is 2019-SR-017. We obtained the oral informed consent from each subject who participated in the survey.

AUTHOR CONTRIBUTIONS

YH and YS: methodology, software, and writing—review and editing. YH, YS, and WL: writing—original draft preparation. YS, JY, WL, BQ, ZH, JL, and YH: investigation and data curation. YS and JY: visualization. YH: conceptualization, resources, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Cost-Effectiveness Analysis of Five Systemic Treatments for Unresectable Hepatocellular Carcinoma in China: An Economic Evaluation Based on Network Meta-Analysis

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Background and Objective: Unresectable hepatocellular carcinoma (uHCC) is the main histological subtype of liver cancer and causes a great disease burden in China. We aimed to evaluate the cost-effectiveness of five first-line systemic treatments newly approved in the Chinese market for the treatment of uHCC, namely, sorafenib, lenvatinib, donafenib, sintilimab plus bevacizumab (D + A), and atezolizumab plus bevacizumab (T + A) from the perspective of China's healthcare system, to provide a basis for decision-making.

Methods: We constructed a network meta-analysis of 4 clinical trials and used fractional polynomial models to indirectly compare the effectiveness of treatments. The partitioned survival model was used for cost-effectiveness analysis. Primary model outcomes included the costs in US dollars and health outcomes in quality-adjusted life-years (QALYs) and the incremental cost-effectiveness ratio (ICER) under a willingness-to-pay threshold of $33,521 (3 times the per capita gross domestic product in China) per QALY. We performed deterministic and probabilistic sensitivity analyses to investigate the robustness. To test the effect of active treatment duration on the conclusions, we performed a scenario analysis.

Results: Compared with sorafenib, lenvatinib, donafenib, D + A, and T + A regimens, it yielded an increase of 0.25, 0.30, 0.95, and 1.46 life-years, respectively. Correspondingly, these four therapies yielded an additional 0.16, 0.19, 0.51, and 0.86 QALYs and all four ICERs, $40,667.92/QALY gained, $27,630.63/QALY gained, $51,877.36/QALY gained, and $130,508.44/QALY gained, were higher than $33,521 except for donafenib. T + A was the most effective treatment and donafenib was the most economical option. Sensitivity and scenario analysis results showed that the base-case analysis was highly reliable.

Conclusion: Although combination therapy could greatly improve patients with uHCC survival benefits, under the current WTP, donafenib is still the most economical option.

Keywords: unresectable hepatocellular carcinoma, partitioned survival, cost-effectiveness analysis, fractional polynomial, network meta-analysis

INTRODUCTION

The 2020 Global Cancer Burden Report released by the WHO International Agency for Research on Cancer stated that liver cancer accounts for 8.3% of cancer-related deaths and is the third leading cause of cancer deaths worldwide (1). Hepatocellular carcinoma (HCC) is the main histological subtype of liver cancer, accounting for approximately 90% of cases of primary hepatic carcinoma (2, 3). Study has shown that the incidence of HCC in China is 35/100,000 population and the burden of disease in China accounts for ∼50% of the global burden (4). A survey and analysis of patients with liver cancer in 13 provinces and cities from 2012 to 2014 showed that the average annual direct medical costs for each case were ¥44,850 (5), which represents a major social and economic burden. Although in early stages, the disease can be cured by resection, liver transplantation, or ablation, most patients present with unresectable hepatocellular carcinoma (uHCC) and have a poor prognosis (6–8).

The conventional treatment regimens of uHCC are mainly chemotherapy and radiotherapy (9). Sorafenib is the first molecularly targeted drug to systematically treat uHCC (10), which was approved by the United States Food and Drug Administration (FDA) for the treatment of advanced uHCC in 2007 and it was the sole targeted drug approved by the FDA in the following 10 years. With the subsequent advent of more molecularly targeted drugs, survival in patients with uHCC has been greatly extended. These drugs include those for first-line treatment, such as lenvatinib and donafenib, and drugs for the second-line treatment such as regorafenib, cabozantinib, apatinib, and ramucirumab. The results of analysis for the Chinese population in the REFLECT trial (11, 12) showed that compared with sorafenib, lenvatinib significantly increased patients' overall survival (OS) and progression-free survival (PFS) and increase objective response rate (ORR) by 18%; therefore, it is currently the first choice for increasingly more clinical experts. Chinese subgroup data of the IMbrave150 trial in 2019 (13, 14) showed that the "T + A" regimen [PD-L1 inhibitor atezolizumab (T) combined with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (A)] increased ORR greatly, and the median OS was more than double that of the sorafenib regimen. Based on the published 14-month data of the phase II/III ORIENT-32 clinical trial (15) in Chinese patients with uHCC, the ORR of sintilimab (D) plus bevacizumab (hereinafter referred to as the "D + A" regimen) was 16% higher than that of the sorafenib regimen, and the OR and PFS rates were 0.65 and 0.53, respectively. The results of the phase II/III ZGDH3 trial (16) investigating donafenib and sorafenib in first-line treatment of advanced HCC in the Chinese population showed that the OS of patients who received the donafenib regimen was significantly higher than the OS of those who received the sorafenib regimen.

The above clinical trial protocols have been approved for liver cancer in China and the control groups are treated with sorafenib. Sorafenib and lenvatinib were approved in 2008 and 2017 and were included in the catalog of medical insurance category B drugs in 2017 and 2021, respectively. Both the D + A and donafenib regimens were approved in 2021 and have been included in the catalog of medical insurance drugs recently. T + A was approved in 2020, but it is the only treatment that has not been covered by medical insurance so far. In the first two quarters of 2021, according to sales data of public hospitals in 20 key Chinese cities, namely, Beijing, Nanjing, and Shanghai, sales (17) of sorafenib, lenvatinib, and atezolizumab totaled ¥124, ¥108, and ¥16 million, respectively; sales data for sintilimab and donafenib are unavailable.

At present, there are no studies on the cost-effectiveness of donafenib and D + A in the treatment of advanced hepatocarcinoma and no studies comparing the cost-effectiveness of T + A, D + A, donafenib, and lenvatinib in pairs or groups. The survival data of the IMbrave150 and RELFECT trials have been updated; furthermore, prices of some drugs have dropped sharply after a new round of healthcare talks. Hence, we used updated Chinese subgroup data and the latest drug prices to re-evaluate the cost-effectiveness of lenvatinib and T + A vs. sorafenib, and drugs for first-line treatment in the above five regimens were compared in groups to provide a basis for decision-making.

MATERIALS AND METHODS

Model Structure

In this study, a partitioned survival model was used to simulate the survival status of patients with uHCC in different periods under various treatments, namely, PFS, progressive disease (PD), and death. The longest simulation period was 10 years, which simulated 97% of the deaths in all groups, about life-long time for advanced liver cancer, and the cycle length was 1 month. Microsoft Excel 2019 was used for model building.

Our target population was patients with uHCC receiving first-line treatments in China. To determine the most cost-effective first-line systemic treatment regimen for uHCC in this study, we compared five regimens approved in China: (1) sorafenib, (2) lenvatinib, (3) donafenib, (4) atezolizumab plus bevacizumab (T + A), and (5) sintilimab plus bevacizumab (D + A). **Figure 1** shows the tree diagram and bubble diagram. Patients would be treated with second-line therapy when their disease progressed, which mainly included tyrosine kinase inhibitor (TKI) therapy (18, 19), immunotherapy (20), and best supportive care (BSC). Furthermore, we assumed that all the patients received BSC 3

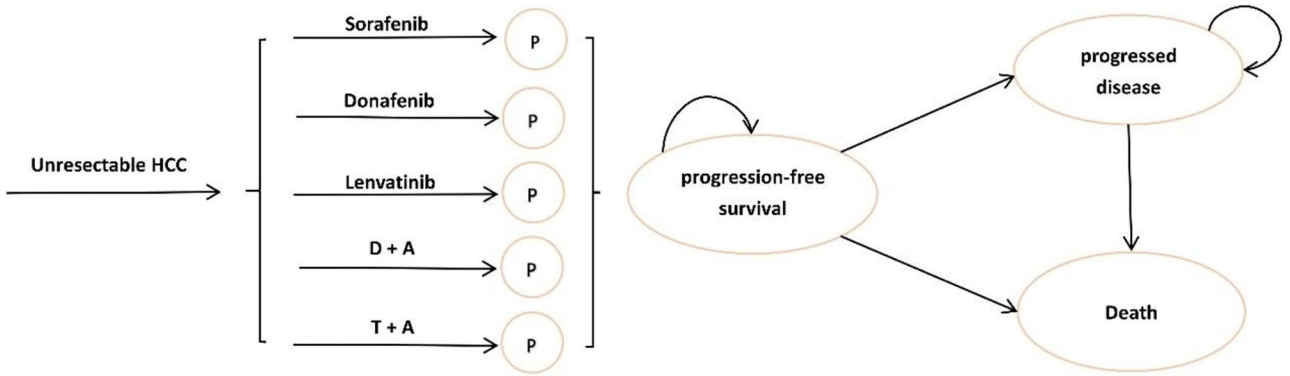

FIGURE 1 | Model structure of a decision tree combining the partitioned survival model. (HCC, hepatocellular carcinoma; P, progression-free survival; D + A, sintilimab plus bevacizumab; T + A, atezolizumab plus bevacizumab).

months before they died in the base-case analysis. A detailed description of the survival model selection was shown in **Supplementary Method** in the supplement.

Clinical Data

We used Chinese subgroup data from the IMbrave150 trial (13), REFLECT trial (11), ORIENT-32 trial (15), and ZGDH3 trial (16) to explore the cost-effectiveness of sorafenib, lenvatinib, T + A, D + A, and donafenib in the treatment of uHCC. The PFS curve of the IMbrave150 Chinese subgroup covered only 16 months of observation and the hazard ratio (HR) of this subgroup was 0.60, which was very close to the HR of the global population (0.59) (14). Therefore, it was assumed that the Chinese subgroup and the treatment group in the total population had the same level of improved PFS relative to the control group; the updated PFS curve of the total population of the IMbrave150 trial was used to replace the PFS curve of the Chinese subgroup. The detailed information of each trial is shown in **Supplementary Table 1** in the supplement. The baseline characteristics (namely, age, sex ratio, ethnicity, and indications) of patients in the four trials were basically the same and comparable. The original PFS and OS curves of the four groups are shown in **Supplementary Figure 1** in the supplement. The overall quality of the included literature was high, but there was a risk of bias in blinded selection, more details are given in **Supplementary Figure 2**.

Model Survival and Progression Estimates

We used GetData Graph Digitizer (version 2.26) to extract survival data from PFS and OS curves. Guyot's method was used to reconstruct individual patient data (21), which is the most accurate data reproduction method currently known for cases in which individual patient data are not available (22). To indirectly compare different regimens and get time-varying HR, we fitted a series of first-order fractional polynomial (FP) models with power parameters −2, −1, −0.5, 0, 0.5, 1, 2, and 3, which included common survival distributions, such as Jansen (23). The calculation formula of time-varying HR is presented in Equations 1, 2, d_0 and d_1 are two key parameters for calculating HR. The log cumulative hazards plots of each trial were used to examine the proportional hazards hypothesis over time. The deviance information criterion (DIC) was used to assess model fit and choose the best model (24, 25). The filtered models were checked by the corresponding survival curves finally. Fixed-effect Bayesian models were used to estimate treatment effects *via* Markov chain Monte Carlo algorithms. Non-informative priors were used to allow the observed trial data to explain effect estimates. We used the R (version 4.1.0), with 3 parallel Markov chains consisting of 100,000 samples after a 10,000 samples burn-in. Finally, we chose the first-order FP model (power parameter = −2) for both OS and PFS, more details are shown in **Table 1**, the fitted curves are given in **Supplementary Figure 4**. For PFS, we did not consider the first-order FP model (power parameter = 1) that had smaller DIC as the fitted survival curve violated the clinical reality distinctly judged by clinical experts. Log cumulative hazards plots that showed non-proportional hazards are given in **Supplementary Figure 3**, OS and PFS curves fitted by all first-order FP models are shown in **Supplementary Figure 5**. The goodness-of-fit results are shown in **Supplementary Table 2** in the supplement. Life-years of all regimens calculated by NMA are given in **Table 2**.

$$Ln(h(t)) = \beta_0 + \beta_1^* t^{\mathrm{P}}, with\ \ t^0 = \log(t) \tag{1}$$

$$\begin{aligned} Ln(HR_{12}) &= Ln(h(t))_1 - Ln(h(t))_2 \\ &= (\beta_{10} - \beta_{20}) + (\beta_{11} - \beta_{21})^* t^p = d_0 + d_1^* t^p \end{aligned} \tag{2}$$

We derived the expected survival curves for lenvatinib, donafenib, D + A, and T + A by applying the hazard ratios to the reference survival curve. The OS and PFS curves of sorafenib as a reference were derived from the ZGDH3 trail (16), in which OS and PFS curves are the most mature, respectively, the data maturity of OS and PFS was more than 88 and 95%. These data points were then used to fit the following parametric survival functions: Weibull, log-normal, log-logistic, exponential, gamma, and Gompertz models. The eligible survival function was chosen based on the lowest value

TABLE 1 | Model parameters.

Item	Mean (range)	Distribution	Sources
Clinical input			
Survival model for sorafenib			
Theta for OS	2.40 (2.29–2.50)	Uniform	Lognormal survival model
Sigma for OS	0.95 (0.87–1.04)	Uniform	
Theta for PFS	1.34 (1.25–1.42)	Uniform	
Sigma for PFS	0.77 (0.71–0.84)	uniform	
Parameters for FP model: OS			
d_0: lenvatinib vs. sorafenib[b]	−0.15 (−0.45–0.15)	Uniform	NMA
d_1: lenvatinib vs. sorafenib[b]	−1.60 (−3.72–0.02)	Uniform	
d_0: donafenib vs. sorafenib[b]	−0.18 (−0.37–0.01)	Uniform	
d_1: donafenib vs. sorafenib[b]	−0.17 (−1.39–0.99)	Uniform	
d_0: D+A vs. sorafenib[b]	−0.68 (−1.13– −0.22)	Uniform	
d_1:D+A vs. sorafenib[b]	−0.27 (−2.35–1.78)	Uniform	
d_0: T+A vs. sorafenib[b]	−0.48 (−0.8– −0.16)	Uniform	
d_1: T+A vs. sorafenib[b]	−0.23 (−1.59–1.17)	Uniform	
Parameters for FP model:PFS			
d_0: lenvatinib vs. sorafenib[b]	−0.21 (−0.54–0.13)	Uniform	NMA
d_1: lenvatinib vs. sorafenib[b]	−0.80 (−1.45– −0.17)	Uniform	
d_0: donafenib vs. sorafenib[b]	−0.35 (−0.58– −0.12)	Uniform	
d_1: donafenib vs. sorafenib[b]	0.66 (0.22–1.11)	Uniform	
d_0: D+A vs. sorafenib[b]	−0.51 (-0.77– −0.24)	Uniform	
d_1:D+A vs. sorafenib[b]	−0.04 (−0.57–0.50)	Uniform	
d_0: T+A vs. sorafenib[b]	−0.35 (−0.64– −0.05)	Uniform	
d_1: T+A vs. sorafenib[b]	−1.63 (−2.26– −1.02)	Uniform	
Regorafenib reduction rate	0.38 (0.36–0.40)	Beta	(26)
Sorafenib reduction rate	0.37 (0.35–0.39)	Beta	(13)
Lenvatinib reduction rate	0.23 (0.22–0.24)	Beta	(11)
Donafenib reduction rate	0.23 (0.22–0.24)	Beta	Assumed
Sorafenib administration frequency	0.90 (0.86–0.95)	Beta	(11)
D+A administration frequency	0.93 (0.88–0.98)	Beta	(15)
Lenvatinib administration frequency	0.92 (0.87–0.96)	Beta	(11)
T+A administration frequency	0.95 (0.90–1.00)	Beta	(13)
Donafenib administration frequency	0.92 (0.87–0.96)	Beta	Assumed
Regorafenib administration frequency	0.90 (0.86–0.95)	Beta	(26)
Tislelizumab administration frequency	0.95 (0.90–1.00)	Beta	Assumed
Probability of grade 1–2 adverse reactions in D+A	0.44 (0.42–0.46)	Beta	(15)
Probability of grade 3 or above adverse reactions in D+A	0.55 (0.52–0.58)	Beta	(15)
Probability of grade 1–2 adverse reactions in sorafenib	0.50 (0.47–0.52)	Beta	(11, 13, 15)
Probability of grade 3 or above adverse reactions in sorafenib	0.67 (0.63–0.70)	Beta	(11, 13, 15)
Probability of grade 1–2 adverse reactions in T+A	0.39 (0.37–0.41)	Beta	(13)
Probability of grade 3 or above adverse reactions in T+A	0.59 (0.56–0.62)	Beta	(13)
Probability of grade 1–2 adverse reactions in lenvatinib	0.34 (0.32–0.36)	Beta	(11)
Probability of grade 3 or above adverse reactions in lenvatinib	0.63 (0.60–0.66)	Beta	(11)
Probability of grade 1–2 adverse reactions in donafenib	0.42 (0.34–0.51)	Beta	(16)
Probability of grade 3 or above adverse reactions in donafenib	0.57 (0.46–0.67)	Beta	(16)
Probability of grade 1–2 adverse reactions in regorafenib	0.33 (0.31–0.35)	Beta	(26)
Probability of grade 3 or above adverse reactions in regorafenib	0.67 (0.64–0.70)	Beta	(26)
Continuing to use the original drug after progression with T+A	0.18 (0.17–0.19)	Beta	(13)
Continuing to use targeted treatment after progression with T+A	0.32 (0.31–0.34)	Beta	(13)

(Continued)

TABLE 1 | Continued

Item	Mean (range)	Distribution	Sources
Using Best Support Care after progression with T+A/D+A	0.50 (0.48–0.53)	Beta	(13)
Continuing to use targeted treatment after progression with D+A	0.50 (0.48–0.53)	Beta	Assumed
Continuing to use the original drug after progression with lenvatinib/sorafenib/donafenib	0.03 (0.029–0.032)	Beta	(13)
Continuing to use targeted treatment after progression with lenvatinib/sorafenib/donafenib	0.33 (0.31–0.34)	Beta	(13)
Continuing to use Tislelizumab after progression with lenvatinib/sorafenib/donafenib	0.26 (0.25–0.27)	Beta	(13)
Using Best Support Care after progression with lenvatinib/sorafenib/donafenib	0.38 (0.35–0.41)	Beta	(13)
Cost ($)			
Sorafenib per 12,000 mg (Bayer AG, 200 mg, twice a day)	879.11 (703.29–879.11)	Gamma	Local market[a]
Atezolizumab per 1,200 mg (Roche, 1,200 mg, administration once every 3 weeks)	5,058.76 (4,047.01–5,058.76)	Gamma	Local market[a]
Lenvatinib per 120 mg (PATHEONINC, 12 mg/day, body weight≥60 kg; 8 mg/day, body weight<60 kg)	499.71 (399.77–499.71)	Gamma	Local market[a]
Sintilimab per 100 mg (Innovent Biologics, 1,200 mg, administration once every 3 weeks)	166.57 (133.26–166.57)	Gamma	Local market[a]
Donafenib per 4,000 mg (Zelgen Biopharmaceuticals, 200 mg, twice a day)	399.77 (319.82–399.77)	Gamma	Local market[a]
Bevacizumab per 100 mg (T+A group, Roche, 15 mg/kg, administration once every 3 weeks)	231.34 (185.08–231.34)	Gamma	Local market[a]
Bevacizumab per 100 mg (D+A group, Innovent Biologics, 15 mg/kg, administration once every 3 weeks)	176.75(141.40–176.75)	Gamma	Local market[a]
Regorafenib per 1,120 mg (Bayer AG, 160 mg/day, 3 weeks of medications, then discontinuing for 1 week)	744.85 (372.43–744.85)	Gamma	Local market[a]
Tislelizumab per 100 mg (BeiGene, 200 mg intravenously every 3 weeks)	223.63 (178.91–223.63)	Gamma	Local market[a]
Best support care per month	265.08 (212.06–318.10)	Gamma	(27)
Hospice care cost per patient	1,839 (1,519–2,279)	Gamma	(28)
Cost of follow-up and monitoring per month in PFS[c]	114 (86–143)	Gamma	(28)
Cost of follow-up and monitoring per month in PD[c]	210 (157–262)	gamma	(28)
Cost for treatment of adverse reactions of sorafenib	45.6 (36.5–54.8)	Gamma	(11, 13, 15, 18)
Cost for treatment of adverse reactions of D+A	94.2 (75.4–113.1)	Gamma	(15, 18)
Cost for treatment of adverse reactions of T+A	47.0 (37.6–56.4)	Gamma	(13, 18)
Cost for treatment of adverse reactions of lenvatinib	96.5 (77.2–115.8)	Gamma	(11, 18)
Cost for treatment of adverse reactions of donafenib	48.10 (38.48–57.72)	Gamma	(16, 18)
Cost for treatment of adverse reactions of regorafenib	64.3 (51.5–77.2)	Gamma	(18, 26)
Utilities			
PFS status utility without adverse reactions	0.76 (0.61–0.91)	Beta	(18, 28, 29)
PD status utility without adverse reactions	0.68 (0.54–0.82)	Beta	(18, 28, 29)
Negative utility of Grade 1–2 adverse reactions	0.01 (0.01–0.02)	Beta	(18, 28, 29)
Negative utility of Grade 3 and above adverse reactions	0.16 (0.11–0.20)	Beta	(18, 28, 29)
Other			
Discount	0.05 (0.00–0.08)	Beta	(30)

[a] *As of December 2021.*

[b] *HR-related parameter, more details see Equation 2.*

[c] *Assumed be the same in five treatment groups.*

D + A, sintilimab plus bevacizumab; T + A, atezolizumab plus bevacizumab; PD, progressed disease; PFS, progression-free survival; AE, adverse effects; FP, fractional polynomial; sd, standard deviation.

of the Akaike information criterion (AIC) and visual inspection. The final functions of the sorafenib were log-normal distribution for both the OS and PFS. The log-logistic distribution that had a little lower AIC than the log-normal distribution was judged by clinical experts to have unreasonably fat tails, more details are shown in **Table 1** and **Supplementary Figure 6** in the supplement. The goodness-of-fit results are shown in **Supplementary Table 3**.

TABLE 2 | Results of base-case analysis and scenario analysis.

Drug	Total			Only PFS			Total				Only PFS			
	Cost	Utility (QALY)	Life-years	Cost	Utility (QALY)	Life-years	ICER (Sorafenib as a reference standard)	ICER (Lenvatinib as a reference standard)	ICER (Donafenib as a reference standard)	ICER (D+A as a reference standard)	ICER (Sorafenib as a reference standard)	ICER (Lenvatinib as a reference standard)	ICER (Donafenib as a reference standard)	ICER (D+A as a reference standard)
Base-case analysis														
Sorafenib	16,614.86	0.91	1.38	4,073.32	0.28	0.39	/	/	/	/	/	/	/	/
Donafenib[a]	21,937.99	1.1	1.68	7,740.16	0.41	0.54	27,630.63	/	/	/	29,735.63	/	/	/
Lenvatinib	23,053.83	1.07	1.63	8,611.27	0.36	0.49	40,667.92	Dominated	/	/	60,084.66	Dominated	/	/
D+A	43,195.21	1.42	2.33	18,312.20	0.42	0.58	51,877.36	66,487.88	56,890.35	/	100,367.32	569,830.35	146,227.70	/
T+A[b]	129,281.72	1.77	2.84	71,551.54	0.49	0.67	130,508.44	160,062.01	150,686.12	245,314.77	330,391.06	788,547.23	489,002.93	853,608.32
Scenario analysis														
Sorafenib[a]	19,183.66	0.91	1.38	4,073.32	0.28	0.39	/	/	/	/	/	/	/	/
Donafenib[a]	24,552.34	1.1	1.68	7,740.16	0.41	0.54	27,867.07	/	/	/	29,735.63	/	/	/
Lenvatinib	25,719.93	1.07	1.63	8,611.27	0.36	0.49	41,282.54	Dominated	/	/	60,084.66	Dominated	/	/
D+A	46,355.21	1.42	2.33	18,312.20	0.42	0.58	53,031.48	68,194.54	58,285.35	/	100,367.32	569,830.35	146,226.70	/
T+A[b]	136,163.95	1.77	2.84	71,551.54	0.49	0.67	135,504.93	166,425.92	156,666.76	255,921.76	330,391.06	788,547.23	489,002.93	853,608.32

[a] *Indicates the best cost-effectiveness (willing to pay = three times per capita gross domestic product).*

[b] *Indicates the best clinical effect.*

PFS, progression-free survival, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; D + A, sintilimab plus bevacizumab; T + A, atezolizumab plus bevacizumab.

Costs and Utilities

The utility calculated using the EuroQol-5D scale was used to calculate the incremental cost-effectiveness ratio (ICER). The utility of patients with uHCC in PFS and PD states were 0.76 and 0.68, respectively, which were derived from cost-effectiveness analyses considering Chinese patients with uHCC (18, 28); the negative utility of grades 1–2 adverse reactions was 0.01, and grade 3 and above adverse reactions was 0.16 (28, 29).

In this study, from a health system perspective, only the direct costs of disease treatment, namely, drug costs, follow-up cost, monitoring cost, hospice care cost, and costs for treatment of grades 3–4 adverse reactions were considered. In addition, we assumed that the body weight of a patient was 60 kg; medication information is shown in **Table 1**. Prices for sorafenib, lenvatinib, donafenib, D + A, and T + A were derived from the latest local public bid-winning price (by the end of December 2021). Cost of follow-up and monitoring in PFS or PD were obtained from published literature (28). Specifically, follow-up costs included CT examination, blood test, urinalysis, and blood biochemical examination; costs of monitoring included diagnosis fee, injection fee, nursing fee, and bed fee, more details are given in **Table 1**.

When calculating costs, the administration frequency, reduction rate, and incidence of adverse drug reactions were considered. The administration frequency of each drug was obtained from the clinical trials, but administration frequency data of tislelizumab in Chinese populations were unavailable. According to the characteristics of its mechanism of action and the occurrence of adverse reactions, we assumed that the administration frequency of tislelizumab was consistent with that of atezolizumab. When an adverse drug reaction occurred, the drug dose would be reduced by half in addition to drug withdrawal. The rates of drug reduction were from the clinical data; the incidences of grade 3 adverse reactions for each drug and the average treatment cost per time are shown in **Table 1**. Assuming that all the adverse reactions occurred in the first cycle (29) and costs of adverse reactions were derived from literature (18), more details of adverse reaction costs for each drug are available in **Supplementary Table 4**. Hospice care cost was obtained from a cost-effectiveness analysis in China (28). More details are shown in **Table 1.** All the costs are expressed in US dollars ($1 = ¥6.4838).

Cost-Effectiveness Analysis

In this study, cost and utility were discounted and the annual discount rate was 5%, according to *Guidelines for Evaluation of Chinese Pharmacoeconomics* (30). The effectiveness index was life-years and quality-adjusted life-years (QALYs). The ICER and incremental net monetary benefit (INMB) were used to compare the cost-effectiveness of the treatment regimens. According to WHO recommendations, the ICER threshold for this study, or willingness to pay (WTP), was 3 times per capita gross domestic product in China in 2020, namely, $33,521. INMB >0 means economical, the calculation method of INMB is shown in Equation 3.

$$INMB = WTP^{*}\,(E_2 - E_1) + (C_2 - C_1) \tag{3}$$

Sensitivity Analysis and Scenario Analysis

We performed a one-way sensitivity analysis to explore the cost-effectiveness of each regimen when parameters changed between the upper and lower limits and a cyclone graph was plotted to depict the analysis results, INMB was used as a measure of economic efficiency. Monte Carlo simulation was performed for 10,000 iterations and we conducted probabilistic sensitivity analysis (PSA). We used scatter plots and cost-effectiveness acceptability curves (CEACs) to analyze the cost-effectiveness for each regimen with WTP of different values.

In scenario analysis, we considered patients with uHCC would active treatment until death, which was adopted by similar studies (28, 29).

RESULTS

Base-Case Analysis Results

After simulation to the endpoint, the cumulative OS time limit, effectiveness, and cost-effectiveness of the five treatment regimens (sorafenib, lenvatinib, donafenib, D + A, and T + A) were obtained, as shown in **Table 2**. In terms of effectiveness, compared with OS under the sorafenib regimen, patients who received the lenvatinib, donafenib, D + A, and T + A regimens showed an increase of 0.25, 0.30, 0.95, and 1.46 life-years, and a corresponding increase of 0.16, 0.19, 0.51, and 0.86 QALYs. T + A had the best effectiveness both in the OS and PFS states. In terms of cost-effectiveness, for OS, the ICERs of lenvatinib, donafenib, D + A, and T + A compared with sorafenib were $40,667.92/QALY gained, $27,630.63/QALY gained, $51,887.36/QALY gained, and $130,508.44/QALY gained, respectively, all were more than $33,521 except for donafenib, thus donafenib was the most economical regimen for patients with uHCC in China.

Sensitivity Analysis

One-Way Sensitivity Analysis

Taking $33,521 as the threshold of WTP, we used INMB to measure economic efficiency. **Figures 2A–J** are the cyclone diagrams of different treatment regimens. As shown in **Figure 2**, HR-related parameters and utilities for PD and PFS states, drug prices had the greatest impacts on INMB. Cost-effectiveness conclusions of donafenib compared with sorafenib were affected by HR vs. sorafenib; when the price dropped and OS HRs improved, lenvatinib was likely to be cost-effective compared with sorafenib, and lenvatinib had a chance to be the most effective regimen when the OS HRs of lenvatinib and donafenib vs. sorafenib changed. When other parameters fluctuated in the upper and lower limits, the research results were consistent with the base-case analysis, indicating that our base-case analysis results were relatively stable as a whole.

Probabilistic Sensitivity Analysis

The results of PSA are shown in **Figure 3**. The results showed that, under the chosen WTP, the probabilities that lenvatinib, donafenib, D + A, and T + A had economic advantages over sorafenib were 31.91, 69.21, 3.44, and 0.00%, respectively.

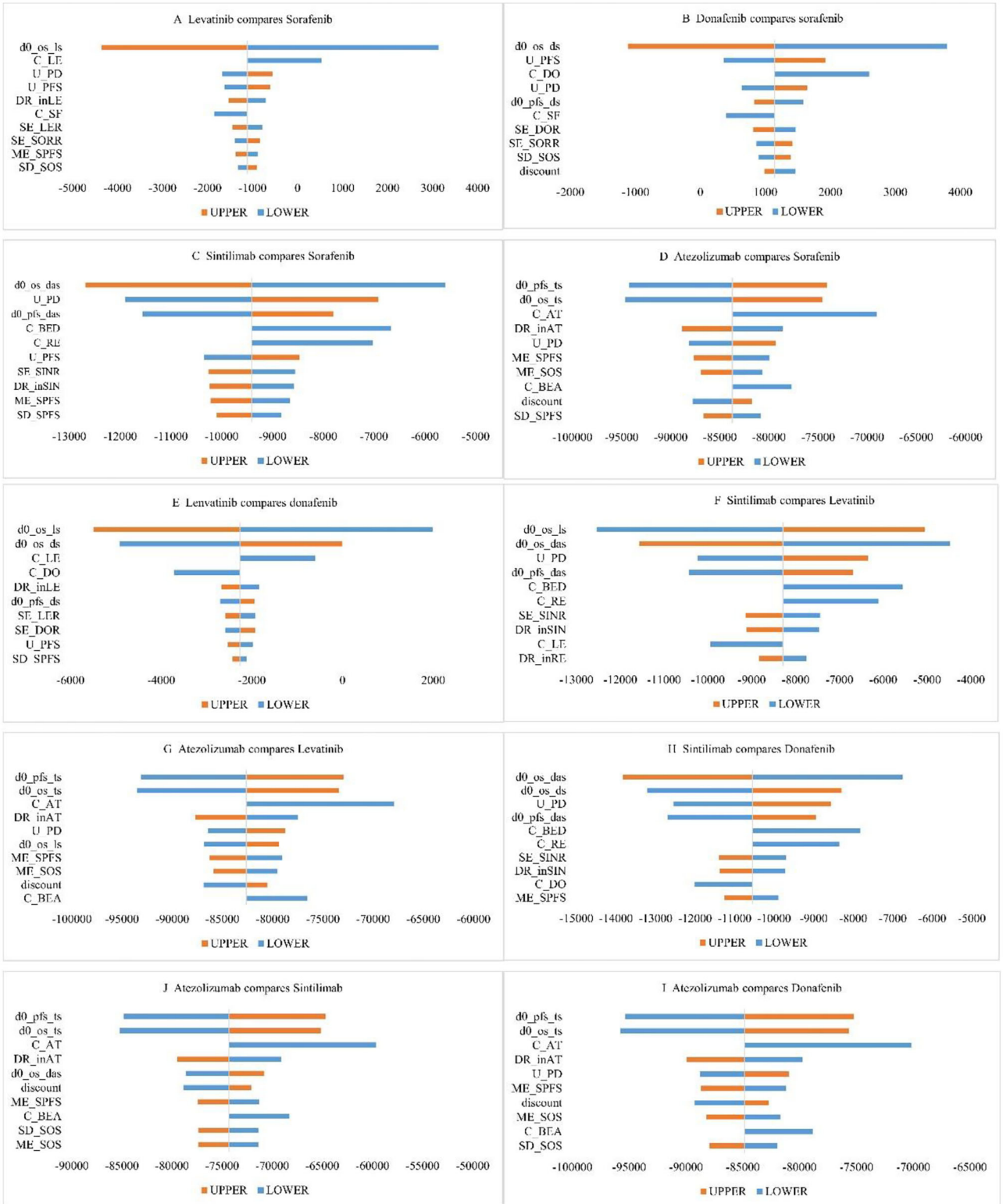

FIGURE 2 | One-way sensitivity analysis chart. (C_AT, unit price of atezolizumab; C_BED, unit price of bevacizumab (D + A group); C_BEA, unit price of bevacizumab (T + A group); C_DO, unit price of donafenib; C_LE, unit price of lenvatinib; C_RE, unit price of regorafenib; C_SF, unit price of sorafenib; DR_inAT, dosage density of T + A; DR_inLE, dosage density of lenvatinib; DR_inSIN, dosage density of D + A; d0_os_das, OS HR (D + A vs sorafenib); d0_os_ds, OS HR (donafenib vs sorafenib);d0_os_ls, OS HR (lenvatinib vs sorafenib); d0_os_ts, OS HR (T + A vs sorafenib); d0_pfs_das, PFS HR (D + A vs sorafenib); d0_pfs_ds, PFS HR (donafenib

(Continued)

FIGURE 2 | vs sorafenib); d0_pfs_ts, PFS HR (T + A vs sorafenib); ME_SOS, theta for lognormal model of OS (sorafenib); ME_SPFS, theta for lognormal model of PFS (sorafenib); SD_SOS, sigma for lognormal model of OS (sorafenib); SD_SPFS, sigma for lognormal model of PFS (sorafenib); SE_DOR, probability of TKIs therapy after donafenib progression; SE_LER, probability of TKIs therapy after levatinib progression; SE_SINR, probability of TKIs therapy after D + A progression; SE_SORR, probability of TKIs therapy after sorafenib progression; U_PFS, utility for PFS; U_PD, utility for PD).

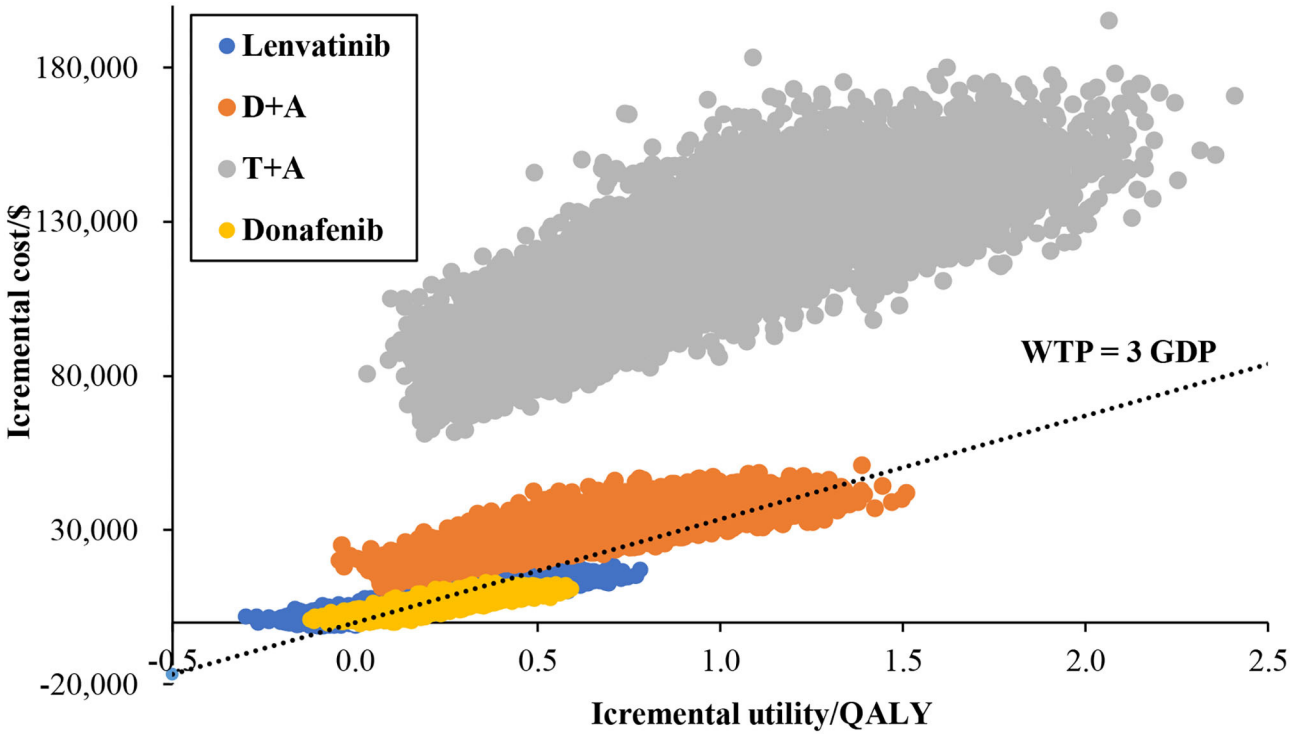

FIGURE 3 | Base-case probabilistic sensitivity analysis: scatter plot (10,000 iterations).

Figure 4 depicts the CEAC, which showed that when using a range of WTP thresholds of $0–27,600/QALY gained, sorafenib was always the most economical option; when WTP was in the range $27,600–66,500, donafenib was the most economical option; when WTP was in the range $66,500–245,300, D + A was the most economical option; and when WTP exceeded $245,300, T + A was the most economical option. Taking the threshold level in China today into account, donafenib was currently the most cost-effective option.

Scenario Analysis Results

The results of each scenario analysis are shown in **Table 2**. Assuming active treatment continued until death, the ICERs of lenvatinib, donafenib, D + A, and T + A compared with sorafenib were $41,282.54/QALY, $27,867.07/QALY, $53,031.48/QALY, and $135,504.93/QALY, respectively. Overall, the results of scenario analysis were consistent with the conclusions of the base-case analysis, verifying the robustness of the conclusions of the base-case analysis. The scatter plot and CEAC are given in **Supplementary Figure 7** in the supplement.

DISCUSSION

In this study, we explored the cost and effect of sorafenib, lenvatinib, donafenib, D + A, and T + A in the treatment of uHCC. The final result showed that the T + A regimen was the most effective and the ranking of cost-effectiveness was as follows: donafenib > sorafenib > lenvatinib > D + A > T + A. Both the deterministic sensitivity analysis and PSA proved the robustness of the results. The scenario analysis showed that active treatment duration would not affect the conclusion.

To date, several articles have evaluated the cost-effectiveness of lenvatinib and sorafenib and T+A and sorafenib in the treatment of patients with uHCC in China. Wen et al. (18) and Hou and Wu (28) evaluated the cost-effectiveness of T + A and sorafenib from the perspective of the healthcare system in China and the conclusions were consistent with those of this study. Cai et al. (31) confirmed that lenvatinib was economical compared to sorafenib when considered donations. Relevant literature outside of China (29, 32–34) showed that ICERs of lenvatinib and T + A compared with sorafenib were significantly higher than the threshold in China, which indicated

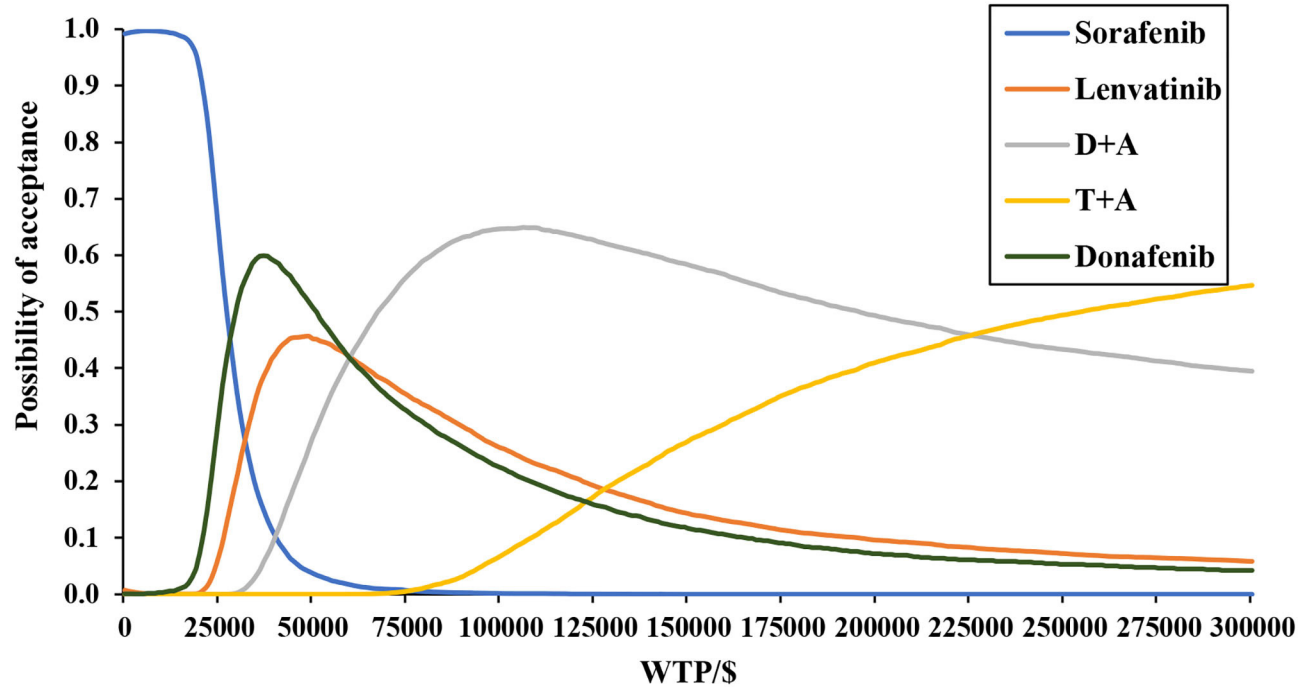

FIGURE 4 | Base-case probabilistic sensitivity analysis: cost-effectiveness acceptability curve (10,000 iterations).

that lenvatinib and T + A were not more cost-effective than sorafenib in China.

Donafenib has listed in 2021 and was included in the latest medical insurance list. The ZGDH3 trial (16) showed that donafenib improved OS and PFS survival compared with sorafenib, and the price of donafenib dropped by 69% recently, so donafenib was economical compared to other targeted drugs, namely, sorafenib and lenvatinib. Immunosuppressive agents tend to be more expensive, such as atezolizumab and sintilimab combined with VEGF inhibitor. Furthermore, while these drugs prolonged survival (13, 15), they also caused a great economic burden of disease, which may be another reason why combined therapies were not economical. Given that the threshold level will not change much in the next few years, assuming that it remains unchanged, it is expected that the price of D + A drops by 64% and the price of T + A drops by 81%, which will be more cost-effective than donafenib at the current price level.

With no direct randomized controlled trials between groups of drugs, indirect comparisons are necessary. Most previous studies (18, 29, 32–38) have used a common control drug as a bridge and adopted the constant HR assumption. This method requires that the KM curves of the test group and control group obey the assumption of equal proportions. However, the survival curves of drugs (11, 13, 15, 16, 39–43) do not obey the above assumptions usually. Jansen et al. (23) developed fractional polynomials based on non-proportional hazards, and (network) meta-analysis of survival data with models where the treatment effect is represented with several parameters using fractional polynomials can be more closely fitted to the available data than meta-analysis based on the constant hazard ratio. The 4 trials included in this study were all verified to be non-proportional hazards ratios; hence, the FP model based on non-proportional hazards was used.

When the disease progresses, patients may choose a variety of second-line treatments, and the survival time in the PD state is not uniform, which makes the calculation of the treatment cost of PD status very difficult. Similar economic evaluation studies (28, 29) directly chose the average cost of second-line treatment from other research, which ignored the heterogeneity of patients in different studies and also did not reflect the target patients' survival status in PD state well. In our studies, we carefully considered the patient's subsequent treatment options and calculated the cost during PD state based on the patient's selected treatment options and survival status.

To the best of our knowledge, it is the first cost-effectiveness analysis of donafenib and D + A in the treatment of uHCC, and the efficacy and cost-effectiveness of first-line treatment of uHCC approved in China were compared in groups for the first time. This study is important for patients, clinicians, and payers, given the uncertainty about the optimal treatment for uHCC, which causes serious morbidity and mortality in China. Furthermore, our cost-effectiveness analysis can inform value-based decision-making for health systems. In addition, we closely modeled the observed the Kaplan–Meier curves and constructed a network meta-analysis based on the FP model with which time-varying

HRs were calculated. This analysis is necessary given that non-proportional hazards were detected in the chosen trials, which has not been addressed by previous reviews (35–38).

However, owing to the lack of direct comparisons of survival data among drugs, uncertainty remains in the results. In addition, owing to a lack of individual data, we assumed that bodyweight is 60 kg and that adverse reactions occur in the first cycle, which affects the calculation of the cost and utility to a certain extent. Regarding the choice of treatment regimens after disease progression, there is no real-world evidence, so the best hypothesis was put forth according to actual clinical applications. Finally, costs and utilities came from different groups, contributing to the bias of results to some extent.

CONCLUSION

In this study, we showed that the effectiveness during the OS period was ranked as follows: T + A > D + A > donafenib > lenvatinib > sorafenib and the ranking of cost-effectiveness was as follows: donafenib > sorafenib > lenvatinib > D + A > T + A. Although combination therapies (D + A and T + A) have greatly improved the survival benefit of patients, donafenib is still the most economical option for patients with uHCC due to its low price. It is expected that these regimens may be more widely adopted when the price of these drugs drops and the WTP threshold increases in the future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The conception and design of this study were primarily conducted by WT. The drafting of the article was mainly the responsibility of MZ and XP. All authors have reviewed the analysis, interpretation of the data, contributed to the drafting of the manuscript, revising the manuscript for important intellectual content, approved the final version to be published, and agree to be accountable for all the aspects of this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.869960/full#supplementary-material

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Examining Primary Care Physicians' Intention to Perform Cervical Cancer Screening Services Using a Theory of Planned Behavior: A Structural Equation Modeling Approach

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Background: Promoting cervical cancer screening (CCS) is undoubtedly effective in combating severe public health problems in developing countries, but there are challenges to its implementation. Understanding the factors influencing primary care physicians' intentions to provide CCSs to rural women is crucial for the future implementation of screening programs. The aim of this study was to assess the intentions of primary care physicians to provide cervical cancer screening services (CCSSs) to rural women and their determinants.

Methods: This cross-sectional study included 1,308 primary care physicians in rural primary health care, and the data collection tool was developed based on the theory of planned behavior (TPB), which included demographic characteristics, the basic constructs of TPB, and the degree of knowledge of CCSSs as an extended variable of the TPB model. Structural equation modeling was used to analyze the relationships between each factor.

Results: Pathway analysis found that TPB is an appropriate theoretical basis for predicting primary care physicians' intent to provide CCSSs ($\chi 2/df = 2.234 < 3$, RMSEA = 0.035, and SRMR = 0.034). Meanwhile, the structural equation model showed that attitude ($\beta = 0.251$, $p < 0.001$), subjective norm ($\beta = 0.311$, $p < 0.001$), perceived behavioral control ($\beta = 0.162$, $p < 0.001$), and knowledge level ($\beta = 0.152$, $p < 0.01$) positively predicted primary care physicians' intention to provide CCSSs.

Conclusions: TPB model, with the addition of knowledge, was useful in predicting primary care physicians' intention to provide CCSSs for rural Chinese women. The findings of this study provide a reference for the government and hospitals to develop strategies to improve the intent of primary care physicians to provide CCSSs.

Keywords: cervical cancer, primary care physicians, theory of planned behavior (TPB), intention, structural equation modeling

INTRODUCTION

Cervical cancer is one of the two most common cancers with high mortality rates, and it has the second-highest incidence globally among female malignant tumors, only behind breast cancer (1, 2). According to the World Health Organization, most new cases of cervical cancer occur in developing countries, with limited global medical resources (3, 4). As the largest developing country with a large population, China has an enormous cervical cancer burden and disparities between different regions. Research has shown that in 2012, there were about 61,691 new cases of cervical cancer in China, and this number will continue to reach 93,500 by 2030 if the situation does not improve (5). As stated by the International Agency for Research on Cancer, the cervical cancer screening (CCS) program is an effective strategy to address its incidence and mortality (6, 7), and the prevalence of cervical cancer in developed countries has significantly decreased with well-established screening programs (8, 9). Since 2009, the Government of China has launched NCCSPRA, a free National Cervical Cancer Screening Program in Rural Areas, which provides free cervical cancer screening services (CCSSs) to rural women aged 35 to 64. Despite the initiatives taken by the Chinese government, there were still many women in rural China who were either underscreened or never examined. Research conducted in 2011 found that the CCS rate in China was only 21.4% (10), which is significantly lower than in Finland (79.2%) (11) and Spain (65.6%) (12). Without appropriate action, cervical cancer continues to be a serious health concern that threatens the health and lives of rural Chinese women.

During the implementation of the screening program, rural women's general perceptions of CCS and their actual screening behavior can be changed by primary care physicians (13). Several studies (14, 15) have found that suggestions from primary care physicians can promote women's participation in cancer screening. One study (16) found that physician recommendations are an important predictor of patient mammography use; Grady (17) suggested that women would be more willing to participate in breast cancer screening programs with physicians' encouragement. The participation of Chinese women in a quantitative study (18) indicated that none of them had received any suggestions or information on the CCS from primary care physicians, hindering their participation in the CCS. All these studies have demonstrated the need to explore primary care physicians' intentions to provide CCSSs to rural women. However, most previous studies (19, 20) have focused on women's intention in CCS and few have addressed the factors that influence screening services provided by primary care physicians. Therefore, it is necessary to investigate the predictors of intention to provide CCSSs among primary care physicians in rural areas.

Ajzen's theory of planned behavior (TPB) (21) is a widely used social cognitive theory. TPB has been successfully used in different populations (22, 23), especially among primary care physicians, to understand the potential motivations for behavior. For example, Guibo (24) demonstrated the TPB's ability to understand the intention of Spanish nurses to use physical restraints, and Rich's research (25) revealed the efficacy of TPB in explaining medical physicians' behaviors. All of these studies have supported the utility of TPB in exploring the factors associated with behavioral intention among primary care physicians. Meanwhile, evidence-based research and meta-analyses (26, 27) have shown that TPB has more accurately defined constructs and greater explanatory power than other psychological theories or models such as HBM and TRA; therefore, in this study, it was hypothesized that the TPB could be a fundamental framework for identifying key determinants of providing CCS behavior among primary care physicians who have worked in rural areas in China. The results of the current study are expected to provide useful suggestions for improving CCS intent among primary care physicians, and policy recommendations for CCS program implementation can be developed based on the findings.

RESEARCH MODEL AND HYPOTHESIS DEVELOPMENT

A research model and related hypotheses (**Figure 1**) were developed based on the TPB and existing literature. According to the TPB (21), the intention is the proximal psychological predictor of individual behavior and is determined by attitude toward behavior (AB), subjective norms (SN), and perceived behavior control (PBC). Attitude toward behavior (in this case, primary care physicians' behavior of providing CCSSs) refers to the degree to which a person has a favorable or unfavorable evaluation of its performance (21), and is shaped by two components: behavioral beliefs (b) and outcome evaluation (e) of the behavior, which can be expressed by the following equation: $AB = \sum b_i e_i$ (i refers to the measurement project) (21, 28). SN refers to an individual's estimation of the attitude toward the behavior of their significant others. Similar to AB, SN is also determined by two distinct factors: normative beliefs (n) and motivation to comply (m) with normative beliefs, and the equation to evaluate SN is as follows: $SN = \sum n_i m_i$ (i means the measurement project) (21, 28). PBC refers to the degree of acceptance of an individual's perception of the performance of the behavior and includes control beliefs (c) and perceived power (p), as shown in the equation: $PBC = \sum c_i p_i$ (i means the measurement project) (21, 28). The research model is virtualized in **Figure 2**.

In this study, AB referred to primary care physicians' evaluation of the CCSSs outcomes. As recognized in TPB, AB is the most significant indicator of BI (21), and several previous studies have shown that attitude plays an important role in predicting primary care physicians' intention to provide medical services. A study conducted by Kim et al. (29) showed that attitude was a determinant of nurses' intention to provide medical care for SARS patients. At the same time, research conducted by Galaviz et al. (30) found that Mexican physicians' attitudes affect their intentions to prescribe physical activity (PA). Based on the TBP model and prior studies, the following hypothesis was proposed:

Hypothesis 1: Attitude is positively associated with primary care physicians' intention to provide CCSSs

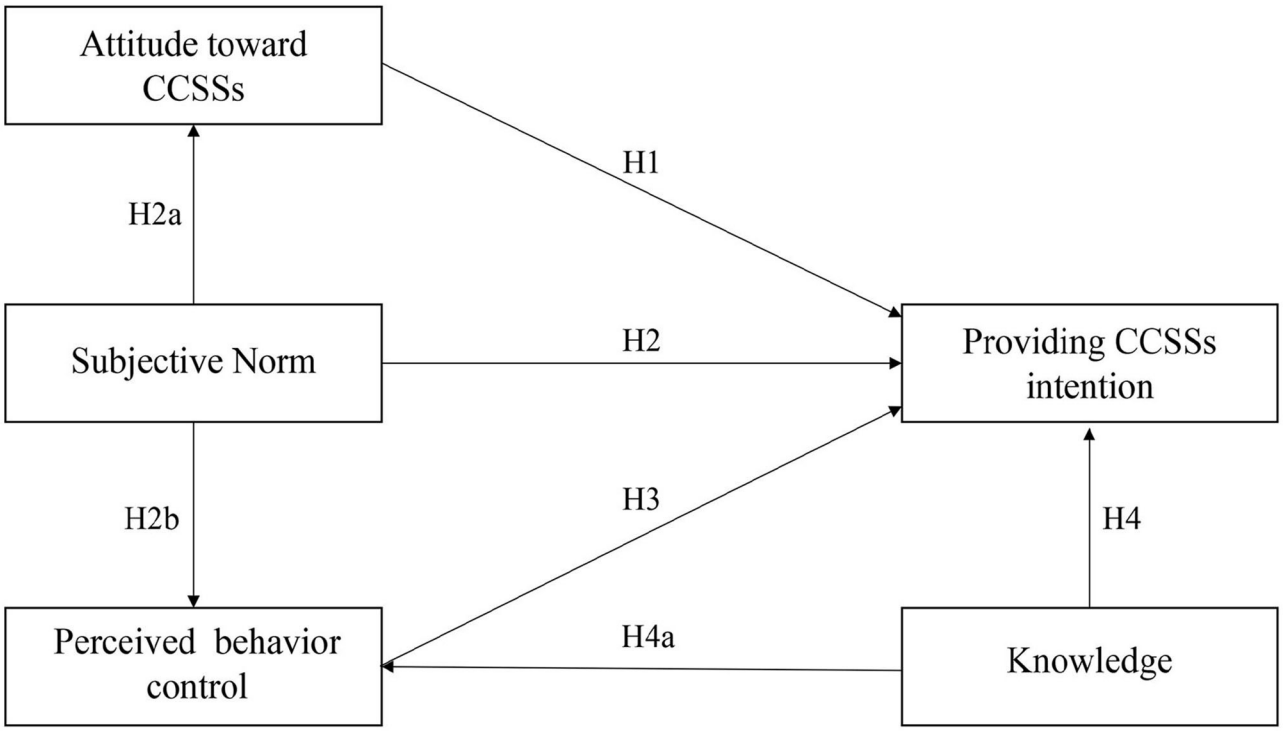

FIGURE 1 | The research model of primary care physicians' providing CCSSs intention.

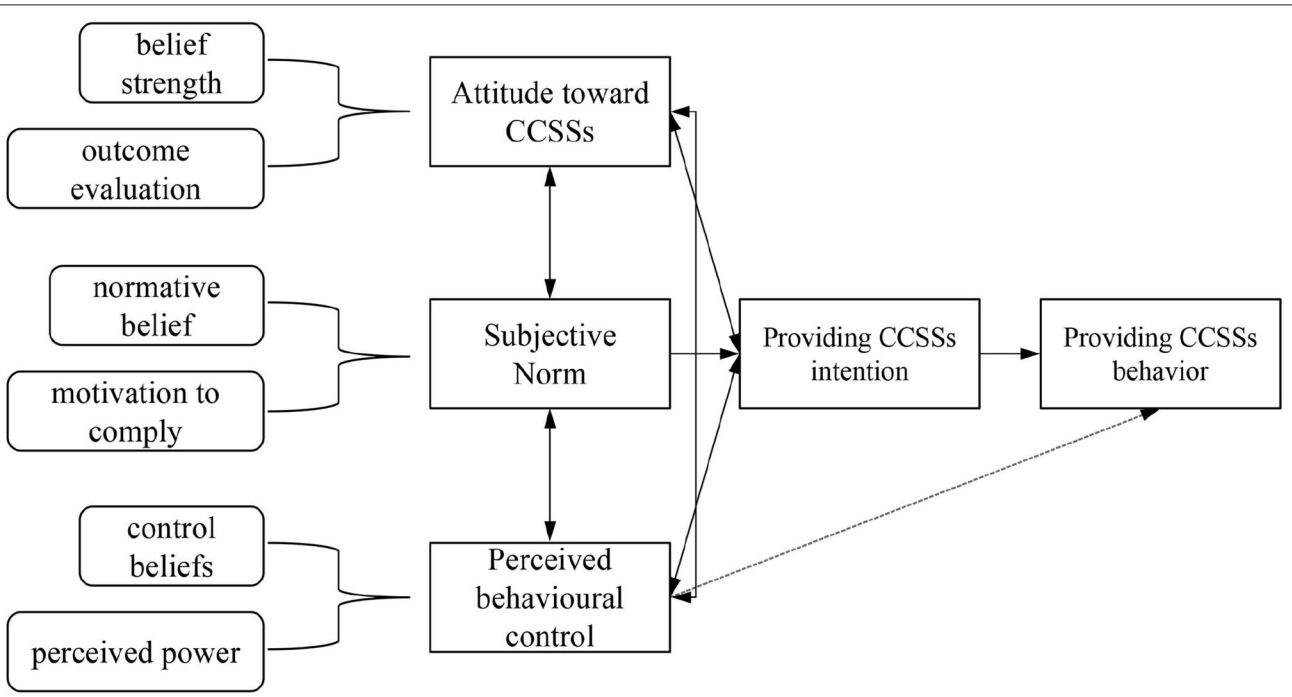

FIGURE 2 | A Structural model of the theory of planned behavior.

In the present study, SN arises from the perception of primary care physicians as to whether their leaders, peers, and patients are applying the idea that they should provide CCSSs to rural women. In the TPB model (21), SN affects an individual's BI and is associated with AB and PBC. In a recent study, Nantha et al. (31) found that subjective norms can affect primary care physicians' intention to provide sick leave to patients. Herbert et al. (32) applied the TPB model in the context of clinical service behavior, indicating that physicians' intention to provide medication therapy management services (MTMS) was affected by their opinions on this service. Moreover, the opinion of colleagues on CCSSs can change the attitudes of primary care physicians. Administrators, policymakers, and the general public's acceptance of CCSSs can help them remove barriers to providing CCSSs for rural women. Therefore, the following hypothesis was proposed:

Hypothesis 2: Subjective norm is positively associated with primary care physicians' intention to provide CCSSs.
Hypothesis 2a: Subjective norm affects primary care physicians' attitude toward CCSSs.
Hypothesis 2b: Subjective norm affects primary care physicians' PBC of providing CCSSs.

The current study referred to the ease of providing CS services by a primary care physician. According to the TPB model, PBC affects BI (21). Previous research (33) has demonstrated that PBC is an indicator of physicians' intentions to provide clinical pharmacy services. A similar result was found in a study by Frankfurter et al. (34) and Liu et al. (35). Based on previous literature, we formulated the following hypothesis:

Hypothesis 3: PBC is positively associated with primary care physicians' intention to provide CCSSs

Studies (36, 37) have shown that the predictive utility of TPB can be increased by adding new variables such as knowledge level. General knowledge has been identified as a potential predictor of primary care physicians' intention to provide clinical services. On one hand, several studies (38, 39) have shown that knowledge about cancer screening was significantly and positively associated with primary care physicians' intention to provide CCSSs, and research on the application of TPB (40, 41) also revealed a link between knowledge and PBC. On the other hand, physicians who have sufficient CCS knowledge are more likely to understand the benefits of CCSSs and would have a more positive attitude toward CCSSs. Studies (42) have also found an association between knowledge and attitudes. Moreover, since the classification of medical and financial resources existed in different regions, lack of knowledge has become a common problem that makes it harder for primary care physicians to provide CCSSs (43). Subsequently, we added the knowledge level to the research model, which may have a potential effect on primary care physicians' BI and PBC of providing CCSSs, and the following hypotheses were posited:

Hypothesis 4: knowledge of CCSSs has a positive impact on primary care physicians' intention to provide CCSSs.
Hypothesis 4a: knowledge of CCSSs is positively associated with primary care physicians' PBC.
Hypothesis 4b: knowledge of CCSSs is positively associated with the attitudes of primary care physicians.

METHODS

Sampling and Data Collection

In this cross-sectional study, multi-stage stratified sampling was carried out to select samples in rural areas of Jiangsu. In the first stage, six (Lianyungang, Yancheng, Yangzhou, Nanjing, Changzhou, and Wuxi) out of 13 cities in Jiangsu province were selected based on location and level of economic development. Two counties from each selected district and two towns from each selected county were then randomly chosen. Thus, 26 towns were selected for this study. A convenience sampling method was used to select participants in the 26 towns, who were primary care physicians working in public health care institutions. Those who were either sick or incapable of responding were excluded from this study. The minimum sample size was computed using Raosoft (www.raosoft.cpm/samplesize.html) (44) with a confidence level of 95%, margin of error of 5%, and a response distribution of 50%; the recommended sample size was 384. All data were collected between March 30th and June 1st, 2020.

Questionnaire

The questionnaire was adapted from the TPB model (21) and previous studies (28, 30, 45). To compile the questionnaire, first, several in-depth interviews based on the literature and the TPB model were conducted with rural primary care physicians who worked in different areas to explore the specific attitude, subjective norms, PBC, and intentions toward CCSSs. A pilot study was also conducted to evaluate the cultural sensitivity of the questionnaires, and a small group of people (including several experts and 30 primary care physicians) were asked to complete and assess the entire questionnaire. Each participant was also expected to revise the wording, phrasing, and overall construct. Based on the participants' feedback, a few modifications were made to improve the instruments' validity and reliability. Two measurements were included in the formal survey instrument: the sociodemographic characteristics of primary care physicians (e.g., gender, monthly income, level of education) and the CCSSs behavior intention questionnaire. The latter contained five subscales: attitude toward CCSSs (six items), SN (six items), PBC (eight items), behavioral intention to provide CCSSs (three items), and knowledge level of CCSSs (five items). The questionnaire was constructed as follows:

Attitude Subscale

The attitude was evaluated by multiplying two components: behavioral belief and outcome evaluation. There were three items that were used to measure behavioral beliefs (e.g., "I think providing CCSSs for rural women can save the cancer treatment costs") with a five-point rating scale ranging from 1 (strongly disagree) to 5 (strongly agree). Other items were used to evaluate outcomes; for example, the item "I think saving the cancer treatment costs is" was followed by a rating scale ranging

from 1 (not necessary at all) to 5 (very necessary). The overall attitude score was calculated by computing behavioral beliefs with the outcome evaluation, and a higher score indicated that primary care physicians had a more positive attitude toward performing CCSSs.

Subjective Norm Subscale

The SN was calculated by multiplying the products of "normative beliefs" and "motivation to comply". Normative beliefs were measured by three items (e.g., "I think that most of my colleagues support me to provide CCSSs"), with a five-point rating scale ranging from 1 (strongly disagree) to 5 (strongly agree) as response options. Three items were used to evaluate the physician's motivation to comply (e.g., "Overall, I usually follow the suggestions given by my peers") with a five-point rating scale ranging from 1 (strongly disagree) to 5 (strongly agree). After multiplying these two products, it was found that higher scores were closely associated with a higher SN.

Perceived Behavioral Control Subscale

According to the TPB model, the PBC subscale is measured by multiplying two components: controlled belief and perceived control. Three items were used to examine the control belief (e.g., "I think, the equipment of our hospital is") and the response options ranged from 1 (don't have it at all) to 5 (very sufficient). Perceived control was also evaluated by three items (e.g., the item "I think, lacking equipment will make my CCS work"). A response scale ranging from 1 (very difficult) to 5 (not difficult at all) was the response option for the perceived control items. After multiplying these two components, it was concluded that the higher the scores, the higher the PBC of primary care physicians in performing CCSSs.

Behavior Intention Subscale

BI toward CCSSs was measured by three items, such as "I plan to provide CCSSs," "I am willing to provide CCSSs" and "I try to provide the CCSSs," the response scale ranging from 1 (strongly disagree) to 5 (strongly agree) with higher scores indicating that physicians have greater intention to engage in CCS program.

Knowledge Subscale

Five questions were designed to evaluate primary care physicians' knowledge level of CCSSs, including potential risk factors, screening methods and symptoms of cervical cancer. A two-dimensional scale was used in these questions (right = 1, wrong = 0), with possible overall scores ranging from 0–5. Higher scores indicated that primary care physicians had sufficient knowledge about CCS.

Data and Statistical Analysis

The hypothesis model was analyzed by structural equation modeling (SEM) using Amos version 23.0 (IBM SPSS Amos, Armonk, NY, USA), which is a sophisticated statistical technique suitable for theoretical testing and has been widely applied in various scientific fields. First, exploratory factor analysis (EFA) was conducted using principal axis factor (PAF) analysis, and all data were screened by Kaiser–Meyer–Olkin (KMO) test of sampling adequacy and Bartlett's test of sphericity. Second, confirmatory factor analysis (CFA) was performed to conduct a satisfactory measurement model, and construct validity, convergent validity, and discriminant validity were evaluated to test whether the samples matched the theoretical model. Third, SEM was used to analyze the hypothesized research model and relationships among the variables. The fit indices for the model included the chi-square value of minimum sample/degree of freedom (CMID/DF), root mean square residual (RMR), standardized RMR (SRMR), root mean square error of approximation (RMSER), normed fit index (NFI), comparative fit index (CFI), and Tucker-Lewis index (TLI). The model was considered suitable for the samples as long as the following thresholds were met: $\chi 2/df < 3$, CFI > 0.90, NFI > 0.90, TLI > 0.90, SRMR < 0.08, and RMSEA < 0.05 (46).

Ethics Approval

This study was approved by the Ethics Committee of Sir Run Run Hospital, Nanjing Medical University. The grant number is 2019-SR-017. All participants provided verbal informed consent.

RESULTS

Participants' Profile

In total, 1,308 primary care physicians were asked to complete a self-assessed questionnaire. After removing the invalid and incomplete responses, 1,120 valid questionnaires were finally obtained (valid response rate, 85.6%). As recommended by Bagozzi and Yi (47), the number that was used was considered adequate for further SEM analysis. The demographic profile of respondents is presented in **Table 1**. Most primary care physicians (91.3%) were women, whereas only 8.7% were men. Income differences among primary care physicians were evident: approximately 407 (36.2%) primary care physicians' salary was 3,000–5,000 RMB, 475 (42.4%) were paid 5,000–8,000 RMB, and only 11% received over 8,000 RMB per month. In terms of years of practice, primary care physicians' duration of work experience was long; approximately 45.8% of them had worked in hospitals for 20 years or more. A total of 475 (62.6%) primary care physicians had an undergraduate degree, indicating a high level of education. Almost half (43.7%) were employed in township health centers and 6.3% in rural maternal and child health centers.

Descriptive Analysis

The participants in this study showed a relatively positive attitude toward providing CCSSs to rural women; the average mean score of the three items used to evaluate the attitude of primary care physicians was 19.27 ± 4.45, with a positive response rate of 83%. For the variable SN, the average mean score was 17.76 ± 3.99, and the average positive response rate was 81.8%, both lower than the variable attitude, indicating that the participants in this study did not feel very well-supported when doing the CCS work. Among the TPB key variables, primary care physicians scored the lowest for the PBC variable (average mean = 12.11 ± 3.62, positive responses = 16.7%), meaning that the resources available to the participants were insufficient to enable them to provide CCSSs to rural women. The participants in the study showed a strong

TABLE 1 | Demographics and relevant characteristics of participants (*n*=1120).

Demographic variables	Frequency (*N*)	Percentage (%)
Gender		
Male	97	8.7
Female	1023	91.3
Monthly income (RMB)		
≤3000	115	10.3
3000–5000	407	36.3
5000–8000	475	42.4
≥8000	123	11
Year of practice		
3 or less	62	5.5
4–10	218	19.5
11–20	316	28.2
>20	513	45.8
Level of Education		
Master	20	1.8
Bachelor	701	62.6
Associate degree	313	27.9
Others	86	7.7
Type of hospital		
Township Health Center	489	43.7
Village clinic	65	5.8
Rural Community Health Center	407	36.3
Rural Maternal and Child Health Center	70	6.3
Other	89	7.9

TABLE 2 | Convergent validity test ($n = 560$).

Variables		Factor loading	CR	AVE
AB	AB1	0.642	0.837	0.635
	AB2	0.873		
	AB3	0.854		
Subjective norm	SN1	0.833	0.744	0.897
	SN2	0.888		
	SN3	0.864		
Perceived behavioral control	PBC1	0.732	0.803	0.508
	PBC2	0.771		
	PBC3	0.755		
	PBC4	0.577		
Behavior intention	BI1	0.840	0.891	0.733
	BI2	0.940		
	BI3	0.781		

AB, attitude toward behavior; SN, subjective norm; PBC, perceived behavior control; BI, behavior.

TABLE 3 | Discriminant validity test ($n = 560$).

Variable	Attitude	SN	PBC	BI
Attitude	**0.797**			
SN	0.651***	**0.866**		
PBC	0.248***	0.3357***	**0.713**	
BI	0.506***	0.512***	0.417***	**0.856**

*SN, subjective norm; PBC, perceived behavioral control; BI, behavior intention. Diagonals (in bold) represent the square root of the AVE. ***$p < 0.001$.*

intention to provide CCSSs to rural women, with an average mean score of 4.14 ± 0.59 (with a possible score ranging from 0–5) and an average positive response rate of 79.2%. In terms of knowledge level, the primary care physicians in this study showed a satisfactory level of knowledge of CCSSs, with an average mean score of 3.85 ± 1.11 (with a possible score ranging from 0–5), and approximately 67.5% of the total knowledge score for primary care physicians reached a minimum of 4. The question regarding initial screening methods of CCS had the lowest correct ratio; only 47.8% of primary care physicians answered it correctly.

Instrument Reliability and Validity

In this study, half (*N*=560) of the original data were used for exploratory factor analysis (EFA). The KMO test and the Bartlett sphericity test were performed to determine whether the questionnaire was suitable for factor analysis. Results suggested that KMO = 0.855 > 0.7, with a significant Bartlett test of sphericity ($p < 0.001$) was suitable for the validity estimate (48). The maximum variance method was used to rotate all TPB factors (including attitude, SN, PBC, and BI), and the results showed that all factor eigenvalues were > 1 and the factor load for each item was > 0.5, indicating that the scale of the four-factor questionnaire can be well-explained by the measurement items. These four factors explained 19.849, 19.158, 18.298, and 17.517% of the variation, respectively, and the cumulative variance contribution rate was 74.823%.

Based on the sample of 560, the CFA was conducted to analyze the measurement model. The fit indices of the TPB model were as follows: $\chi 2/df = 1.692 < 3$, RMSEA = 0.035 < 0.05, SRMR = 0.030 < 0.08, CFI = 0.990 > 0.9, TLI = 0.986 > 0.9 and NFI = 0.975 > 0.9, all of these indices were acceptable. The factor loadings of all items exceeded the recommended threshold of 0.5 for convergent validity (49), and the CR and AVE of each construct also exceeded the recommended threshold of 0.7 and 0.5 (50), respectively (**Table 2**). In addition, discriminant validity was found to be acceptable when the AVE of each construct exceeded the absolute correlation value for that construct (49) (**Table 3**).

Test of Structural Equation Model

As the TPB based measurement model was accepted, the final model was built on the basis of the TPB variables and the knowledge factor for cervical cancer. The fit parameters for the extended model are as follows: $\chi 2/df = 2.234 < 3$, RMSEA = 0.033 < 0.05, SRMR = 0.034 < 0.08, CFI = 0.981 > 0.9, TLI = 0.978 > 0.9 and NFI = 0.967 > 0.9. All indices fall within the appropriate range, indicating a good fit between the data and the theoretical model. A final structural model with the estimated standardized coefficients is shown in **Figure 3**, and the estimation results of the hypotheses presented in **Table 4** show that they were all supported. As indicated by the results, an attitude in favor of

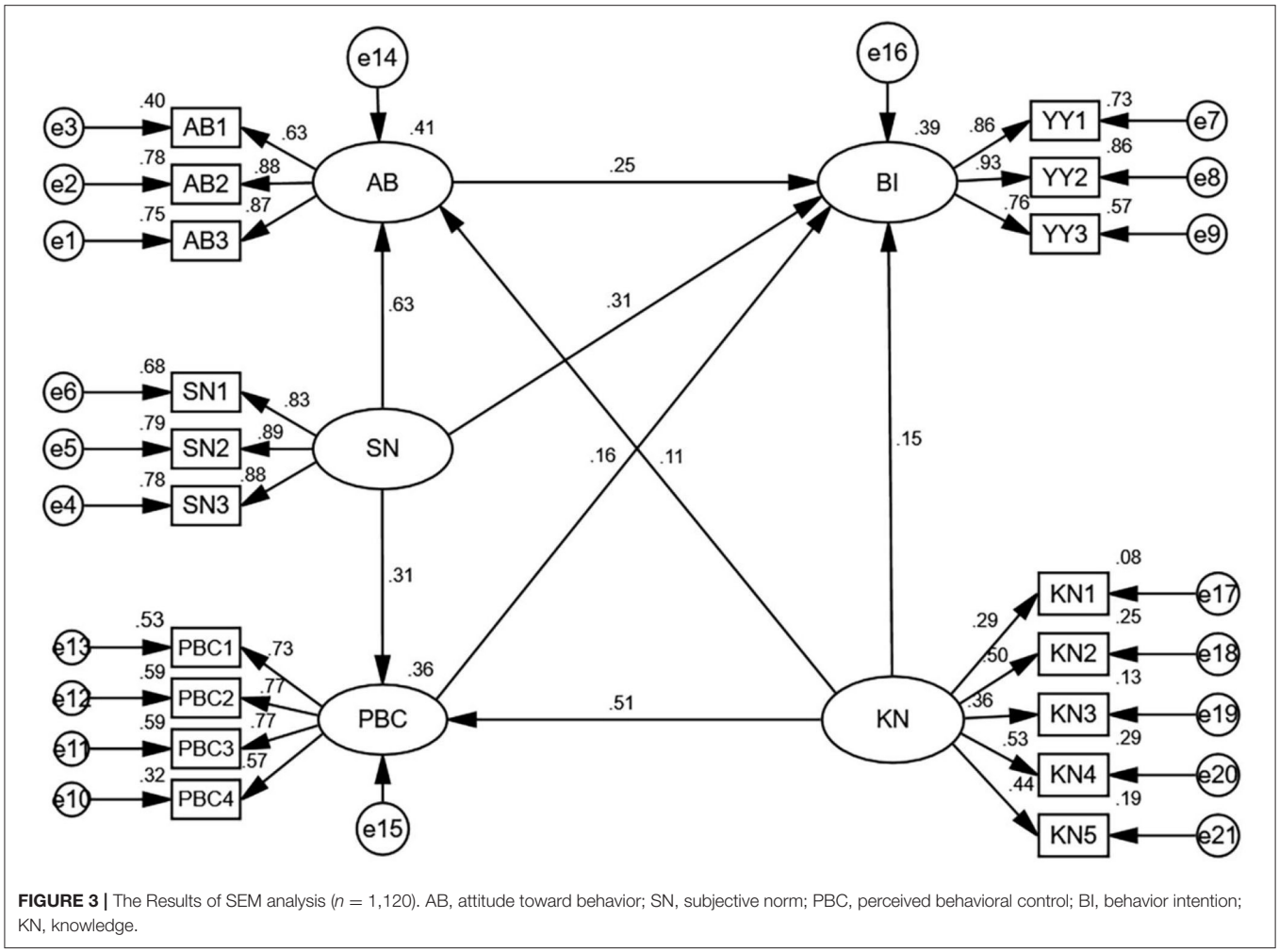

FIGURE 3 | The Results of SEM analysis (n = 1,120). AB, attitude toward behavior; SN, subjective norm; PBC, perceived behavioral control; BI, behavior intention; KN, knowledge.

TABLE 4 | Results of structural equation modeling analysis.

The hypothesis (H)	S.E.	C.R.	Estimate	p	Supported
H1:Behavior intention ← Attitude	0.005	6.384	0.251	***	Yes
H2:Behavior intention ← Subjective norm	0.006	7.564	0.311	***	Yes
H2a:Attitude ← Subjective norm	0.035	19.876	0.630	***	Yes
H2b:Perceived behavior control ← Subjective norm	0.017	8.858	0.309	***	Yes
H3:Behavior intention ← Perceived behavior control	0.012	3.802	0.162	***	Yes
H4:Behavior intention ← Knowledge	0.256	3.018	0.152	**	Yes
H4a:Perceived behavior control ← Knowledge	1.487	6.010	0.510	***	Yes
H4b:Attitude ← Knowledge	1.448	2.968	0.109	**	Yes

$^{**}p < 0.01$, $^{***}p < 0.001$.

CCS was associated with higher intentions to provide CCSSs (β = 0.251, $p < 0.001$); SN of providing CCSSs was significantly associated with primary care physicians' intentions (β = 0.311, $p < 0.001$), attitude (β = 0.630, $p < 0.001$), and PBC (β = 0.309, $p < 0.001$), and greater PBC was linked to a higher intention to provide CCSSs (β = 0.162, $p < 0.001$). The knowledge level of CCS was significantly and positively associated with primary care physicians' BI to provide CCSSs (β = 0.152, $p < 0.01$), as well as a predictor of attitude (β = 0.109, $p < 0.01$) and PBC (β = 0.510, $p < 0.001$).

Test of Indirect Effect

Each variable was also tested for its direct, indirect, and total effects. As presented in **Table 5**, the primary care physicians' SN impacted their behavioral intention to provide CCSSs directly and indirectly through attitude and PBC, with a total

TABLE 5 | Results of direct and indirect analysis.

Path (effects from X to Y)	Direct Effect	Indirect Effect	Total Effect
Bebavior intention ← Attitude	0.251	0.000	0.251
Behavior intention ← Subjective nrom	0.311	0.208	0.520
Behavior intention ← Perceived behavior control	0.162	0.000	0.162
Behavior intention ← Knowledge	0.152	0.110	0.262

standardized effect of 0.52. The knowledge level about CCSSs not only affected BI directly but also had a negligible effect on BI indirectly through PBC and attitude (standardized indirect effect = 0.11). Among all variables, SN had the largest effect on behavioral intention to provide CCSSs, with a standardized direct effect of 0.31, followed by attitude, PBC, and related knowledge.

DISCUSSION

This study examined the complicated predictors of primary care physicians' intention of providing CCSSs to rural women. In accordance with the hypotheses based on the TPB and earlier studies, the result of the path analysis test ascertained that primary care physicians' attitude, SN, PBC and knowledge level can all positively affect their intention to perform the CCSSs. This finding indicates that a primary care physician with a favorable attitude, support from significant others, higher perceived power to control the barriers to screening, and sufficient screening knowledge would also have a stronger intent to provide CCSSs to rural women. This finding was consistent with prior TPB-based studies conducted in Saudi Arabia (51), Finland (52), and China (53). This is the first known study to use a theoretical model to assess primary health care physicians' intention to perform CCSSs.

In general, primary care physicians in this study showed a strong intention to provide CCSSs, with an average positive intention rate of 79.2%. The high intention of primary care physicians to provide CCSSs in this study may be due to the new healthcare reform initiated in 2009 by the Chinese government, which aimed at improving the primary care workforce. Research (54) has shown that the primary care system, particularly the maternal and child health system, has since been strengthened. Meanwhile, in 2009, the Chinese government launched the NCCSPRA to provide free CCSSs to eligible rural women. At the same time, some municipal authorities have started to fund and organize local screening projects, and many primary care physicians have since been organized and trained. In addition, most of the participants in this study were women, which is consistent with some previous studies (55, 56) that indicated that CCSSs were still primarily conducted by female physicians. This was partly due to the embarrassment that rural women experienced when facing male physicians during cervical cancer screening.

The attitude toward CCSSs was positively and significantly related to the BI to execute this behavior. A similar finding was revealed by Heena et al. (57) that the health professionals' attitudes toward breast cancer screening can positively influence their decision to adopt this method. Moreover, some researchers (58, 59) have considered AB to be a strong predictor of BI in the TPB model; thus, this may be an effective approach to focus on the benefits of performing CCSSs among primary care physicians. Based on the results of this survey, positive beliefs such as cost savings due to CCSSs, a sense of self-fulfillment and satisfaction were significant motivators for the intention to provide CCSSs. This could be explained by Maslow's hierarchy of needs theory (60), which stipulates that everyone has a desire to be respected. Primary care physicians also need to perceive recognition and a sense of contribution when performing CCSSs. Therefore, strategies should emphasize the positive outcomes of CCSSs work. For example, publicizing successful CCSSs cases and providing financial and material rewards can motivate primary care physicians.

The SN was a fairly good predictor of primary care physicians' intent to provide CCSSs, suggesting that primary care physicians who had a stronger intention to perform screenings work had the support of their colleagues, patients, and leaders. Meanwhile, the SN can not only have a direct effect on the BI to provide CCSSs but can also affect BI through AB and the PBC. This means that support from significant others will ensure that primary care physicians have a more positive attitude toward CCSSs and feel more confident in their CCSSs work. This finding was consistent with some previous studies, research done in Kenya (61) revealed that subjective norms accounted for the greatest variance in primary care physician examination behavior. Galaviz et al. (30) suggested that Mexican physicians' intention to prescribe PA is primarily influenced by their subjective norms of this behavior. This research is somewhat different from a Canadian study (62) that found no significant association between SN and BI in Canadian nurses, perhaps because there is a sociocultural difference between the two countries, and strong social support and less individualism can make Chinese primary care physicians value their family and colleagues' opinions. Among SN, approval from leaders, peers, and patients was a significant determinant of primary care physicians' intentions. Therefore, it is desirable for hospitals to establish an enabling environment in which the implementation of CCSSs is encouraged. Bulletin boards and related cultural products that highlight the advantages of CCSSs can be used to create an ideal atmosphere. It is also important to create a harmonious atmosphere between primary care physicians and rural women. Research (19) has shown that due to poor communication, some rural women in China have negative and distrustful perceptions of primary care physicians and often feel uncomfortable in medical facilities, which may explain the low screening rate among rural Chinese women. Therefore, it is essential that hospitals provide appropriate training to primary care physicians in communicating skills with patients. The government should also take initiatives to improve public awareness of support and participation in CCSSs. In addition, supervisors and senior physicians who accept CCSSs can play an exemplary and prominent role for other primary care physicians.

According to the TPB, PBC was a crucial factor in predicting BI, indicating that lack of time, equipment, and skill training would be a barrier for primary care physicians to perform CCS for rural women. The results of this study concur with several current and past studies (52, 63). Given the disparities in financial and medical resources between urban and rural regions in China, primary care facilities, especially in resource-poor areas, have long been unable to attract and retain experienced, high-quality physicians. Participants in this study scored the lowest in the PBC variable, which revealed that primary care physicians in rural areas still face barriers in their screening work, that can prevent them, as primary care physicians, from performing CCSSs. Research has shown that the majority of rural hospitals do not have sufficient resources and funding to organize CCS for rural women. According to the NCWCH (5), at the county level in China, 41.7% of maternal and children health (MCH) facilities are either in deficit or in a state of a balanced budget, and only 7.2% have equipment for pathological examination. In addition, lack of time, equipment, and skill training has been identified as the main barrier for physicians to provide medical services in Mexico (30), Brazil (64), Canada (65), and Europe (66), posing significant barriers for primary care physicians to provide rural women with qualified CCSSs. Thus, PBC may be a significant predictor of medical services in developed and developing countries. The health authority equipping primary care physicians with the skills and resources on CCSSs would provide a pathway to improve their CCSSs delivery behaviors. Also, an expert panel can be established to assist primary care physicians in resolving CCS problems.

Knowledge of CCSSs was significantly associated with primary care physicians' intentions. It was also a predictor of their attitudes toward PBC. The results of this study indicate that physicians who have more knowledge about CCSSs would have more PBC and a more positive attitude toward CCSSs, as well as greater intent to provide CCSSs to rural women. Overall, primary care physicians in this study demonstrated an adequate level of knowledge about CCSSs. This may be due to the high level of education and lengthy work experience of the participants in this study. Research has revealed that physicians with higher education levels would also have a higher level of knowledge about medical services (39); 64.4% of the primary care physicians in this study had an undergraduate degree or higher. Although the overall level of knowledge in this study was high, there were still some troubling findings: only 47.8% of primary care physicians correctly answered the questions regarding CCS initial screening methods; if primary care physicians lack sufficient knowledge of screening methods, they may give improper advice to women seeking CCSSs. These results demonstrate the importance of improving the knowledge level of primary care physicians, which can be done by providing clinical guidelines regarding CCSSs. Regular lectures and enhanced medical education are also worth pursuing strategies to improve the intentions of primary care physicians to provide CCSSs.

This study had several limitations. First, as this was a cross-sectional study, it was not possible to assess the causal relationships among different factors. More rigorous experiments relating to the intentions of primary care physicians are therefore expected in the future. Second, primary care physicians had a positive attitude toward CCSSs, which may have been caused by social desirability bias. Future research should seek more reliable measures of their attitudes. Third, the study measured the BI of primary care physicians to provide CCSSs rather than actual behavior. While the BI is an important predictor of an individual's behavior, a physician's BI may not necessarily reflect actual CCSSs' behavior. Therefore, primary care physicians' actual behaviors in providing CCSSs should be measured in future studies. The main strength of this study was the large sample size (n = 1,120) and the strong theoretical basis employed. The findings of this study also fill a gap in the literature on the intentions of primary care physicians to provide CCSSs to rural women, which can be used as a reference for future management and intervention.

CONCLUSION

This study provided support for the efficacy of TPB and its potential constructs to test predictors of CCS behavior among primary care physicians in rural China. The study concluded that AB, SN, PBC, and knowledge level could be potential determinants in explaining and predicting primary care physicians' intention to provide CCSSs. SN was the strongest predictor of primary care physicians' BI. It can not only affect BI directly but also *via* AB and PBC; thus, it is important that hospitals provide a supportive environment for primary care physicians. Some promising strategies should also be introduced that focus on educating primary care physicians about the value of CCSSs and helping them eliminate barriers to the delivery of CCSSs.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study's ethical admission was approved by the Ethics Committee of Sir Run Run Hospital, Nanjing Medical University. The grant number is 2019-SR-017. We obtained the oral informed consent from each participant in this survey.

AUTHOR CONTRIBUTIONS

YH and ZH: methodology, software, and writing—review and editing. YH, ZH, YS, and YM: writing—original draft preparation. ZH, YS, KC, LL, LW, and YH: investigation and data curation. ZH and YS: visualization. YH: conceptualization, resources, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Predictive Factors for Acute Postoperative Pain After Open Radical Gastrectomy for Gastric Cancer

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Background: Pain has become an important factor in evaluating patients' quality of life and clinical treatment. For gastric cancer (GC) patients, open radical gastrectomy (OG) causes significant trauma to the body, increases patients' pain after operation, and delays early recovery. The aim of this study was to investigate the predictive factors of acute pain after OG within postoperative 72 h.

Methods: From March 2020 to September 2021, 307 patients who underwent OG were included in the study in Nanjing Drum Tower Hospital. The predictors included demographic predictors, pathological data, surgical predictors, and intraoperative predictors. The pain scores at 12, 24, 48, and 72 h after operation were evaluated by numeric rating scale (NRS). The predictors of acute pain were determined by univariate and multivariate analysis.

Results: The average pain score (NRS) of patients showed a downward trend over time within 72 h after OG. Multivariate analysis indicated that total gastrectomy (OR 1.823, 95% CI 1.094–3.040, $P < 0.05$), AJCC TNM stage (II) (OR.232, 95% CI 0.062–0.872, $P < 0.05$), AJCC TNM stage(III) (OR.185, 95% CI 0.049–0.698, $P < 0.05$), BMI (kg/m^2) (OR 1.75, 95% CI 1.029–2.976, $P < 0.05$), distant metastasis (OR 3.054, 95% CI 1.019–9.155, $P < 0.05$), intraoperative transfusion (OR 2.246, 95% CI 1.267–3.982, $P < 0.01$) were significant predictive factors for acute pain after OG.

Conclusion: Reasonable postoperative acute pain control was the prerequisite for accelerating the postoperative rehabilitation of patients. In order to reduce the occurrence of excessive or insufficient analgesia, it was necessary for patients who underwent OG to formulate appropriate analgesics according to risk factors.

Keywords: gastric cancer, surgery, postoperative, acute pain, predictor

INTRODUCTION

Gastric cancer (GC) is a common malignant tumor of the digestive system, posing a significant risk to human health. According to global cancer statistics, GC has the fifth-highest incidence rate, and was the third leading cause of cancer deaths (1). The only hope for curing cancer stomach was radical gastrectomy (2). Depending on the tumor's location, it could remove all or part of the stomach. According to the classification of surgical methods, radical gastrectomy could be mainly divided into laparoscopic radical gastrectomy (LRG) and OG. LRG has developed rapidly since Kitano reported it for early GC in 1994 and has many advantages, including reducing bleeding, alleviating pain, and accelerating recovery (3–6). The therapeutic effect of LRG in patients with GC was increasingly prominent, especially for patients with early GC. The incidence of postoperative complications was lower, and the prognosis was better than OG (7, 8). However, for patients with advanced GC, clinical application's therapeutic effect and safety were still controversial. Moreover, surgery cost is relatively high because of high requirements for the technical level of equipment and physicians. The effectiveness and safety of LRG have also become the focus of clinicians and patients. Studies have shown that OG is safer when enlarged lymph nodes (ESLNs) are >2.5 cm (9). OG could effectively remove the lesions of patients and remove the surrounding lymph nodes as much as possible to improve the prognosis of patients and the survival rate of patients. However, it causes great trauma to the body, which increases the patients' pain invisibly. Moderate to severe postoperative acute pain could cause a strong stress response in patients, leading to decreased immune function, and a greater risk of postoperative tumor recurrence and metastasis, which directly and indirectly affects the prognosis (10).

Therefore, the study of factors affecting postoperative acute pain has important clinical significance for optimizing postoperative acute pain management (11). Doctors, nurses, and pharmacists need to understand the influencing factors of postoperative analgesic effect of the operation, intervene with these factors, and formulate individualized analgesic schemes, so as to reduce the occurrence of excessive or insufficient analgesia. In this article, 307 patients with GC after OG were followed up, and the factors that may affect the postoperative analgesic effect were analyzed, so as to provide reference for the formulation of postoperative analgesic scheme.

METHODS

Patient and Public Involvement

This study was a retrospective single-center real-world study without any intervention in the treatment. This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital, and the Ethics Committee agreed to waive the informed consent. GC patients who underwent OG at Nanjing Drum Tower Hospital from March 2020 to September 2021 were reviewed. Patients who met the following eligibility criteria were included: diagnosis of primary GC and accepted OG. All participants were Han Chinese. Patients with these conditions were excluded: remnant GC, history of other malignant tumors, quitting operation, and incomplete data.

Perioperative Anesthesia and Surgical Procedure

All the research predictors were from patients who were anesthetized by the same team of anesthesiologists and operated by the same team of physicians. All patients underwent general anesthesia and OG.

Anesthesia information: All patients underwent total intravenous anesthesia. No premedication. The intravenous infusion pathway was established after the patient reached the operating room. Anesthesia was induced with midazolam (0.1 mg/kg), etomidate (0.2 mg/kg), cisatracurium besylate (0.4 mg/kg), and sufentanil (0.4 mg/kg). Target-controlled infusion (TCI) pump was used to maintain anesthesia with a target blood concentration of 4∼6 mg/mL propofol; some patients were given patient-controlled intravenous analgesia (PCA) after surgery.

All patients underwent OG. The patients were placed in the supine position as the surgical position and subjected to general anesthesia. The abdominal region of the patients was routinely disinfected. The 15–20 cm around the navel in the middle of the upper abdomen was taken as the surgical incision. The subcutaneous tissue of the patients was stripped layer by layer to expose the lesions. The anatomical position of the organs in the abdominal cavity was carefully explored. The ultrasonic knife was used to complete the operation of gastric dissociation. The operator should strictly abide by the principle of tumor-free operation. At the same time, the corresponding lymph tissue should be cleaned according to the specific position of the tumor tissue. After the operation, the bleeding was completely stopped, and the abdominal cavity was thoroughly rinsed with sterile distilled water. The incision was sutured after the operation and covered with sterile dressing. Finally, the drainage tube was placed on the abdominal wall.

Postoperative Analgesia

Postoperative patients received standard postoperative analgesia. PCA was given 10 min before the end of the operation. Fentanyl (adult: 15–20 mg/kg) was continuously infused, dexamethasone 10 mg, ondansetron 8 mg, diluted with normal saline, and the total volume was 100 ml. Dexamethasone and ondansetron prevent nausea or vomiting. The program was used for continuous infusion of background speed of 2 mL/h, a bolus dose of 0.5 mL, and lock for 15 min. Flurbiprofen axetil (50 mg b.i.d), parecoxib (40 mg b.i.d), or dezocine (10 mg b.i.d) as analgesics alleviate inflammation. If the patient complained of unbearable pain, intravenous pethidine was used as a rescue analgesic needed.

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists physical status; CRP, C-reactive protein; ESLNs, Enlarged lymph nodes; GC, Gastric cancer; GPCR, G protein-coupled receptors; LRG, Laparoscopic radical gastrectomy; NMDA, *N*-methyl-*D*-aspartic acid; NRS, Numerical rating scale; OG, Open radical gastrectomy; PCA, Patient-controlled intravenous analgesia; TCI, Target-controlled infusion; TNM, Tumor node metastasis; WHO, World health organization.

Pain Intensity Measurement

Pain monitoring during hospitalization. The measurements were assessed using the American Society of Pain Guidelines for Postoperative Pain Management and the Chinese Society of Anesthesia Guidelines for Postoperative Pain Management. Pain measurement was performed at multiple time points (12, 24, 48, 72 h after operation) after the operation. The pain intensity was measured by NRS. NRS pain intensity score ranged from 0 to 10, 0 was painless, 10 was the most painful. Due to the implementation of postoperative acute pain management in our hospital, only 29.3% of patients after OG with NRS score $\geq$3 under the joint action of medical care and pharmacists. NRS = 3 as the cut-off value was not suitable for this study. Therefore, the NRS $<$ 2 was classified as a good analgesic effect (no pain), NRS $\geq$ 2 was classified as a poor analgesic effect (pain). Evaluating and recording NRS scores at multiple time points. Postoperative vomiting was recorded during follow-up. All the administrations were completed by the same postoperative acute pain management team composed of trained pharmacists.

Predictors

The predictors included demographic predictors, pathological data, surgical predictors, and intraoperative predictors. We collected the participants' age, gender, BMI, diabetes, hypertension, previous abdominal surgery, pre-operative hemoglobin (g/L), pre-operative albumin (g/L), carcinoembryonic antigen, and pre-operative chemo- or radio-therapy before operation. We also recorded intraoperative information, such as American Society of Anesthesiologists physical status (ASA) score, total gastrectomy, or not intraoperative blood loss (ml), intraoperative fentanyl dosage (mg), intraoperative dexmedetomidine dosage (mg), and duration of operation (min). According to postoperative pathological data, we recorded tumor location, tumor size (cm), Lauren's histology, pathological grading, lymph node metastasis, depth of invasion, distant metastasis, lymphovascular invasion, and perineural invasion. Pathologic staging was evaluated according to the 8th American Joint Committee on Cancer (AJCC) staging system of GC.

Statistics Analysis

IBM SPSS Statistics software (version 25.0; Chicago, IL) was used for statistical analysis. All continuous predictors were expressed by mean $\pm$ SD or median and quartiles (25th, 75th). All classification predictors were represented by percentages.

According to the distribution characteristics of data, Student *t* test or Mann- Whitney *U* test was used for univariate analysis to evaluate the related factors of patients. Categorical predictors were analyzed using the chi-squared test. In order to determine the risk factors for predicting poor analgesic effect, binary logistic regression was performed for multivariate analysis. Values of $P <$ 0.05 were considered statistically significant.

RESULTS

A total of 354 patients were close to participate in this study. 15 patients with gastric stump cancer, 10 patients who abandoned surgery, 14 patients with other malignant tumor histories, and 8 patients who had incomplete data were excluded from the study. Therefore, 307 patients were available for analysis (**Figure 1**).

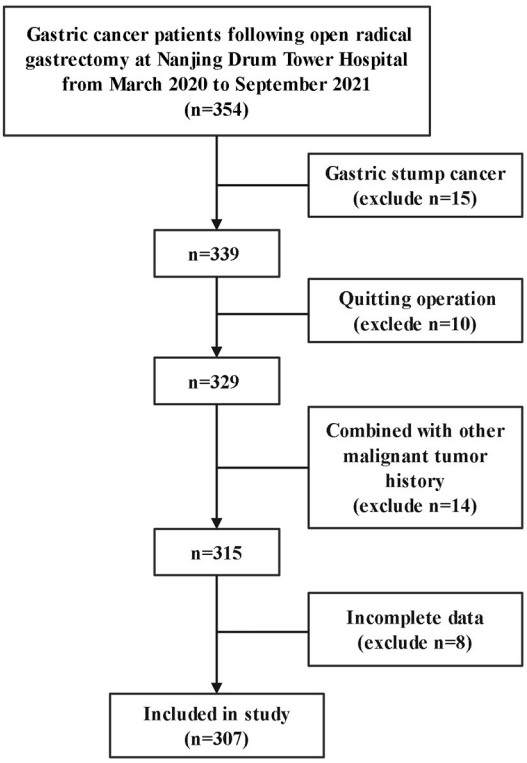

FIGURE 1 | Research flowchart. A total of 307 patients were included in this study.

Descriptive Statistics

Demographics information, underlying diseases, data on surgery, and ASA classification were collected by researchers. Descriptive statistics for the patient characteristics are presented in **Table 1**. The mean patient age was 76.97 $\pm$ 9.80 years old, and 70 of the patients (22.8%) were female; 183 (59.6%) GC patients received total gastrectomy; 117 (38.1%) patients had hypertension; 46 (15.0%) patients had diabetes. Within 72 h after operation, a total of 197 (64.3%) patients suffered pain (NRS $\geq$ 2). PCA was provided for 21 (6.8%) patients for postoperative analgesia. For all patients, the average pain score changes at 24, 48, and 72 h after the operation are shown in **Figure 2**.

Univariate Analysis

Our study assessed the pain scores at 24, 48, and 72 h after surgery. **Table 2** showed the data analysis results. At postoperative 24 h, whether total gastrectomy was performed or not ($P <$ 0.05), and AJCC TNM stage ($P <$ 0.05) was related to postoperative acute pain after OG. At postoperative 48 h, BMI ($P <$ 0.01), diabetes ($P <$ 0.05), hypertension ($P <$ 0.05), Lauren's histology ($P <$ 0.05), intraoperative blood loss ($P <$ 0.05), and duration of operation ($P <$ 0.05)

TABLE 1 | Patient characteristics.

		Postoperative NRS at 24 h		Postoperative NRS at 48 h		Postoperative NRS at 72 h	
Predictors	Results ($n = 307$)	NRS < 2	NRS ≥ 2	NRS < 2	NRS ≥ 2	NRS < 2	NRS ≥ 2
Number of scores recorded		110 (35.8%)	197 (64.3%)	191 (62.2%)	116 (37.8%)	151 (49.2%)	156 (50.8%)
Age, years	65.97 ± 9.80	66.69 ± 9.25	65.57 ± 10.09	66.33 ± 9.64	65.39 ± 10.06	66.03 ± 9.98	65.92 ± 9.66
Gender, *n* (%)							
Female	70 (22.8%)	20 (18.2%)	50 (25.4%)	46 (24.1%)	24 (20.7%)	30 (19.9%)	40 (25.6%)
Male	237 (77.2%)	90 (81.8%)	147 (74.6%)	145 (75.9%)	92 (79.3%)	121 (80.1%)	116 (74.4%)
BMI, kg/m^2							
<21	80 (26.1%)	29 (26.2%)	51 (25.9%)	40 (20.9%)	40 (34.5%)	31 (20.5%)	49 (31.4%)
≥21	227 (73.9%)	81 (73.6%)	146 (74.1%)	151 (79.1%)	76 (65.5%)	120 (79.5%)	107 (47.1%)
Diabetes							
No	261 (85.0%)	90 (81.8%)	171 (86.8%)	155 (81.2%)	106 (91.4%)	122 (80.8%)	139 (89.1%)
Yes	46 (15.0%)	20 (18.2%)	26 (13.2%)	36 (18.8%)	10 (8.6%)	29 (19.2%)	17 (10.9%)
Hypertension							
No	190 (61.9%)	68 (61.8%)	122 (61.9%)	116 (60.7%)	74 (63.8%)	85 (56.3%)	105 (67.3%)
Yes	117 (38.1%)	42 (38.2%)	75 (38.1%)	75 (39.3%)	42 (36.2%)	66 (43.7%)	51 (32.7%)
Previous abdominal surgery							
No	233 (72.6%)	80 (72.7%)	143 (72.6%)	136 (71.2%)	87 (75.0%)	113 (74.8%)	110 (70.5%)
Yes	84 (27.4%)	30 (27.3%)	54 (27.4%)	55 (28.8%)	29 (25.0%)	38 (25.2%)	46 (29.5%)
Pre-operative hemoglobin, g/L							
<120	166 (54.1%)	62 (56.4%)	104 (52.8%)	106 (55.5%)	60 (51.7%)	92 (60.9%)	74 (47.4%)
≥120	141 (45.9%)	48 (43.6%)	93 (47.2%)	85 (44.5%)	56 (48.3%)	59 (39.1%)	82 (52.6%)
Pre-operative albumin, g/L							
<35	46 (15.0%)	16 (14.5%)	30 (15.2%)	28 (14.7%)	18 (15.5%)	21 (13.9%)	25 (16.0%)
≥35	261 (85.0%)	94 (85.5%)	167 (84.8%)	163 (85.3%)	98 (84.5%)	130 (86.1%)	131 (84.0%)
Carcinoembryonic antigen							
<0.5	68 (22.1%)	22 (20.0%)	46 (23.4%)	43 (22.5%)	25 (21.6%)	38 (25.2%)	30 (19.2%)
0.5–10	214 (69.7%)	77 (70.0%)	137 (69.5%)	130 (68.1%)	84 (72.4%)	98 (64.9%)	116 (74.4%)
>10	25 (8.1%)	11 (10.0%)	14 (7.1%)	18 (9.4%)	7 (6.0%)	15 (9.9%)	10 (6.4%)
Pre-operative chemo- or radio-therapy							
No	294 (95.8%)	105 (95.5%)	189 (95.9%)	182 (95.3%)	112 (96.6%)	147 (97.4%)	147 (94.2%)
Yes	13 (4.2%)	5 (4.5%)	8 (4.1%)	9 (4.7%)	4 (3.4%)	4 (2.6%)	9 (5.8%)

(Continued)

TABLE 1 | Continued

		Postoperative NRS at 24 h		Postoperative NRS at 48 h		Postoperative NRS at 72 h	
Tumor location							
Upper 1/3	127 (41.4%)	37 (33.6%)	90 (45.7%)	80 (41.9%)	47 (40.5%)	65 (43.0%)	62 (39.7%)
Middle 1/3	72 (23.5%)	31 (28.2%)	41 (20.8%)	50 (26.2%)	22 (19.0%)	37 (24.5%)	35 (22.4%)
Lower 1/3	87 (28.3%)	35 (31.8%)	52 (26.4%)	48 (25.1%)	39 (33.6%)	40 (26.5%)	47 (30.1%)
2/3 or more	21 (6.8%)	7 (6.4%)	14 (7.1%)	13 (6.8%)	8 (6.9%)	9 (6.0%)	12 (7.7%)
Tumor size (cm)							
<3	79 (25.7%)	34 (30.9%)	45 (22.8%)	54 (28.3%)	25 (21.6%)	37 (24.5%)	42 (26.9%)
3–6	149 (48.5%)	51 (46.4%)	98 (49.7%)	92 (48.2%)	57 (49.1%)	76 (50.3%)	73 (46.8%)
>6	79 (25.7%)	25 (22.7%)	54 (27.4%)	45 (23.6%)	34 (29.3%)	38 (25.2%)	41 (26.3%)
Lauren's histology							
Intestinal type	152 (49.5%)	104 (68.9%)	109 (69.9%)	65 (59.1%)	87 (44.2%)	101 (52.9%)	51 (44.0%)
Diffuse type	58 (18.9%)	39 (25.8%)	43 (27.6%)	18 (16.4%)	40 (20.3%)	30 (15.7%)	28 (24.1%)
Mixed type	97 (31.6%)	8 (5.3%)	4 (2.6%)	27 (24.5%)	70 (35.5%)	60 (31.4%)	37 (31.9%)
Pathological grading							
Poorly differentiated	124 (40.4%)	42 (38.2%)	82 (41.6%)	74 (38.7%)	50 (43.1%)	59 (39.1%)	65 (41.7%)
Moderate differentiated	161 (52.4%)	60 (54.4%)	101 (51.3%)	103 (53.9%)	58 (50.0%)	80 (53.0%)	81 (51.9%)
Well differentiated	22 (7.2%)	8 (7.3%)	14 (7.1%)	14 (7.3%)	8 (6.9%)	12 (7.9%)	10 (6.4%)
Lymph node metastasis							
N0	116 (37.8%)	44 (40.0%)	72 (36.5%)	74 (38.7%)	42 (36.2%)	55 (36.4%)	61 (39.1%)
N1	40 (13.0%)	17 (15.5%)	23 (11.7%)	25 (13.1%)	15 (12.9%)	21 (13.9%)	19 (12.2%)
N2	59 (19.2%)	17 (15.5%)	42 (21.3%)	35 (18.3%)	24 (20.7%)	30 (19.9%)	29 (18.6%)
N3	92 (30.0%)	32 (29.1%)	60 (30.5%)	57 (29.8%)	35 (30.2%)	45 (29.8%)	47 (30.1%)
Depth of invasion							
T1–2	102 (33.2%)	39 (35.5%)	63 (32.0%)	62 (32.5%)	40 (34.5%)	45 (29.8%)	57 (36.5%)
T3–4	205 (66.8%)	71 (64.5%)	134 (68.0%)	129 (67.5%)	76 (65.5%)	106 (70.2%)	99 (63.5%)
Distant metastasis							
No	290 (94.5%)	107 (97.3%)	183 (92.9%)	182 (95.3%)	108 (93.1%)	139 (92.1%)	151 (96.8%)
Yes	17 (5.5%)	3 (2.7%)	14 (7.1%)	9 (4.7%)	8 (6.9%)	12 (7.9%)	5 (3.2%)
Lymphovascular invasion							
No	169 (55.0%)	58 (52.7%)	111 (56.3%)	106 (55.5%)	63 (54.3%)	84 (55.6%)	85 (54.5%)
Yes	138 (45.0%)	52 (47.3%)	86 (43.7%)	85 (44.5%)	53 (45.7%)	67 (44.4%)	71 (45.5%)

(Continued)

TABLE 1 | Continued

		Postoperative NRS at 24 h		Postoperative NRS at 48 h		Postoperative NRS at 72 h	
Perineural invasion							
No	144 (46.9%)	58 (52.7%)	86 (43.7%)	92 (48.2%)	52 (44.8%)	72 (47.7%)	72 (46.2%)
Yes	163 (53.1%)	52 (47.3%)	111 (56.3%)	99 (51.8%)	64 (55.2%)	79 (52.3%)	84 (53.8%)
AJCC TNM stage							
I	83 (27.0%)	32 (29.1%)	51 (25.9%)	53 (27.7%)	30 (25.9%)	36 (23.8%)	47 (30.1%)
II	65 (21.2%)	31 (28.2%)	34 (17.3%)	43 (22.5%)	22 (19.0%)	35 (23.2%)	30 (19.2%)
III	139 (45.3%)	44 (40.0%)	95 (48.2%)	83 (43.5%)	56 (48.3%)	70 (46.4%)	69 (44.2%)
IV	20 (6.5%)	3 (2.7%)	17 (8.6%)	12 (6.3%)	8 (6.9%)	10 (6.6%)	10 (6.4%)
ASA score							
II	20 (6.5%)	6 (5.5%)	14 (7.1%)	11 (5.8%)	9 (7.8%)	11 (7.3%)	9 (5.8%)
III	251 (81.8%)	91 (82.7%)	160 (81.2%)	156 (81.7%)	95 (81.9%)	121 (80.1%)	130 (83.3%)
IV	35 (11.4%)	13 (11.8%)	22 (11.2%)	24 (12.6%)	11 (9.5%)	18 (11.9%)	17 (10.9%)
V	1 (0.3%)	0 (0.0%)	1 (0.5%)	0 (0%)	1 (0.9%)	1 (0.7%)	0 (0%)
Total gastrectomy							
No	124 (40.4%)	36 (32.7%)	88 (44.7%)	76 (39.8%)	48 (41.4%)	57 (37.7%)	67 (42.9%)
Yes	183 (59.6%)	74 (67.3%)	109 (55.3%)	115 (60.2%)	68 (58.6%)	94 (62.3%)	89 (57.1%)
Intraoperative blood loss, ml							
<100	15 (4.9%)	8 (7.3%)	7 (3.6%)	13 (6.8%)	2 (1.7%)	8 (5.3%)	7 (4.5%)
≥100	292 (95.1%)	102 (92.7%)	190 (96.4%)	178 (93.2%)	114 (98.3%)	143 (94.7%)	149 (95.5%)
Intraoperative transfusion, ml							
<100	240 (78.2%)	82 (74.5%)	158 (80.2%)	147 (77.0%)	93 (80.2%)	108 (71.5%)	132 (84.6%)
≥100	67 (21.8%)	28 (25.5%)	39 (19.8%)	44 (23.0%)	23 (19.8%)	43 (28.5%)	24 (15.4%)
Intraoperative fentanyl dosage, mg	0.63 ± 0.22	0.64 ± 0.21	0.62 ± 0.23	0.64 ± 0.21	0.60 ± 0.25	0.64 ± 0.21	0.61 ± 0.24
Intraoperative dexmedetomidine dosage, mg	38.47 ± 18.95	38.25 ± 21.71	38.59 ± 17.29	38.61 ± 18.97	38.23 ± 19.02	39.59 ± 17.17	37.39 ± 20.53
Duration of operation, min							
<180	92 (30.0%)	31 (28.2%)	61 (66.3%)	49 (25.7%)	43 (37.1%)	51 (33.8%)	41 (26.3%)
≥180	215 (70.0%)	79 (71.8%)	136 (44.3%)	142 (74.3%)	73 (62.9%)	100 (66.2%)	115 (73.7%)
Postoperative PCA							
No	286 (93.2%)	104 (94.5%)	182 (92.4%)	176 (92.1%)	110 (94.8%)	139 (92.1%)	147 (94.2%)
Yes	21 (6.8%)	6 (5.5%)	15 (4.9%)	15 (7.9%)	6 (5.2%)	12 (7.9%)	9 (5.8%)

(Continued)

TABLE 1 | Continued

		Postoperative NRS at 24 h		Postoperative NRS at 48 h		Postoperative NRS at 72 h	
Preventive analgesia							
No preventive analgesia	9 (2.9%)	4 (3.6%)	5 (2.5%)	4 (2.1%)	5 (4.3%)	4 (2.6%)	5 (3.2%)
Flurbiprofen axetil (50 mg b.i.d)	123 (40.1%)	38 (34.5%)	85 (43.1%)	77 (40.3%)	46 (39.7%)	61 (40.4%)	62 (39.7%)
Parecixib (40 mg b.i.d)	29 (9.4%)	13 (11.8%)	16 (8.1%)	21 (11.0%)	8 (6.9%)	13 (8.6%)	16 (10.3%)
Dezocine (10 mg b.i.d)	146 (47.6%)	55 (50.0%)	91 (46.2%)	89 (46.6%)	57 (49.1%)	73 (48.3%)	73 (46.8%)

Predictors are shown as mean ± SD, median with median (25th, 75th) when appropriate.
ASA Classification, American Society of Anesthesiologists physical status; BMI, body mass index; NRS, Numerical Rating Scale; AJCC, American Joint Committee on Cancer; TNM, Tumor Node Metastasis; PCA, Patient-controlled intravenous analgesia.

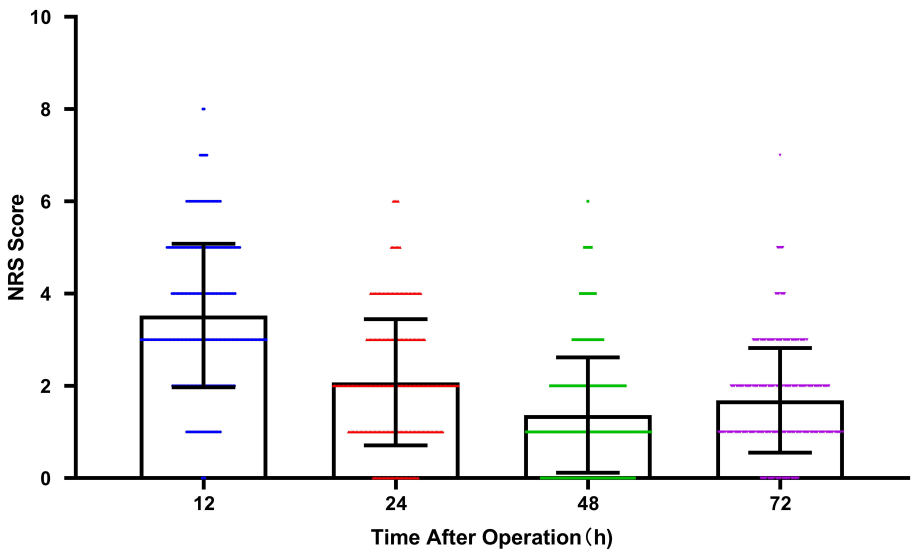

FIGURE 2 | The average pain score (NRS) with time after operation at 12, 24, 48, and 72 h. Scatter plot with bar. The plot represented mean with SD. Color symbols represented individual values. (NRS, Numerical Rating Scale).

were related to postoperative acute pain. At postoperative 72 h, BMI ($P < 0.05$), diabetes ($P < 0.05$), pre-operative hemoglobin ($P < 0.05$), intraoperative blood transfusion ($P < 0.01$) were related to postoperative acute pain. BMI and diabetes were both associated with postoperative acute pain at 48 and 72 h. In addition, there was a difference in the patient sources between groups, but this difference did not reach statistical significance. We used these predictors in the multivariate analysis.

Multivariate Analysis

To determine the risk factors of pain after OG, binary logistic regression was used to investigate the predictors that showed a significant difference ($P < 0.05$) in the univariate analysis (**Table 3** and **Figure 3**). After 24 h post-operation, the significant predictors included total gastrectomy (OR 1.823, 95% CI 1.094–3.040, $P < 0.05$), AJCC TNM stage (II) (OR 0.232, 95% CI 0.062–0.872, $P < 0.05$), and AJCC TNM stage (III) (OR 0.185, 95% CI 0.049–0.698, $P < 0.05$). After operation 48 h, the significant predictors included BMI (kg/m^2) (OR 1.75, 95% CI 1.029–2.976, $P < 0.05$). After operation 72 h, the significant predictors included distant metastasis (OR 3.054, 95% CI 1.019–9.155, $P < 0.05$), intraoperative transfusion (OR 2.246, 95% CI 1.267–3.982, $P < 0.01$).

DISCUSSION

As one of the most common malignant tumors of the digestive system, GC posed a serious threat to people's lives and health (12). The results of this study showed that the pain scores of patients showed a downward trend over time within 72 h after

TABLE 2 | Univariate analysis of predictive factors for pain within 72 h after OG.

	Postoperative NRS at 24 h	Postoperative NRS at 48 h	Postoperative NRS at 72 h
Predictors	***P value***	***P value***	***P value***
Age, years	0.308	0.509	0.917
Gender, *n* (%)	0.149	0.492	0.228
BMI, kg/m^2	0.928	0.009*	0.03*
Diabetes	0.241	0.015*	0.041*
Hypertension	0.985	0.592	0.047*
Previous abdominal surgery	0.979	0.469	0.396
Pre-operative hemoglobin, g/L	0.547	0.520	0.018*
Pre-operative albumin, g/L	0.872	0.838	0.603
Carcinoembryonic antigen	0.581	0.537	0.185
Pre-operative chemo- or radio-therapy	0.841	0.594	0.175
Tumor location	0.179	0.325	0.792
Tumor size, cm	0.279	0.332	0.815
Lauren's histology	0.457	0.040*	0.144
Pathological grading	0.838	0.752	0.820
Lymph node metastasis	0.512	0.953	0.942
Depth of invasion	0.535	0.715	0.210
Distant metastasis	0.108	0.417	0.049*
Lymphovascular invasion	0.541	0.839	0.841
Perineural invasion	0.127	0.570	0.789
AJCC TNM stage	0.028*	0.817	0.622
ASA score	0.744	0.392	0.603
Total gastrectomy	0.041*	0.783	0.353
Duration of operation, min	0.610	0.034*	0.152
Intraoperative blood loss, ml	0.147	0.045*	0.742
Intraoperative transfusion, ml	0.250	0.509	0.005*
Postoperative PCA	0.472	0.367	0.450
Preventive analgesia	0.419	0.458	0.951
Intraoperative fentanyl dosage, mg	0.280	0.860	0.288
Intraoperative dexmedetomidine dosage, mg	0.593	0.865	0.311

ASA Classification, American Society of Anesthesiologists physical status; BMI, body mass index; NRS, Numerical Rating Scale; AJCC, American Joint Committee on Cancer; TNM, Tumor Node Metastasis; PCA, Patient-controlled intravenous analgesia.
*$P < 0.05$.

surgery. However, the pain score at 72 h was slightly higher than that at 48 h, which may be related to wound dressing change and drainage tube removal. Some patients had a tolerance to analgesics, and the withdrawal of PCA (48–72 h after surgery).

To determine independent predictors of pain after OG within 72 h, we used binary logistic regression models after univariate analysis. There were so many variables included in this study, including demographics information, pathological data, and surgical data. Univariate analysis was carried out to screen out some variables which may be meaningful. And then binary logistic regression analysis was performed on variables with differences ($P < 0.1$). Binary logistic regression analysis used backward conditional, eliminated non-local variables step by step, and finally got 5 significant predictive factors ($P < 0.05$). It could not only explain the correlation between variables and postoperative acute pain after OG, but also reflect the strength of the correlation through OR value. In this study, total gastrectomy, AJCC TNM stage (I), BMI≥21 kg/m^2, distant metastasis, intraoperative blood transfusion (≥100 ml) were risk factors for postoperative acute pain.

In our study, total gastrectomy or proximal or distal gastrectomy was an important factor affecting postoperative acute pain. Total gastrectomy had potential advantages in improving the long-term survival rate and reducing the incidence of residual GC (13). Compared with proximal or distal gastrectomy, total gastrectomy had a longer operation time and more intraoperative blood loss. Activated injury receptors or immune cells released a large number of endogenous inflammatory mediators (14). At the same time, injury receptors expressed one or more cell surface receptors, such as G protein-coupled receptors (GPCR) and *N*-methyl-*D*-aspartic acid (NMDA). These receptors specifically recognized the corresponding inflammatory mediators, enhancing the excitability nerve fibers, and improving the sensitivity of injury receptors to injurious stimuli (15). Laparoscopic distal gastrectomy for TNM stage I-III GC had less blood loss, less postoperative pain, and mild inflammatory response (16).

We found that BMI correlated with postoperative acute pain ($P = 0.039$) after OG. Most studies from Asian Centers used BMI value of 25 kg/m^2 as the critical value for dividing patients into obesity, which was inconsistent with the current definition of obesity by the WHO (17). In a meta-analysis, the effect of obesity on the prognosis of GC after resection was studied, and BMI ≥ 30 was defined as obesity (18). Intraoperative blood loss was reported in 4 studies and was lower in the non-obese group, but the difference was not statistically significant (19–22). Similarly, non-obese patients could be observed in wound infection decreased trend, but this did not reach the level of statistical significance (22). Excessive visceral fat wrapped in the main blood vessels of the upper abdomen may affect the recognition of the best anatomical plane, and the operation time may be longer. Increased blood loss, increased risk of wound infection, and prolonged operation time were potential factors for postoperative acute pain.

Our study suggested that patients at different TNM stages of cancer may respond differently to postoperative acute pain. A retrospective study investigated the effect of postoperative systemic inflammation on prognosis in patients with TNM stage I GC, and suggested that early postoperative serum C-reactive protein (CRP) level (cut-off value was 13.9 mg/dL) could predict the long-term prognosis of radical gastrectomy (23). Saito et al. evaluated the effect of CRP peak level on prognosis in patients with advanced GC after radical gastrectomy

TABLE 3 | Binary logistic regression analysis for outcome postoperative NRS at 24, 48, 72 h.

Predictors	Outcome: NRS ≥ 2 at postoperative 24 h		
	Model 1		
	OR (95% CI)	*P value*	
Total gastrectomy	1.823 (1.094–3.040)	0.021*	
AJCC TNM stage			
I	(reference)		
II	0.232 (0.062–0.872)	0.031*	
III	0.185 (0.049–0.698)	0.013*	
IV	0.369 (0.102–1.332)	0.128	

Predictors	Outcome: NRS ≥ 2 at postoperative 48 h			
	Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*
BMI, kg/m^2	1.699 (0.995–2.900)	0.052	1.75 (1.029–2.976)	0.039*
Duration of operation, min	1.565 (0.933–2.625)	0.090	1.587 (0.95–2.652)	0.078
Diabetes	2.205 (1.02–4.765)	0.044*	2.09 (0.977–4.473)	0.057
Lauren's histology				
Intestinal type	(reference)			
Diffuse type	0.841 (0.487–1.454)	0.536		
Mixed type	1.558 (0.788–3.081)	0.202		
Intraoperative blood loss, ml	0.223 (0.048–1.042)	0.056	0.234 (0.051–1.076)	0.062

Predictors	Outcome: NRS ≥ 2 at postoperative 72 h			
	Model 4		Model 5	
	OR (95% CI)	*P*	OR (95% CI)	*P*
BMI, kg/m^2	1.663 (0.957–2.890)	0.071	1.697 (0.992–2.905)	0.054
Diabetes	1.791 (0.909–3.528)	0.092	1.939 (0.997–3.771)	0.051
Hypertension	1.209 (0.732–1.996)	0.459		
Pre-operative hemoglobin, g/L	0.767 (0.454–1.297)	0.322		
Distant metastasis	2.821 (0.932–8.535)	0.066	3.054 (1.019–9.155)	0.046*
Intraoperative transfusion, ml	1.876 (0.983–3.581)	0.056	2.246 (1.267–3.982)	0.006*

(Continued)

TABLE 3 | Continued

BMI, body mass index; NRS, Numerical Rating Scale; AJCC, American Joint Committee on Cancer; TNM, Tumor Node Metastasis.

**P < 0.05.*

Explanation for models Binary logistic regression models 1,2,4 were constructed using predictors found to be significant in the univariate analysis (p < 0.05). Models 3,5 were derived from models 2,4 respectively with non-significant predictors eliminated in stepwise process called backward conditional. The resulting models include only significant predictors (p < 0.05). The reported odds ratios (all significant ones are above 1) suggest that one unit increase in predictor score (or having categorical predictor) is associated with increase odds of pain.

and identified CRP peak level (cut-off value was 12 mg/dL) as an independent prognostic factor (24). CRP is synthesized by the liver, mainly regulated by interleukin-6, and may upregulate pro-inflammatory and anti-inflammatory cytokines (25). Recently, some studies have shown that postoperative systemic inflammation is significantly correlated with the postoperative prognosis of cancer patients through evaluating serum CRP level (25–27). The increase of postoperative CRP level in patients with GC may predict the increase of inflammatory level, and strong inflammatory response may cause serious postoperative acute pain.

According to the 8th AJCC TNM classification system, no matter the depth of tumor penetrating the gastric wall (T) and the number and state of lymph nodes (N), distant metastasis is divided into stage IV. Patients at the IV stage usually suffer from a long and painful illness. Postoperative patients in our hospital would use non-steroidal anti-inflammatory drugs combined with opioids analgesia. Opioids play an analgesic effect by simulating the physiological role of endogenous opioid peptides (28). Patients with advanced GC faced low cholesterol levels due to malnutrition. Low cholesterol levels may reduce the activity of opioids (29). Studies have shown that patients with lung cancer at low cholesterol levels need higher doses of opioids to achieve the same level of pain control (30). Our study also confirmed that patients with distant metastasis were more likely suffer acute pain than patients with early GC after surgery.

In our study, blood transfusion was an independent predictor of postoperative acute pain. Blood transfusion could save a life in many cases but had a negative influence on immune

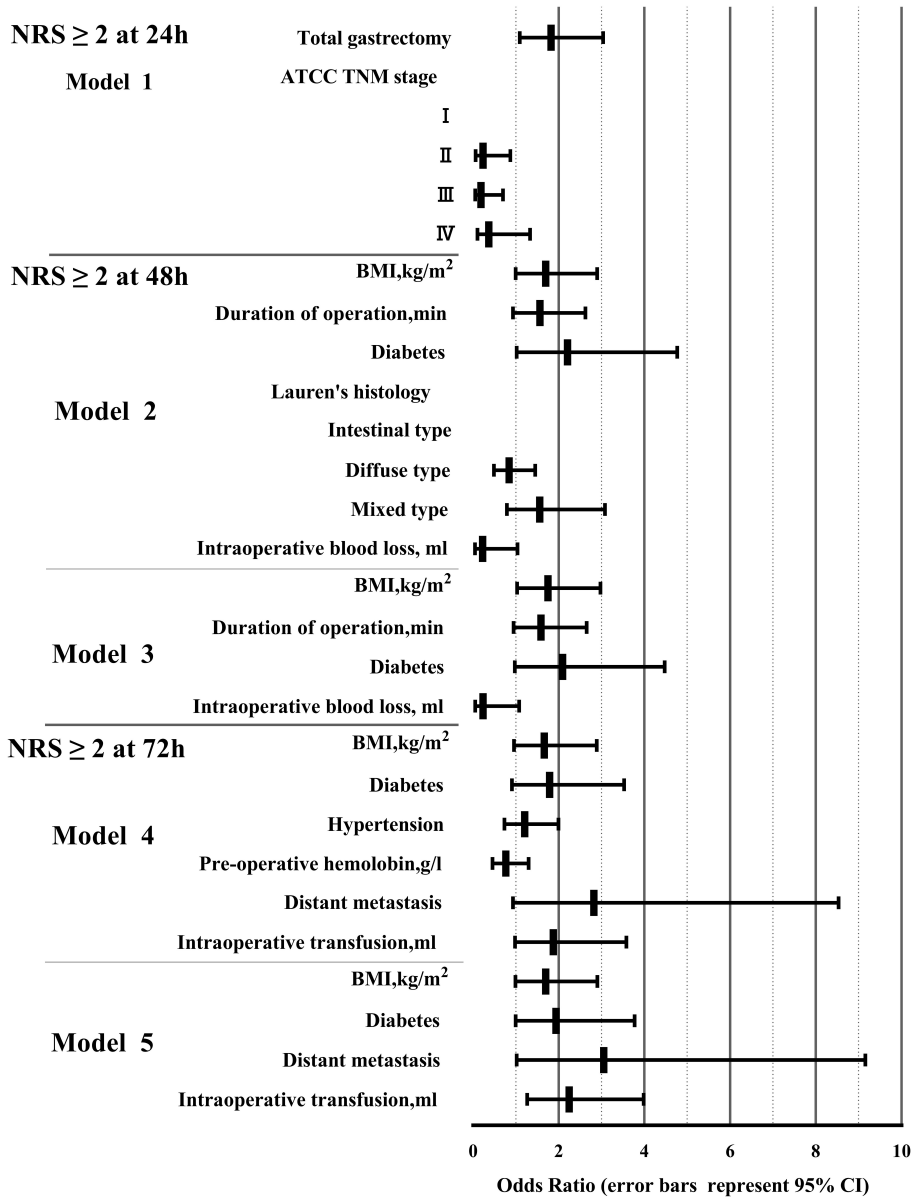

FIGURE 3 | Binary logistic regression model results. (BMI, body mass index; NRS, Numerical Rating Scale; AJCC, American Joint Committee on Cancer; TNM, Tumor Node Metastasis).

regulation, postoperative infection, and tumor metastasis, and recurrence (31). Immunomodulation of the innate and adaptive immune system occurred after exposure of the recipient to the many cell-bound and soluble antigens which were expressed on viable and decaying cells in the transfusion (32). Blood transfusion was associated with infectious complications following gastrointestinal surgery (33). The activation of inflammation during blood transfusion was closely related to the severity of postoperative pain. A meta-analysis also confirmed that the restrictive allogeneic blood transfusion strategy could reduce the perioperative infection rate without increasing the incidence of complications such as cardiac events or mortality (34). Retrospective analysis of a single central database also confirmed that perioperative blood transfusion was independently associated with poor prognosis in patients with GC (35).

Our study also had some limitations. We only evaluated and explored the possible factors affecting pain within 72 h after

surgery. There was no study on the influencing factors of pain 3 days and long-term after surgery. At the same time, our research was limited to OG, and there was no study on the influencing factors of pain after LRG and robotic radical gastrectomy for GC. In addition, postoperative acute pain was affected by genetic polymorphism related to pharmacokinetics, pharmacodynamics of analgesics (36) and psychology, and we had not studied these influencing factors.

Pain has become an important factor in evaluating patients' quality of life and clinical treatment. Medical staff should predict the influencing factors of postoperative acute pain, formulate reasonable analgesic schemes, and reduce the occurrence of excessive analgesia and insufficient analgesia. Reasonable postoperative pain control was the prerequisite for accelerating the postoperative rehabilitation of patients.

Total gastrectomy, AJCC TNM stage (I), BMI ($\geq$21, kg/m^2), distant metastasis, and intraoperative transfusion ($\geq$100 ml) were significantly associated with pain after OG within postoperative 72 h. To reduce the occurrence of excessive analgesia and insufficient analgesia, formulating appropriate analgesics according to these risk factors was necessary for patients who underwent OG.

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 Ethics Committee of Nanjing Drum Tower Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HX and JW: design. JW and HX: writing. ZM and JW: analysis. WG and MH: methodology. JW and WG: data curation. All authors read and approved the final manuscript.

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Cost-Effectiveness of Nivolumab Immunotherapy vs. Paclitaxel or Docetaxel Chemotherapy as Second-Line Therapy in Advanced Esophageal Squamous Cell Carcinoma in China

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This study aimed to evaluate and compare nivolumab's cost-effectiveness with chemotherapy in patients with advanced esophageal squamous cell carcinoma from the Chinese healthcare system perspective. To this end, the researchers utilized a partitioned survival model with three mutually exclusive health stages. The characteristics of the patients used as inclusion and exclusion criteria in this model were the same as those used for patients with advanced esophageal squamous cell carcinoma in the ATTRACTION-3 study. The ATTRACTION-3 trial, which took place between January 7, 2016 and November 12, 2018, also yielded important clinical data. Data on medical and economic preferences were collected from real-world clinical practices. Costs, quality-adjusted life years, and incremental cost-effectiveness ratio were calculated for the two therapy options. The model uncertainty was investigated using a deterministic and probabilistic sensitivity analysis. When compared to chemotherapy, nivolumab was linked with an increase of 0.28 quality-adjusted life years with an increased cost of US$ 36,956.81 per patient in the base case analysis of a hypothetical sample of 419 patients. The incremental cost-effectiveness ratio in the deterministic sensitivity analysis was US$ 132,029.46/quality-adjusted life year, with a 48.02% probability of being cost-effective at willingness-to-pay thresholds of US$ 132,029.22/quality-adjusted life year. The incremental cost-effectiveness ratio remained greater than US$ 80,000/quality-adjusted life year in the deterministic sensitivity analyses. To be more cost-effective and remain below the threshold of 37,653 US$/quality-adjusted life year, which the Chinese population can afford, nivolumab's price would have to be lowered sharply by 53.50%. Nivolumab is clinically beneficial but not cost-effective when compared to chemotherapy. A substantial reduction in nivolumab's drug acquisition cost would be necessary to make it cost-effective for immunotherapy.

Keywords: cost-effectiveness, partitioned survival model, therapy, drug acquisition cost, esophageal squamous cell carcinoma

INTRODUCTION

Esophageal cancer is one of the seven major malignant tumors worldwide and is the sixth leading cause of mortality among all malignancies (1, 2). Esophageal cancer incidence, prevalence, and histological type vary among geographic regions. For instance, North America and Western Europe have the highest rates of esophageal cancer, (3, 4) where its most common subtype is adenocarcinoma. Meanwhile, in Asia, including China, Japan, and Korea, esophageal squamous cell carcinoma (ESCC) is more common (5, 6). Advanced esophageal cancer is a rapidly fatal disease (7). Approximately 40% of patients with esophageal cancer are diagnosed when the disease is advanced, and the median survival time is 8–10 months. The 5-year survival rate is predicted to be below 5%. Furthermore, patients with advanced esophageal cancer have limited options for second-line treatments, (8, 9) with no accepted standard of care, although paclitaxel, docetaxel, or irinotecan are used (10–12). Publications summarizing data from retrospective analyses have reported that the median survival and overall response rate are comparable among paclitaxel, docetaxel, and irinotecan (13–15). In addition, Nivolumab, an anti-programmed death 1 (PD-1) inhibitor, has shown antitumor activity in patients with advanced esophageal cancer (16, 17). ATTRACTION-3, (18) a published clinical trial of nivolumab, reported clinical efficacy of treatment in terms of longer overall survival (OS) compared with chemotherapy using paclitaxel or docetaxel.

Recently, given their antitumor activity, PD-1 inhibitors are being used in the treatment of several types of squamous cell tumors (19–21). This treatment comes at a high cost and increases patients' financial burden (22). Though a therapy's clinical effectiveness is desirable, its economic cost is an important consideration for healthcare policymakers while selecting treatment options. If the cost of PD-1 inhibitors is high, it may outweigh the benefit of their antitumor effect. Based on the ATTRACTION-3 trial data, our study attempted to assess the cost-effectiveness of nivolumab immunotherapy and paclitaxel/docetaxel chemotherapy treatment alternatives by measuring and comparing therapy costs and effectiveness from the perspective of the Chinese society.

MATERIALS AND METHODS

Target Population

This study was conducted at Fujian Medical University Cancer Hospital, Fuzhou, China. The study was designed by referring to the International Council for Harmonization E6 guidelines for Good Clinical Practice, the Declaration of Helsinki principles, and applicable laws and regulations. The reporting criteria of the Consolidated Health Economic Evaluation Reporting Standards were followed when writing the economic evaluation section (23).

Abbreviations: ESCC, esophageal squamous cell carcinoma; PD-1 inhibitor, anti-programmed death 1; PD stage, progressive disease; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; AE, adverse events; PFS, progression-free survival; OS, overall survival; WTP, willingness-to-pay.

The target population in the model was the same as that used in the ATTRACTION-3 clinical trial. The ATTRACTION-3 trial is a global, multicenter, randomized, open-label, phase 3 study. The trial covered 90 cancer centers and hospitals across Asia, North America, and Western Europe. A total of 419 patients were recruited for this study, who received at least one cycle of the assigned therapy. From the 419 patients, 210 were assigned to receive nivolumab and 209 to receive chemotherapy (144 and 65 patients were assigned to receive paclitaxel and docetaxel, respectively). Patients included in the study were at least 20 years old and diagnosed with unresectable esophageal cancer, either squamous or adenosquamous cell carcinoma. The diagnoses were confirmed by histological or cytological features. At least one measurable lesion should have been present (a major resected lesion in the cervical or thoracic esophagus or at the esophagogastric junction). They should have had tumor progression or recurrence after the first-line treatment (including chemoradiotherapy). Other inclusion criteria were: a 0–1 Eastern Cooperative Oncology Group performance status and adequate organ function. The treatment continued until any of the following events occurred: disease progression as defined by the Response Evaluation Criteria in Solid Tumors version 1.1, the occurrence of unacceptable toxicity levels, patient withdrawal, or at the investigator's discretion.

Model Construction

The cost-effectiveness of treatment with nivolumab and chemotherapy with paclitaxel or docetaxel was assessed using a partitioned survival model (24) based on the ATTRACTION-3 trial data. This model has often been used in testing medical costs and efficacy outcomes of metastatic oncology modeling (25–28). The model has three mutually exclusive health stages (**Figure 1**): progression-free stage (patient entered until disease progression occurred), progressive disease (PD) stage (patient was alive after the disease progression began), and terminal stage. The length of each model cycle was defined as 60 days, and the time horizon was assessed at 36 months in our model, which matched the actual progress of the ATTRACTION-3 trial. The model's key output variables were cost, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER).

Cost

In our model, clinical costs were considered, including drug acquisition, laboratory tests, radiologic images, drug administration, disease progression visits, treatment-related adverse events (AE), and terminal costs. These costs were direct costs, which were converted to US$ at the rates prevailing in November 2021. The data on costs were collected from the National Health Commission of China, Fujian Provincial Health Commission, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, and expert consensus.

The administered doses of nivolumab and chemotherapy were included in the drug acquisition cost. The evaluated drugs in the model included nivolumab (Bristol-Myers Squibb), paclitaxel (Bristol-Myers Squibb), and docetaxel (Aventis Pharma S. A.). The listed drug prices, obtained from the National Health Commission of the People's Republic of China in 2021, were

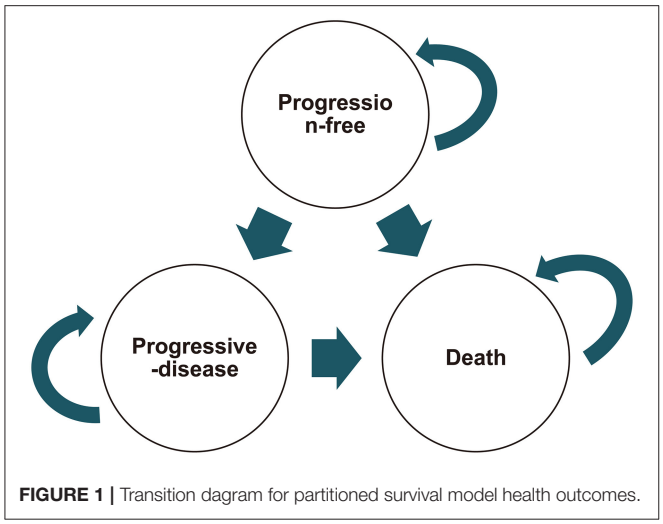

FIGURE 1 | Transition dagram for partitioned survival model health outcomes.

nivolumab at US$ 718 per 4 ml: 40 mg and US$ 1, 448 per 10 ml: 100 mg; paclitaxel at US$ 77 per 5 ml: 30 mg; and docetaxel at US$ 142 per 0.5 ml: 20 mg. The dosing frequency and intensity were based on the ATTRACTION-3 trial's published data. Nivolumab's dose, administered intravenously, was 240 milligrams on day 1 of each 2-week treatment cycle (each treatment cycle lasted 6 weeks). Chemotherapy was administered with a dose of 100 mg/m^2 of paclitaxel on day 1 of each 1-week cycle (6 weeks per cycle followed by 1 week off) or with a dose of 75 mg/m^2 of docetaxel on day 1 of each 3-week cycle (each treatment cycle was 3 weeks). Since body surface area was not reported in the ATTRACTION-3 trial, we assumed a body surface area of 1.71 m^2 to calculate the doses of paclitaxel and docetaxel. This body surface area was based on a mean height of 1.64 m and a mean bodyweight of 64 kg, which were the mean values of the Chinese population in 2020, as published by the National Bureau of Statistics of the People's Republic of China. Therefore, the dose of nivolumab was set at 240 mg. The mean doses of paclitaxel and docetaxel per patient in the chemotherapy group were 115 and 275 mg, respectively. The cost was determined at the patient level for all vials.

The standard charges of the Fujian Provincial Health Commission in 2021 were used to compute the expenses of laboratory testing, radiologic imaging, medicine administration, disease progression visits, and AE-related costs. Terminal costs were estimated according to the relevant legal interpretations of the Supreme People's Court in trials of personal injury compensation cases (29).

Laboratory tests and radiologic imaging costs assumed that the schedule of assessments in typical clinical trials was followed while performing these tests. Therefore, all laboratory tests and radiologic images in our model were not assumed to have been performed at the onset of treatment (first day of each model cycle). The costs of these laboratory tests and radiologic imaging were accounted for whenever they were performed as required by the treatment duration, histology, and time horizon. From 28 days before the baseline until the completion of treatment, the 12-lead electrocardiogram, Hepatitis B virus and Hepatitis C virus serology, hematology, serum chemistry, coagulation tests, urinalysis, thyroid function, tumor assessment, and pulmonary function test were conducted. Hematology, serum chemistry, 12-lead electrocardiogram, coagulation, and urinalysis were performed within 14 days before the baseline. These tests were repeated and reviewed before nivolumab, paclitaxel, or docetaxel administration. Hepatitis B virus and Hepatitis C virus serology tests, including Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C virus antibodies, were performed within 14 days of the baseline. Patients who were Hepatitis B surface antigen-positive were not enrolled until further definite testing with Hepatitis B virus DNA titers showed a satisfactory protective level of anti-HBs. Pulmonary function tests, including spirometry and assessment of diffusion capacity, were performed within 28 days of the baseline to determine enrollment suitability. Thyroid function tests were performed within 7 days of the baseline to determine the levels of free triiodothyronine, free thyroxine, and thyroid stimulating hormone, and were repeated three times and each time the drug was administered intravenously thereafter (nivolumab, 6 weeks; paclitaxel, 3 weeks; docetaxel, 9 weeks). Tumor assessments were performed using contrast-enhanced computed tomography scans of the neck, chest, and abdomen within 28 days of the baseline, every 6 weeks for 1 year, and every 12 weeks thereafter, until disease progression or death, whichever occurred first. For patients who could not be subjected to computed tomography because of contrast dye allergies, magnetic resonance imaging was used. For each patient, the same radiographic procedure was used throughout the study.

For nivolumab and chemotherapy, drug administration expenses were examined separately, including preventative medicine, hospitalization, nursing, and drug infusion expenditures. Patients in both arms of the trial were assumed to be routinely monitored until death, and medical examination and visit expenditures were expected to be incurred when disease progression occurred. Terminal costs were allocated when a patient died; the costs for these services were assumed to be equal in both arms. The one-time cost of a funeral by burial was characterized as the terminal cost. Our model included the $\geq$3-grade treatment related to AE, as reported in the ATTRACTION-3 trial. The related treatment cost calculations for the nivolumab group were derived from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities Version 4.2021 (30). The treatment cost for the chemotherapy group was based on the expert consensus of clinical practitioners.

Utility Scores

The ATTRACTION-3 trial did not report the utility scores. Various scholars have used the reported quality-of-life data as utility scores for cost-effectiveness analyses regarding esophageal cancer treatment (31–37). There may be considerable uncertainty regarding ESCC's impact on QALYs, especially given the current uncertainty in published reports regarding the value for utility score assessment. The only realistic assumption supported by these published reports and current practices is that the utility scores in second-line esophageal cancer treatment would eventually decline as the disease progressed to death (38–40). This is because decreased functioning or worsening symptoms

TABLE 1 | Key input parameters to our model and ranges of the sensitivity analyses.

Input parameters	Base case value	Lower bound	Upper bound	Distribution	Source
Clinical input					
PFS survival model of nivolumab	Nivolumab PFS survival data	–	–	Fixed in model	ATTRACTION-3 trial
PFS survival model of chemotherapy	Chemotherapy PFS survival data	–	–	Fixed in model	ATTRACTION-3 trial
OS survival model of nivolumab	Nivolumab OS survival data	–	–	Fixed in model	ATTRACTION-3 trial
OS survival model of chemotherapy	Chemotherapy OS survival data	–	–	Fixed in model	ATTRACTION-3 trial
Utility input					
PFS	0.74	0.59	0.89	Beta	(34, 37)
PD	0.58	0.46	0.70	Beta	(34, 37)
Drug acquisition					
Nivolumab (Bristol-Myers Squibb) per 240 mg	$3,614.08	$2,891.26	$4,336.90	Gamma	National Health Commission of China
Docetaxel (Bristol-Myers Squibb) per 20 mg	$997.19	$797.75	$1,196.63	Gamma	National Health Commission of China
paclitaxel (Aventis Pharma S A) per 40 mg	$459.60	$367.68	$551.52	Gamma	National Health Commission of China
Drug administration				Gamma	
Preventive medication per administered intravenously	$93.93	$75.14	$112.72	Gamma	Local medical data
Infusion fee per administered intravenously	$1.86	$1.49	$2.23	Gamma	Local medical data
Hospitalization fee per administered intravenously	$39.14	$31.31	$46.97	Gamma	Local medical data
Laboratory tests and scans					
ECG	$4.23	$3.38	$5.07	Gamma	Fujian Provincial Health Commission, (18, 43)
Hematology	$3.91	$3.13	$4.70	Gamma	Fujian Provincial Health Commission, (18, 43)
Serum chemistry	$28.18	$22.54	$33.81	Gamma	Fujian Provincial Health Commission, (18, 43)
Urinalysis	$4.70	$3.76	$5.64	Gamma	Fujian Provincial Health Commission, (18, 43)
Coagulation parameters	$10.42	$8.34	$12.50	Gamma	Fujian Provincial Health Commission, (18)
Thyroid function	$23.48	$18.79	$28.18	Gamma	Fujian Provincial Health Commission, (18, 43)
Pulmonary function tests	$61.05	$48.84	$73.26	Gamma	Fujian Provincial Health Commission, (18)
HBV and HCV serology	$11.28	$11.28	$19.12	Gamma	Fujian Provincial Health Commission, (18)
HBV DNA	$23.64	$23.64	$62.78	Gamma	Fujian Provincial Health Commission, (18)
Radiologic images	$435.58	$234.82	$919.69	Gamma	Fujian Provincial Health Commission, (18, 43)
Treatment-emergent AE (grade 3–5) in nivolumab group					
Rash	$80.00	$60.00	$100.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Diarrhea	$14,000.00	$8,000.00	$20,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Decreased appetite	$825.00	$150.00	$1,500.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Stomatitis	$2,550.00	$100.00	$5,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Nausea	$800.00	$100.00	$1,500.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Arthralgia	$350.00	$100.00	$600.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Neutrophil count decreased	$1,575.00	$150.00	$3,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Anemia	$5,500.00	$1,000.00	$10,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
White blood cell count decreased	$1,575.00	$150.00	$3,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Neutropenia	$1,575.00	$150.00	$3,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Peripheral sensory neuropathy	$15,000.00	$10,000.00	$20,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Febrile neutropenia	$2,650.00	$300.00	$5,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Neuropathy peripheral	$15,000.00	$10,000.00	$20,000.00	Gamma	NCCN Clinical Practice Guidelines in Oncology (30)
Treatment-emergent AE (grade 3–5) in chemotherapy group					
Rash	$35.00	$20.00	$50.00	Gamma	Expert consensus of clinical practices
Diarrhea	$312.50	$25.00	$600.00	Gamma	Expert consensus of clinical practices

(Continued)

TABLE 1 | Continued

Input parameters	Base case value	Lower bound	Upper bound	Distribution	Source
Decreased appetite	$825.00	$150.00	$1,500.00	Gamma	Expert consensus of clinical practices, (35)
Stomatitis	$125.00	$50.00	$200.00	Gamma	Expert consensus on the diagnosis and prevention of acute oral mucositis caused by antitumor therapy
Nausea	$350.00	$100.00	$600.00	Gamma	CSCO guidelines for the prevention and treatment of antitumor treatment-related nausea and vomiting, (35)
Arthralgia	$0.00	$0.00	$0.00	Gamma	Expert consensus of clinical practices
Neutrophil count decreased	$1,575.00	$150.00	$3,000.00	Gamma	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (37)
Anemia	$275.00	$50.00	$500.00	Gamma	CSCO clinical practice guidelines for tumor-associated anemia, (34)
White blood cell count decreased	$1,575.00	$150.00	$3,000.00	Gamma	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (44)
Neutropenia	$1,575.00	$150.00	$3,000.00	Gamma	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (45)
Peripheral sensory neuropathy	$25.00	$0.00	$50.00	Gamma	ASCO clinical practice guidelines, (43)
Febrile neutropenia	$2,650.00	$300.00	$5,000.00	Gamma	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (37)
Neuropathy peripheral	$25.00	$0.00	$50.00	Gamma	ASCO clinical practice guidelines
Terminal cost					
Expenditure on funeral	$4,517.85	$3,614.28	$5,421.42	Gamma	Local data
Discount rate	0.05	0	0.08	Fixed in model	(46)

OS, overall survival; PFS, progression-free survival; PD, progressive disease; AE, adverse events; NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology.

during and after second-line treatment is inevitable (41). Therefore, in our model, we assumed the utility score to decline linearly from progression-free survival (PFS) to the point of PD and then to the point of death. The utility score was determined to be 0.74 in PFS and 0.58 in PD (34, 37). Mortality's utility score was 0.

Sensitivity Analyses

A deterministic sensitivity analysis (31, 42) was conducted by adjusting all the model's input parameters. **Table 1** presents characteristics of the model's costs and outcome parameters. **Table 2** presents laboratory tests, scans, and ≥3 grade treatment-emergent AE costs and treatment details. The discount rate for both costs and health outcomes was 5% per year, range from 0 to 8% (46). Cost of HBV and HCV serology, HBV DNA, radiologic images, and ≥grade 3 AE-related costs were based on the clinical practices estimation for value range, other parameters were changed by 20% in both directions. When one of the input parameters was altered, the others remained unchanged. A probabilistic sensitivity analysis was executed using a Monte Carlo simulation (34, 47). A total of 10,000 simulated iterations were run. Each time, a random sample was taken from the distributions of all the parameters. The parameter categories were used to make assumptions about distributions, the cost parameters were assumed to Gamma distribution, and utility parameters were assumed to Beta distribution (48).

Statistical Analysis

In our model, the cost and health outcomes of the three mutually exclusive health states, as well as deterministic and probabilistic sensitivity analyses, were computed using Excel 2016. The clinical efficacy and safety data of second-line therapy for advanced ESCC were obtained from the ATTRACTION-3 trial. In the ATTRACTION-3 trial, statistical analyses were completed using SAS 9.4. OS and PFS were estimated using the Kaplan-Meier method, with a two-sided, 0.05 significance level, log-rank test. We performed a survival analysis similar to the ATTRACTION-3 trial for estimating the survival curve. Statistical analyses were undertaken using SPSS 26.0. OS was estimated using the Kaplan-Meier method, with a two-sided, 0.05 significance level, log-rank test. Further, PFS was estimated using the life table method.

RESULTS

Base-Care Analysis

The median OS in the ATTRACTION-3 study was 10.9 months for the nivolumab group and 8.4 months for the chemotherapy

TABLE 2 | Laboratory tests, scans and treatment-emergent grade3–5 AE details.

Input parameters	Test/scans/treatment details	Source
Laboratory tests and scans		
ECG	12-lead ECG	Fujian Provincial Health Commission, (18, 43)
Hematology	Red blood cell count, hemoglobin, platelet count, auto-cell count, neutrophil count, lymphocyte count	Fujian Provincial Health Commission, (18, 43)
Serum chemistry	ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen or urea (preferably blood urea nitrogen>, total protein, albumin, creatine, blood sugar, lactate dehydrogenase, K + ∼ Na +, Ca2+, Mg2+, Cl-	Fujian Provincial Health Commission, (18, 43)
Urinalysis	White blood cells, red blood cells, urine protein	Fujian Provincial Health Commission, (18, 43)
Coagulation parameters	APTT, PT, FIB, TT, INR	Fujian Provincial Health Commission, (18)
Thyroid function	TSH, FT3 and FT4	Fujian Provincial Health Commission, (18, 43)
Pulmonary function tests	Spirometry and assessment of diffusion capacity	Fujian Provincial Health Commission, (18)
HBV and HCV serology	HBsAg, HBcAb, and HCV antibody	Fujian Provincial Health Commission, (18)
HBV DNA	HBV DNA	Fujian Provincial Health Commission, (18)
Radiologic images	Contrast-enhanced CT or MRI for neck, chest, and abdomen	Fujian Provincial Health Commission, (18, 43)
Treatment-emergent AE (grade 3–5) in nivolumab group		
Rash	Glucocorticoid therapy, supplemented with proton pump inhibitors to prevent gastrointestinal reactions	NCCN Clinical Practice Guidelines in Oncology (30)
Diarrhea	1. Perform blood routine, liver and kidney function, electrolytes, stool routine, stool culture, thyroid function, abdominal and pelvic enhanced CT, colonoscopy, etc. 2. Nutritional support 3. Glucocorticoid therapy, if glucocorticoid therapy is invalid within 48 h or worsening, consider adding infliximab while continuing to use glucocorticoids	NCCN Clinical Practice Guidelines in Oncology (30)
Decreased appetite	Megestrol, nutritional support	NCCN Clinical Practice Guidelines in Oncology (30)
Stomatitis	Mouthwash, anti-infection, nutritional support	NCCN Clinical Practice Guidelines in Oncology (30)
Nausea	Antiemetic treatment, nutritional support	NCCN Clinical Practice Guidelines in Oncology (30)
Arthralgia	Glucocorticoid therapy, if glucocorticoid therapy fails, other immunosuppressive drugs such as infliximab, methotrexate, sulfasalazine, or leflunomide may be considered	NCCN Clinical Practice Guidelines in Oncology (30)
Neutrophil count decreased	G-CSF	NCCN Clinical Practice Guidelines in Oncology (30)
Anemia	Blood transfusion, glucocorticoid therapy, if glucocorticoid therapy fails, immunosuppressant can be given	NCCN Clinical Practice Guidelines in Oncology (30)
White blood cell count decreased	G-CSF	NCCN Clinical Practice Guidelines in Oncology (30)
Neutropenia	G-CSF	NCCN Clinical Practice Guidelines in Oncology (30)
Peripheral sensory neuropathy	Close monitoring of neurological symptoms and respiratory function; immunoglobulin or plasma exchange; glucocorticoid therapy	NCCN Clinical Practice Guidelines in Oncology (30)
Febrile neutropenia	G-CSF; antibiotics	NCCN Clinical Practice Guidelines in Oncology (30)
Neuropathy peripheral	Close monitoring of neurological symptoms and respiratory function; immunoglobulin or plasma exchange; glucocorticoid therapy	NCCN Clinical Practice Guidelines in Oncology (30)
Treatment-emergent AE (grade 3–5) in chemotherapy group		
Rash	Dexamethasone, antihistamines	Expert consensus of clinical practices
Diarrhea	Anti-diarrheal treatment	Expert consensus of clinical practices
Decreased appetite	Megestrol, nutritional support	Expert consensus of clinical practices, (35)
Stomatitis	Mouthwash, anti-infective treatment if necessary	Expert consensus on the diagnosis and prevention of acute oral mucositis caused by antitumor therapy
Nausea	Antiemetic treatment	CSCO guidelines for the prevention and treatment of antitumor treatment-related nausea and vomiting, (35)
Arthralgia	/	Expert consensus of clinical practices
Neutrophil count decreased	G-CSF	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (37)
Anemia	Iron supplementation, blood transfusion therapy	CSCO clinical practice guidelines for tumor-associated anemia, (34)

(Continued)

TABLE 2 | Continued

Input parameters	Test/scans/treatment details	Source
White blood cell count decreased	G-CSF	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (44)
Neutropenia	G-CSF	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (45)
Peripheral sensory neuropathy	Nutritional nerve therapy	ASCO clinical practice guidelines, (43)
Febrile neutropenia	G-CSF; antibiotics	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy, (37)
Neuropathy peripheral	Nutritional nerve therapy	ASCO clinical practice guidelines

ECG, electrocardiogram; HBV, hepatitis B virus; HCV, hepatitis C virus; DNA, deoxyribonucleic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; AKP, alkaline phosphatase; APTT, activated partial thromboplastin time; PT, prothrombin time; FIB, fibrinogen; TT, thrombin time; INR, international standard ratio; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; CT, computed tomography; MRI, magnetic resonance imaging.; AE, adverse events; G-GSF, granu1ocyte colony-stimu1ating factor; NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology.

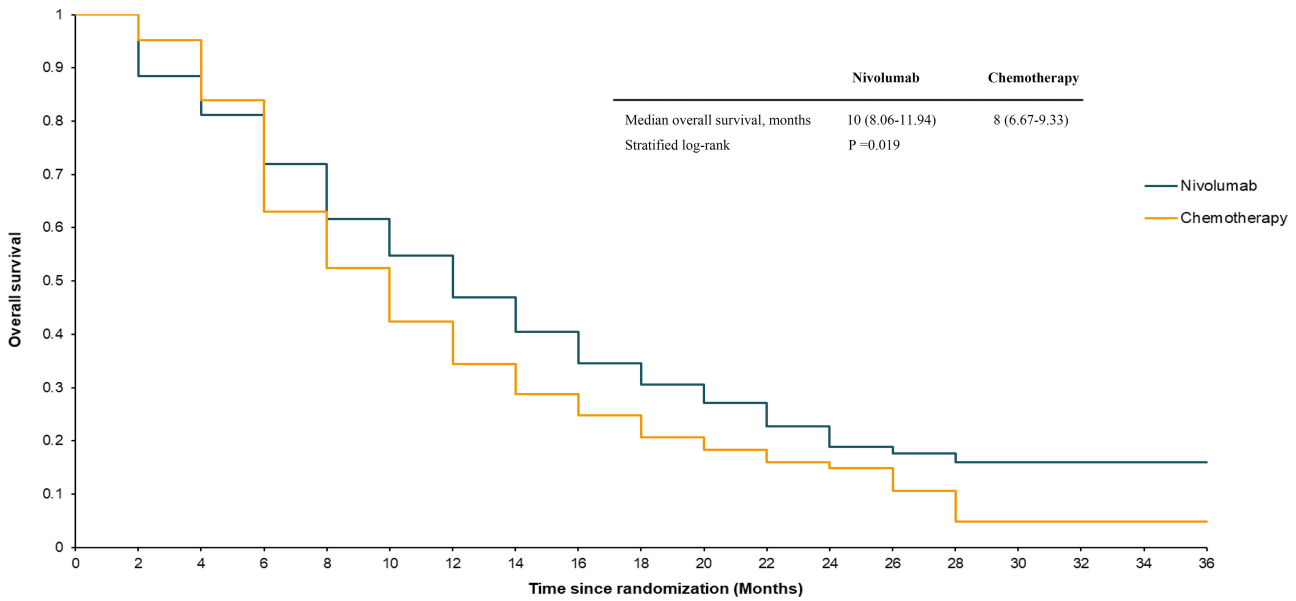

FIGURE 2 | Estimated overall survival curve for the ATTRACTION-3 trial.

group (stratified log-rank, $P = 0.019$) up to the data cut-off point (November 12, 2018). The median PFS in the nivolumab group was 1.7 months, compared to 3.4 months in the paclitaxel or docetaxel treatment group. The ATTRACTION-3 trial also reported details of the survival rate. The 12-month OS in the nivolumab group was 47%, compared to 34% in the chemotherapy group. The 18-month OS in the nivolumab group was 31%, while that in the chemotherapy group was 21%. The 6-month PFS in the nivolumab group was 24%, compared to 17% in the chemotherapy group. The 12-month PFS in the nivolumab group was 12%, while that in the chemotherapy group was 7%.

Our model simulated a hypothetical sample of 419 patients. The model's survival analysis results were remarkably close to the actual clinical trial data. The median OS in the model was 10 months for nivolumab and 8 months for chemotherapy (stratified log-rank, $P = 0.019$) (**Figure 2**). The nivolumab group had a PFS rate of 1.92 months, compared to 3.89 months in the chemotherapy group (**Figure 3**). Furthermore, the survival rate statistics were remarkably similar to the actual clinical study data. The 12-month OS in the nivolumab group was 46.9%, compared to 34.4% in the chemotherapy group. The 18-month OS rate was 30.5% in the nivolumab group and 20.7% in the chemotherapy group. The 6-month PFS was 24.3% in the nivolumab group, while it was 17.7% in the chemotherapy group. The 12-month PFS was 11.9% in the nivolumab group, while it was 7.6% in the chemotherapy group.

During the 3-year study period, nivolumab immunotherapy's cost was US$ 57,624.92 and exceeded paclitaxel/docetaxel chemotherapy's cost of US$ 20,668.11, by US$ 36,956.81. Interestingly, out of this incremental cost, that of drug acquisition was US$ 39,467.00, which exceeded the total incremental cost (US$ 36,956.81). Besides, in the PD stage, the nivolumab group's cost per patient was US$ 45, higher than that of the chemotherapy group, despite the fact

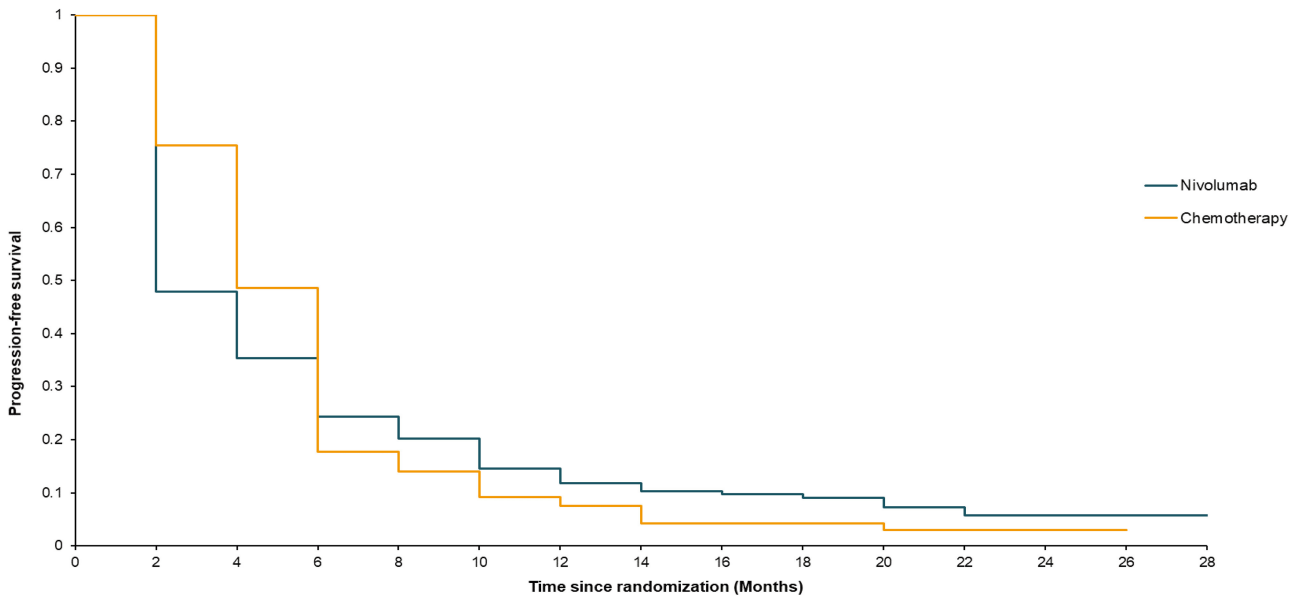

FIGURE 3 | Estimated progression survival curve for the ATTRACTION-3 trial.

TABLE 3 | Results of our model.

Results	Nivolumab group	Chemotherapy group
Total costs	$57,624.92	$20,668.11
QALYs	0.80	0.52
ICER, $/QALYs	$132,029.46	–

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.

that the costs of nivolumab treatment were lower than those of paclitaxel/docetaxel chemotherapy in terms of drug administration, laboratory tests, radiologic images, terminal, and treatment-related AEs. Nivolumab immunotherapy resulted in an improvement of 0.28 QALY (0.80 vs. 0.52) per patient compared with paclitaxel/docetaxel chemotherapy. The ICER for the nivolumab group vs. the chemotherapy group was estimated to be US$ 132,029.46/QALY (**Table 3**).

Sensitivity Analyses

Deterministic Sensitivity Analyses

The findings of the one-way deterministic sensitivity analyses revealed that the model was most sensitive to the nivolumab group's survival time. The model was heavily influenced by the following parameters: chemotherapy group survival time, nivolumab group medication acquisition cost, and utility scores. The top 10 most influencing parameters are presented in a tornado diagram (**Figure 4**). The ICER of nivolumab did not decrease below US$ 80,000/QALY despite the varied ranges for each variable. Nivolumab's drug acquisition must be cut by 53.50% to obtain a more favorable cost-effectiveness under the threshold cost of US$ 37,623.39/QALY, which the Chinese populace can afford.

Probabilistic Sensitivity Analyses

The World Health Organization places the willingness-to-pay (WTP) threshold at three times the GDP per capita (49). In 2021, the GDP per capita of the Chinese population was US$ 12,551, making the WTP threshold US$ 37,653/QALY. The Monte Carlo probabilistic sensitivity analyses revealed that the probability of nivolumab immunotherapy not being a cost-effective option when compared with paclitaxel/docetaxel chemotherapy at a WTP threshold of US$ 37,653/QALY. When the WTP threshold changed to US$ 132,029.22/QALY, the closest number to 132,029.46/QALY in simulated iterations, the probability of nivolumab immunotherapy being cost-effective when compared with paclitaxel/docetaxel chemotherapy increased to 48.02% (**Figures 5**, **6**).

DISCUSSION

The costs associated with healthcare have become one of the world's most serious issues. Many scholars have developed healthcare economic evaluation models to assess the economic effects of immunotherapeutic inhibitors in antineoplastic therapy. These models all agree that in order for a therapy to be cost-effective, it must have two crucial characteristics: a lower cost and a higher effectiveness (50). This expectation was represented as extra cost and incremental QALYs in this study. Nivolumab immunotherapeutic inhibitors had a greater survival rate in advanced ESCC treatment than paclitaxel/docetaxel chemotherapy, however, they would also increase healthcare costs dramatically. Nivolumab costs US$ 132,029.46 for every extra QALY achieved when compared to chemotherapy. From the Chinese healthcare system perspective, this may not be a cost-effective treatment option. At the WTP threshold of US$

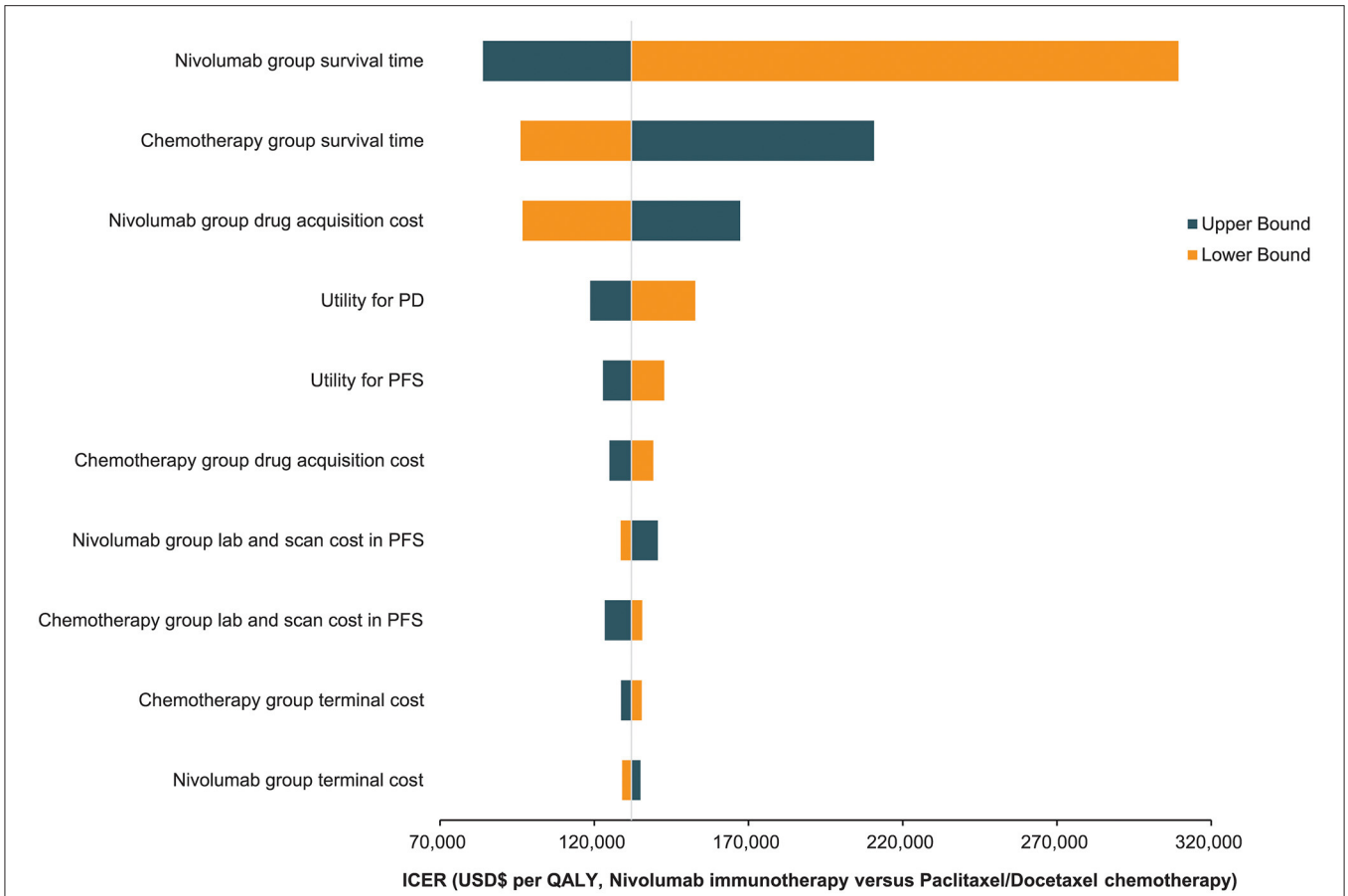

FIGURE 4 | The Top 10 most influencing parameters in Tornado diagram.

132,029.22/QALY, the probabilistic sensitivity analysis revealed that nivolumab was not an economical alternative, with only a 48.02% chance of becoming cost-effective. Moreover, when the WTP threshold changed to US$ 37,544.52/QALY, the probability declined to 0.07%. The ICER of US$ 37,544.52/QALY is nearly the World Health Organization's recommended threshold in 2021. These findings indicate that nivolumab is in effect not a value second-line therapeutic modality in China for advanced ESCC.

Advanced ESCC is a fast and fatal disease. Even with immunotherapy, patients' quality of life suffers due to their dismal prognosis (41). The patients' lives end and their families descend into poverty due to the cost of treating the illness. What makes nivolumab less cost-effective than chemotherapy? Surprisingly, we found that the incremental cost of nivolumab (US$ 39,467.00) was higher than the total incremental cost of its use (US$ 36,956.81). This means that nivolumab acquisition is much costlier than chemotherapy; reducing this immune inhibitor's price can significantly improve the cost-effectiveness of its use. This finding was supported by the one-way sensitivity analyses. After nivolumab group's survival time and chemotherapy group's survival time, the drug acquisition cost of the nivolumab group was the third parameter that had the greatest impact on our model. Although the price of nivolumab in China is cheaper than in some other countries, it must decline by 53.50% to meet the WTP threshold, which is approximately three times the Chinese population's GDP per capita.

Can nivolumab become cost-effective by improving patients' survival time? Whether nivolumab would achieve cost-effectiveness by extending patients' survival time sufficiently so that the cost gap between nivolumab and chemotherapy would be recovered during long-term treatment is unknown. In such cases, PD-1 immunotherapy can provide both clinical and financial benefits in the form of prolonged survival and improved quality of life. An additional two clinical trials [KEYNOTE-181 (51) and ESCORT (52)] also demonstrated that PD-1 inhibitors would improve clinical efficacy in comparison to chemotherapy in advanced ESCC treatment. However, if medical cost is constant, such improvement is not enough to make PD-1 inhibitors more cost-effective than chemotherapy. One-way sensitivity evaluations in our model revealed that if nivolumab becomes a more cost-effective therapy alternative than chemotherapy, the survival time of the nivolumab group would have to be prolonged two additional times. In that case, ICER would achieve US$ 34,148.47/QALY, which is less than three times the Chinese population's GDP per capita. Although

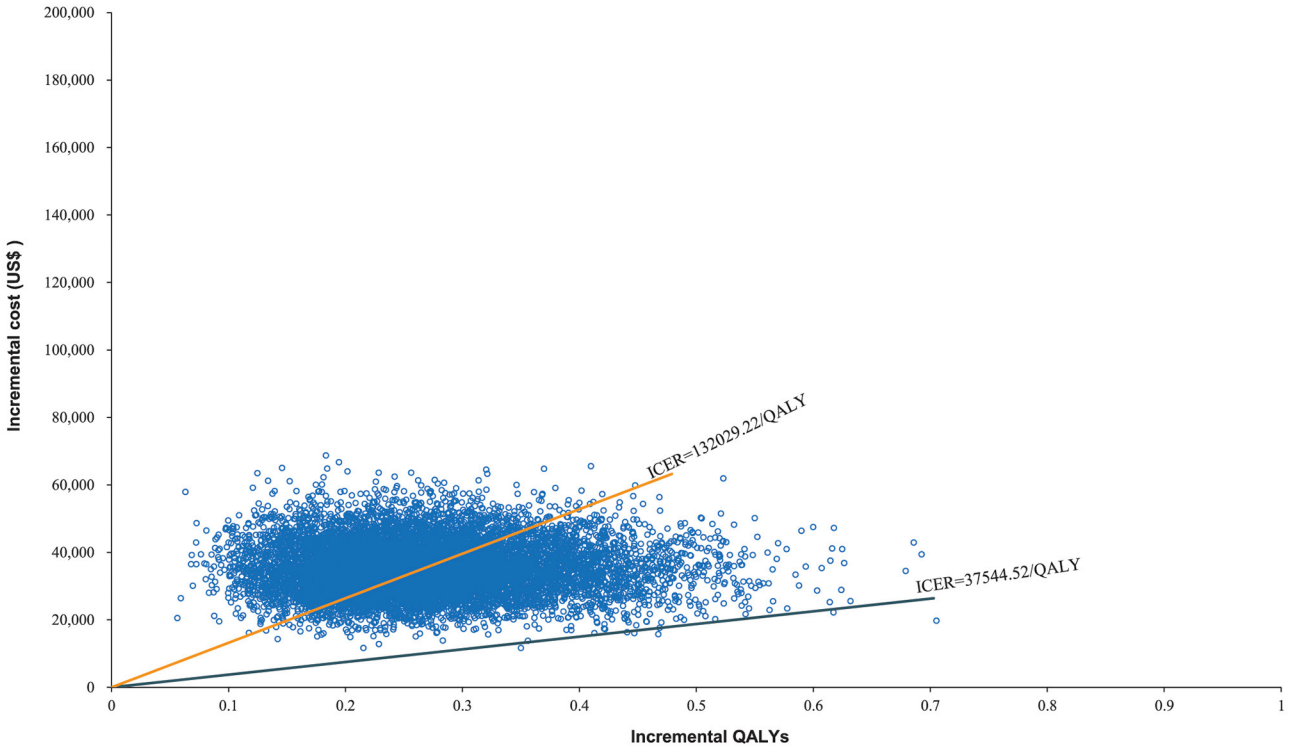

FIGURE 5 | Scatter plot of Monte Carlo sensitivity analysis.

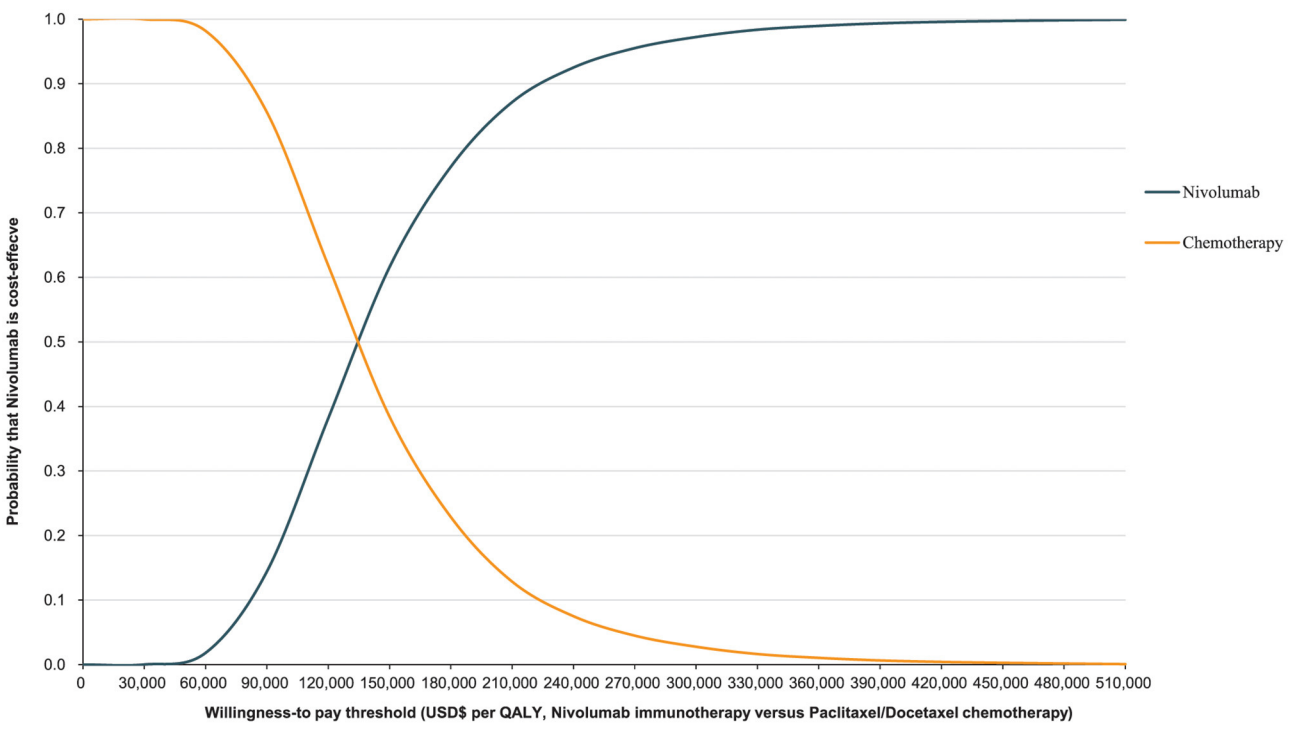

FIGURE 6 | Cost-effectiveness acceptability curve for nivolumab immunotherapy vs. paclitaxel or docetaxel chemotherapy.

similar to the ATTRACTION-3 trial, these two studies found that patients who received PD-1 inhibitors had prolonged survival time than those who received chemotherapy. However, the improvement in survival time as a result of PD-1 inhibitors for advanced ESCC immunotherapy was insufficient. The KEYNOTE-181 trial on 628 patients, comparing pembrolizumab with paclitaxel/docetaxel/irinotecan chemotherapy, showed that the median OS of pembrolizumab (9.3 months) was longer than that of chemotherapy (6.7 months); however, the median PFS at 2.6 months was shorter than 3.0 months in the case of chemotherapy. The ESCORT trial of camrelizumab and docetaxel/irinotecan chemotherapy on 448 patients reported that the median OS with camrelizumab (8.3 months) was longer than that with chemotherapy (6.2 months). The median PFS, in either case, was 1.9 months.

Additionally, nivolumab, pembrolizumab, camrelizumab, and most PD-1 inhibitors (spartalizumab, toripalimab, sintilimab, etc.) are fully human IgG4 monoclonal antibodies. This means their IgG isotypes or mutants with nullified effector functions are similar (53). It seems that the PD-1 inhibitors may still have similar clinical efficacy in advanced ESCC treatment until pharmaceutical production technology does not change. Fortunately, new pharmaceutical manufacturing technologies are being developed to produce a series of PD-1 inhibitors (PD-1/CTLA-4, PD-1/CD47, PD-1/LAG-3, etc.), which could potentially be used in the future to treat advanced ESCC. Meanwhile, in 2019, there was a remarkable medical market revolution in China. The General Office of the State Council of the People's Republic of China implemented a price negotiation of the National Reimbursement Drug List to deal with the challenges of ever-increasing medical expenditures, make drugs more affordable for patients, and make steady efforts to reform the drug procurement system. In 2021, the price of camrelizumab declined sharply from US$ 3,100/200 milligrams to US$ 458/200 milligrams. Driven by the "price reduction and volume increment," if a growing number of PD-1 inhibitors with lower prices than nivolumab become available, the price of nivolumab may be reduced in the future due to market competition. In our model, lowering the price of nivolumab by 53.50% might make it a cost-effective and affordable therapy choice for advanced ESCC patients in the Chinese population.

The ESCORT trial and KEYNOTE-181 trial also reported an economic evaluation of the cost-effectiveness of PD-1 inhibitors by developing a Markov model (35, 43). The findings suggested that in 2019, camrelizumab immunotherapy may not have been a more cost-effective therapeutic choice for advanced ESCC than chemotherapy. Camrelizumab incurred an incremental cost of US$ 24,539 and an effect of 0.283 QALYs compared with docetaxel/irinotecan chemotherapy, whereas the ICER incurred US$ 86,745/QALY. Further, in 2021, pembrolizumab immunotherapy may not have been a more cost-effective therapeutic option for advanced ESCC than chemotherapy. Pembrolizumab demonstrated an incremental cost of US$ 19,054.61 and an effect of 0.09 QALYs compared with paclitaxel/docetaxel/irinotecan chemotherapy, whereas the ICER incurred US$ 202,708.62/QALY. Although the ESCORT trial and KEYNOTE-181 trial have many similarities to the ATTRACTION-3 trial and the cost-effectiveness analysis results are consistent with our findings, the modeling methods are quite different. Initially, we attempted to establish a Markov model for cost-effectiveness analysis. By digitizing the OS and PFS curves from the ATTRACTION-3 trial, we were able to determine time and survival probability using the GetData Graph Digitizer. According to the lowest Akaike information criteria and Bayesian information criterion values, we found that a 2-parameter Weibull distribution was the best-fitting distribution model for the pseudo-individual patient data. However, we found a high degree of bias in the results were obtained using the Markov model compared with the actual ATTRACTION-3 trial results. For example, PFS's transition probability to death was not rigorous; the Markov model needs to calculate the transition probability between different health stages, but PFS's transition probability to death could not be calculated. Therefore, we had to utilize the general Chinese population's mortality rate as the transition probability of PFS to death, an approach also employed in other studies (35, 54). The median survival of patients with advanced ESCC is only 8–10 months, and the expected 5-year survival rate is less than 5% (5). Patients with advanced esophageal cancer had a greater mortality rate than the general population, even at the PFS stage (55, 56). Although the general population's mortality rate is a fixed value, the death rate varies in each model cycle because of the decreased functioning and worsening symptoms (41). Meanwhile, the 2-parameter Weibull distribution showed substantial divergence from the original survival curves. This divergence was evident for both the OS and PFS curves. In this study, patients had a significantly different survival rate in the 2-parameter Weibull distribution than that observed in the ATTRACTION-3 trial, as the trial's time horizon was defined as 3 years. The same divergence was also observed in the Markov model evaluation of the ESCORT trial (35). We carefully checked the references and concluded that this distribution could provide an appropriate fit for the longer-term extrapolation of clinical trial data, but may have inherent uncertainty in the short-term assessment of the survival curve (57, 58). Some previously reported models for the treatment of Non-small cell lung cancer, hepatocellular carcinoma, and melanoma included curve extrapolation (47, 59, 60). When the model simulates time beyond the follow-up period, the distribution of the number of people in each health state cannot be obtained directly from the survival curve. Therefore, a parametric method was used to calculate the survival function. This method assumes that the survival time obeys a particular parametric distribution. However, patients with advanced ESCC have a short-term disease progression and mortality rate, and clinical trials can simulate the disease transition in mutually exclusive health stages without extrapolating the survival data. Therefore, we rebuilt the cost-effectiveness model using the partitioned survival model and accurate data, but did not perform extrapolation beyond the ATTRACTION-3 trial's follow-up period. We believe that this improvement may be more suitable for simulating the treatment of advanced ESCC.

To our knowledge, few studies have empirically investigated the cost-effectiveness of immunotherapy inhibitors for advanced

ESCC. Some of the previous studies analyzed medical and economic data sourced from other studies to reach their conclusions. Therefore, the study's main strength is that it directly compared nivolumab immunotherapy to paclitaxel/docetaxel chemotherapy utilizing original, published trial data as well as clinical expenses, financial data, and utility values gathered in the course of clinical practice. As the price of PD-1 inhibitors decreased significantly after the implementation of the price negotiation of the National Reimbursement Drug List, it became necessary to evaluate the scope of price reduction for both pharmaceutical enterprises and the government. Our model's survival analysis results are extremely similar to the actual data from the ATTRACTION-3 trial. Therefore, the economic evaluation results of our model are reliable and may have reference value for subsequent policy practice.

There are a few limitations in this study. First, our model essentially relied on the ATTRACTION-3 trial; however, patients participating in clinical trials are different from those in real-world clinical practices. This difference might introduce biases in the cost-effectiveness evaluation (61). Due to the lack of global/domestic multicenter phase 4 or real-world studies, phase 3 trials may provide the best clinical evidence available thus far for cost-effectiveness analysis in the treatment of advanced ESCC. Although the frequency of the tests in clinical trials differs from real world experience, which would increase the cost in our model, the model provided a reasonable, albeit imperfect, approximation to the real-world clinical benefit observed in the clinical trials. Second, the model based on the survival analysis did not make the assumption that survival time follows a specific parametric distribution. Although we believe that survival analysis for survival curves estimation has a good fit for the survival curves in the ATTRACTION-3 trial, this method also may increase the complexity of the model. Therefore, in the long-term extrapolation of survival time, the modeling findings may not accurately represent the disease course. The survival curve extrapolation in our model may be improved by incorporating another phase 4 trial or real-world study in our model. Third, AE-related expenditures for grades 1 to 2 were not included in the model, which may have undermined the economic evaluation results. However, as suggested by the deterministic sensitivity analyses, AE-related costs are a minor component of the total cost. Perhaps, collecting more survival follow-up information and safety data in future studies to fully reproduce the clinical course of nivolumab immunotherapy vs. chemotherapy in advanced ESCC may result in a more accurate economic evaluation.

CONCLUSION

This study analyzed the cost-effectiveness of nivolumab immunotherapy compared with docetaxel or paclitaxel in the treatment of advanced ESCC. Nivolumab is clinically beneficial, but such a benefit cannot offset the expensive medical cost, which leads to the conclusion that nivolumab is not a cost-effective therapy option in the treatment of advanced ESCC when compared to chemotherapy. A substantial reduction in nivolumab's drug acquisition cost would be necessary to make its use cost-effective for this immunotherapy. A substantial reduction in nivolumab's price may be achieved through changes in the PD-1 inhibitor market competition in China and the price negotiation of the National Reimbursement Drug List.

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/s.

AUTHOR CONTRIBUTIONS

Y-tL: methodology, original draft writing, software, and data curation. T-xL: writing, reviewing, and editing. JC: software, investigation, and data curation. CW: software, visualization, and data curation. YC: conceptualization, editing, and supervision. All authors contributed to the article and approved the submitted version.

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The Consistency Between the Chinese Essential Medicines List and Treatment Guidelines—Taking Oncology Medicines as an Example

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The concepts of "essential medicine" and "national medicine policy" were first put forward for the first time at the World Health Assembly in 1975 in an effort to alleviate the problem of medicine unavailability in developing and poor countries. The essential medicine system in China has experienced three development stages since 1979, when the concept of essential medicines was first introduced, to actively respond to the call of the World Health Organization. Currently, the essential medicines list published in China is the national essential medicines list (2018 Edition). In this study, we examined the consistency between the essential medicines for treating seven cancers (liver cancer, breast cancer, esophageal cancer, lung cancer, colorectal cancer, gastric cancer, and leukemia) and the recommended medicines by cancer treatment guidelines to determine whether the essential medicines are of high quality for clinical needs. The results indicated that the degree of similarity between oncology medicines on the essential medicines list and oncology medicines recommended by guidelines was low, with the majority falling between 30 and 60%. Therefore, to improve the quality of essential medicines, it is necessary to further improve the matching degree. In addition, to further improve the consistency between the essential medicines list and treatment guidelines, the following suggestions are put forward in this paper: (1). Formulate universal treatment guidelines; (2). When selecting essential medicines, greater consideration should be given to those recommended in the guidelines; (3). The essential medicines list and treatment guidelines should be concurrently updated; (4). The cycle for updating the essential medicines list and treatment guidelines should be shortened.

Keywords: essential medicines list, treatment guidelines, consistency, matching degree, oncology medicine

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INTRODUCTION

The concepts of "essential medicines" and "national medicine policy" were first put forward at the World Health Assembly in 1975 (1), and they quickly became a component of global public health. The 1978 Almaty declaration recognized "the provision of essential medicines" as one of the eight elements of primary health care. The current WHO Expert Committee on the selection and use of essential medicines believe that "essential medicines" are provided based on the disease burden and safety, effectiveness and economy of medicines, to meet the essential medicines needs of the people.

The objective of implementing the essential medicines policy is to provide sufficient quantity, an appropriate dosage form, and quality assurance when the public can afford it (2). WHO proposes the following procedure for selecting essential medicines: first, establish the standard treatment guide or "path" according to the disease spectrum. Then, a list of essential medicines is selected and developed based on the standard treatment guidelines or "path" (3).

To actively respond to the call of the World Health Organization, China's essential medicine system has undergone three development stages since the introduction of the concept of essential medicines in 1979: the establishment stage of the essential medicine system from 1979 to 2009; the formation and improvement of the essential medicine system from 2010 to 2017; and the essential medicine system that has entered a new stage of development from 2018 to date.

In September 2018, the general office of the State Council proposed in its opinions on improving the national essential medicine system that attention should be paid to clinical diagnosis and treatment guidelines and expert consensus when selecting essential medicines. Currently, China selects essential medicines by consulting experts. This selection method relies heavily on clinical medication experience and the subjective judgment of experts, which is not objective enough (4), and treatment guidelines that are closely related to actual clinical needs do not play a great role in the selection of essential medicines.

Treatment guidelines are normative documents formulated for the diagnosis and treatment of a disease based on a comprehensive understanding of clinical evidence and demonstration by peer experts, which are designed to assist doctors and patients in making appropriate medical care decisions for specific clinical conditions (5). The treatment guidelines pay more attention to evidence-based medical evidence such as randomized controlled trials and open clinical trials, and also refer to other levels of evidence, such as literature meta-analyses, making them more scientific and practical.

The formulation process of treatment guidelines is very time-consuming and requires a significant amount of human and financial resources, but countries must still establish their guidance system and update it on a timely basis (6) because treatment guidelines have numerous benefits for patients, doctors, medicine supply managers, and health policymakers. It can improve compliance and availability of medicines for patients, as well as reduce the occurrence of adverse reactions. With the cost-effective methods provided by the guidelines, doctors can make appropriate treatment decisions for specific clinical manifestations, making the diagnosis and treatment of diseases and medicine selection more scientific, standardized, and standard, thereby effectively promoting essential medicines policy and rational medicine use (7, 8). Medicine supply managers are now better able to estimate the demand for medicines and effectively control inventory. For policymakers, the treatment guidelines can be incorporated into the assessment criteria used to evaluate and compare the nursing quality of different medical institutions and doctors (9), ensuring that the treatment guidelines are of great value.

In the past, essential medicines were selected from a list of specified medicines. Currently, essential medicines are selected from a list of therapeutic medicines recommended by treatment guidelines, thus, the selection of essential medicines should be more closely aligned with treatment guidelines (10). The selection of essential medicines combined with treatment guidelines can better improve the quality of essential medicines and establish the needs of medical institutions for essential medicines, which is critical for the diagnosis, treatment, and medication of patients (11). If the matching degree of essential medicines list and treatment guidelines is low, it will reduce doctors' recognition of essential medicines and dampen their excitement for clinical use of essential medicines.

Molds (12) argues that treatment guidelines should be developed first, and the essential medicines list should be composed of the medicines recommended by the guidelines. Only when treatment guidelines and the essential medicines list are developed and used together, as opposed to as single, irrelevant, and possibly contradictory entities, can they have a positive impact on clinical practice (13). The treatment guideline connects the essential medicines list to clinical practice. To supply high-quality medicines for clinical needs, the essential medicines list must be extremely consistent with treatment guidelines. Zeng FD (8) and Feng JJ (14) believed that the selection and dynamic adjustment process of the essential medicines list should be coupled with the formulation of treatment guidelines, and the implementation of the essential medicine list should be combined with the training of treatment guidelines, to promote the improvement of China's essential medicine system and guide clinical rational medicine use. South Africa has established an essential medicine selection model based on clinical guidelines, with treatment guidelines as the core, first to formulate treatment guidelines, and then to formulate an essential medicine list that includes all the drugs recommended in the treatment guidelines (15).

There are still some issues with the clinical application of essential medicines in China. There are disparities, for instance, between essential medicines and the actual medicine demand of a grass-root clinic. Zhang BY (16) analyzed the consistency between the medicines of a neurology department in a hospital and the medicines recommended in relevant guidelines and found that the consistency between the medicines used in hospitals for common diseases and the first-line and second-line medicines listed based on evidence is different. Some of the medicines recommended for clinical by doctors in the guidelines are not on the essential medicines list, indicating that there may be a mismatch between the guidelines and the current essential medicines list. In particular, the dark events of tumor therapy revealed by Dr. Zhang Yu of the Peking University Third Hospital last year once again brought attention to the treatment turmoil in the field of tumors. Ma Jun, director of Harbin Institute of Hematology and tumor and chairman of the board of supervisors of the Chinese Society of Clinical Oncology (CSCO), also pointed out that non-standard treatment is a common problem in tumor treatment (17). Research and analysis of 182 patients with chemotherapy drug reasonableness (18) published by the Journal of North Pharmacy in 2019 found that 37.91% of

the 182 cancer patients were administered chemotherapy drugs inappropriately. The data cited in "Rational use of oncology drugs in 174 lung cancer patients" (19), which was published in the 8th issue of Central South Pharmacy in 2020, revealed that 83.9% of 174 patients with primary lung cancer admitted to a hospital in 2019 exhibited an unreasonable drug use pattern. In only 28 (16.1%) medical records, the oncology medication treatment protocol is plausible. Therefore, to standardize the clinical diagnosis and treatment of tumors, it is critical to formulate high-quality guidelines and a list of essential medicines that matches the guidelines.

Currently, the evaluation of essential medicines focuses primarily on the examination of the safety, effectiveness, and cost-efficiency of essential medicines. The study on the guidelines focuses mostly on guideline interpretation and quality assessment. No article evaluates the quality of essential medicines based on the consistency between the essential medicines list and treatment guidelines. It is necessary to investigate whether there is a mismatch between the essential medicines list and treatment guidelines, and if so, what is the main manifestation of the problem, and how it may be adjusted and improved in the future. China is currently in a critical period of adjusting the essential medicines list. This paper will evaluate whether essential medicines are high-quality medicines for clinical needs from the perspective of the consistency between the oncology drugs in the national essential medicines list (2018 Edition) and the oncology drugs recommended in the treatment guidelines, and will attempt to improve the matching degree between the list and the guidelines through research, as well as improve the role of China's essential medicines list in guiding clinical rational medicine use and accessibility.

METHODS

Firstly, the relevant data on China's disease burden was identified. Using the Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017(20) published by the lancet in 2019, this article analyzed and compared the mortality, years of life loss (YLLs), years of disabled life (YLDs), disability-adjusted life years (DALYs), and other indicators in all provinces in China between 1990 and 2017. This article reveals that cancer is still a serious disease in China. In 2017, eight types of tumors accounted for the top 25 causes of death in YLLs, including lung cancer (third), liver cancer (fifth), gastric cancer (seventh), esophageal cancer (eleventh), colorectal cancer (fifteenth), breast cancer (twenty-first), leukemia (twenty-second), and brain cancer and central nervous system cancer (twenty-third).

Then, using databases such as yaozhi.com and dingxiangyuan medication assistant, we obtained the drug instructions and analyzed the indications of oncology drugs in the national essential medicines list (2018 Edition), and the specific tumors involved were sorted according to the number of medicines used to treat each specific tumor, from greater to lesser. In the 2018 version of the national essential medicines list, there are 35 oncology medicines. Sodium ISO and ondansetron are used as oncology auxiliary medicines. So the above-mentioned medicines were not included in this study. Therefore, this study has collated indications of 33 oncology medicines. Leukemia (17 kinds of essential medicines), breast cancer (16 kinds of essential medicines), lung cancer (13 kinds of essential medicines), esophageal cancer (10 kinds of essential medicines), and gastric cancer (8 kinds of essential medicines) are the five kinds of tumors for which a large number of medicines are available.

Therefore, combined with the number of medicines for each tumor in the essential medicines list and the disease burden, the guidelines for seven specific tumors and the essential medicines list were finally determined. These seven tumors included lung cancer, liver cancer, gastric cancer, esophageal cancer, colorectal cancer, breast cancer, and leukemia.

After identifying the type of tumor, it is vital to locate relevant guidelines, as there are few official guidelines for each disease in China, the majority of which are formulated by relevant organizations, resulting in a significant number of disease-related guidelines of varying quality. Therefore, we formulated relevant standards to screen the guidelines, The specific screening criteria were as follows: (1) unit qualification: it must be a government department, an authoritative discipline association, or an organization with significant influence, such as the Chinese Medical Association, the National Health Commission of the people's Republic of China, the Chinese Medical Doctor Association, the Chinese Society of Clinical Oncology, etc., (21), to ensure the quality of guidelines; (2) Country: issued by the main body of China; (3) Release time: 2015–2022 or the most recent version of the guideline outside of this window, with the most recent version preferred; (4) Text type: the official guide is preferred. In the absence of a guide or if the publication date of the guide is too soon, the expert consensus is selected as appropriate (21); (5) Content of the guide: includes the main contents of tumor medicine therapy.

The essential medicines list and the guidelines will be compared from two perspectives following the screening of the guidelines: (1) compare the consistency between specific essential medicines and medicines recommended by the guidelines published in 2018 and before; (2) compare the consistency between specific essential medicines and medicines recommended by the guidelines published after 2018, which is quantified by the degree of matching. The matching degree formula is: matching degree = A / B * 100%, where A represents the number of medicines not only in the essential medicines list, but also in the guideline-recommended medicines, and B represents the number of drugs recommended in the first line of the guide or the number of medicines recommended in the guideline (when the recommendation level is not specified in the guideline).

The author carried out an expert examination into the problem of matching degree zoning to divide the matching degree into levels. Considering the widespread application of the Delphi method in a variety of disciplines and the varying degrees of methodological advancement, it is evident that this method is maturing. At the same time, to fully express the opinions of experts without being influenced by authoritative views, the Delphi method was used to synthesize the opinions

of numerous experts in this survey. Delphi method involves the anonymous administration of many rounds of questionnaires to experts. Experts can think deeply about the survey problems and fully express their opinions in each round of the survey without worrying about the opinions of other experts. Multiple rounds of surveying will yield convergent expert opinions, with each survey feeding back the survey results from the preceding round to experts. The Delphi method has the advantages of anonymity and multiple rounds of investigation, which can increase the objectivity and reliability of the investigation's findings.

According to the content of this paper's research, 25 experts from medical and pharmaceutical colleges, institutions, departments, and enterprises across the country who have studied or are well-versed in essential medicines, treatment guidelines, and tumor clinical treatment were invited to conduct the survey. The analysis of expert authority degree evaluates the expert authority coefficient (Cr), the basis of expert judgment on matching degree zoning (Ca) and the expert's familiarity with essential drugs and guidelines (Cs). $Cr = (Ca + Cs) / 2$. The research result of $Cr \geq 0.7$ is acceptable. The results of expert authority analysis show that in the first round, Cs was 0.80, Ca was 0.90 and Cr was 0.85; In the second round, Cs was 0.78, Ca was 0.91 and Cr was 0.85; In the third round, Cs was 0.82, Ca was 0.92, Cr was 0.87, and all three rounds' Cr was > 0.7, which was highly authoritative.

The survey involved three rounds of correspondence. In the first round of correspondence, experts received a summary of the matching degree zoning based on a literature review, an explanatory letter, and relevant background information. Then we consulted the experts whether it is necessary to partition the matching degree and score its importance (5-point system) and how to divide the matching degree into several levels. In the first round, 25 experts were consulted and 25 questionnaires were collected. The enthusiasm coefficient of experts was 100%. Through the analysis of the questionnaire, it is found that most experts believe that the matching degree needs to be divided. The coefficient of variation (CV) of the index of matching degree division is 0.11, indicating that the expert opinions are relatively coordinated. On the specific level of matching degree, 23 experts suggested that the matching degree be divided into five levels and two experts suggested that the matching degree be divided into four levels. Therefore, we decided to divide the matching degree into five levels. There are some differences in expert opinions on the division of specific levels. In the second round of correspondence, experts were provided with the modified matching degree zoning based on the opinions of the first round of experts and consulted again. In the second round, 25 experts were consulted, 24 questionnaires were recovered, and the enthusiasm coefficient of experts was 96%. After sorting out the questionnaire, it is found that the expert opinions on the division of most levels are closer, and there are differences between the division of the third level and the fourth level. Therefore, in the third round of correspondence, the matching degree obtained in the second round was fed back to the experts in layers, and the division standards of the third and fourth levels were further consulted. Similarly, 25 experts in the first round were consulted, and 24 questionnaires were collected. The expert enthusiasm coefficient was 96%. In this round of consultation, the opinions of experts tended to be consistent, and finally the matching degree zoning was determined: those with a matching degree of <30% were considered extremely mismatched, 31–50% were considered mismatched, 51–70% were considered more matched, 71– 80% were considered relatively matched, and 81–100% were considered highly matched.

RESULTS

Liver Cancer

In China, liver cancer is one of the most prevalent malignant tumors. It has the fourth-highest incidence and second-highest mortality (20, 22). The essential medicines list (2018 edition) includes five medicines for the treatment of liver cancer. After screening, two guidelines published in 2018 and before are available for comparison: Standard for diagnosis and treatment of primary liver cancer (2017 edition) and Guidelines for diagnosis and treatment of primary liver cancer (2018 edition).

TABLE 1 | Medicines in the list and guidelines for the treatment of liver cancer.

Medicines	Essential medicines list (2018 edition)	Standard for diagnosis and treatment of primary liver cancer (2017 edition)	Guidelines for diagnosis and treatment of primary liver cancer (2018 edition)	Standard for diagnosis and treatment of primary hepatic carcinoma (2019 edition)	Radiotherapy guidelines for primary hepatocellular carcinoma in China (2020 edition)
Oxaliplatin	✓	✓	✓	×	✓
Fluorouracil	✓	×	×	×	×
Arsenite	✓	×	✓	×	×
Doxorubicin	✓	×	×	×	×
Pingyangmycin	✓	×	×	×	×
Sorafenib	×	✓	✓	✓	✓
Cangvatinib	×	×	✓	✓	✓
Donafenib	×	×	×	×	✓
Atilizumab	×	×	×	×	✓
Bevacizumab	×	×	×	×	✓

TABLE 2 | Medicines in the list and guidelines for the treatment of breast cancer.

Medicines	Essential medicines list (2018 Edition)	Chinese Advanced Breast Cancer Consensus Guideline (CABC 2015)	Guidelines for breast cancer diagnosis and treatment (2017 edition)	Breast cancer diagnosis and treatment guideline (2018.V1)	Guidelines for breast cancer diagnosis and treatment (2019 edition)	Chinese Advanced Breast Cancer Consensus Guideline 2020 (CABC3)	Breast cancer diagnosis and treatment guideline (2022)	Guidelines for clinical diagnosis and treatment of advanced breast cancer in China (2020 edition)
cyclophosphamide	✓	✓	✓	✓	✓	×	✓	×
Gemcitabine	✓	✓	✓	✓	✓	✓	✓	✓
Doxorubicin	✓	✓	✓	✓	✓	×	✓	✓
Paclitaxel	✓	✓	✓	✓	✓	✓	✓	✓
Tamoxifen	✓	✓	✓	×	✓	✓	✓	✓
Letrozole	✓	✓	✓	×	✓	✓	✓	✓
Trastuzumab	✓	✓	✓	✓	✓	✓	✓	✓
Capecitabine	✓	✓	✓	✓	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓	✓	✓	✓	✓
carboplatin	✓	✓	✓	✓	✓	✓	✓	✓
Ifosfamide	✓	×	×	×	×	×	×	×
methotrexate	✓	×	✓	×	✓	×	✓	×
Fluorouracil	✓	×	✓	×	✓	×	✓	×
Pingyangmycin	✓	×	×	×	×	×	×	×
vincristine	✓	×	×	×	×	×	×	×
Etoposide	✓	×	×	✓	×	×	×	×
Fulvestrant	×	✓	✓	✓	✓	✓	✓	✓
Pertuzumab	×	✓	×	✓	✓	✓	✓	✓
Changchun Ruibin	×	✓	✓	✓	✓	✓	✓	✓
Pyrroltinib	×	×	×	×	×	✓	×	✓
Docetaxel	×	✓	✓	✓	✓	×	✓	✓
Piperacilli	×	×	×	×	✓	✓	✓	✓
Torremifen	×	✓	✓	×	×	×	✓	✓
Epirubicin	×	✓	✓	✓	✓	×	✓	✓
Doxorubicin liposome	×	✓	✓	×	✓	×	×	✓
Exemestane	×	✓	✓	×	×	×	×	×
Anastrozole	×	✓	✓	×	×	×	×	×
Everolimus	×	✓	×	×	×	×	×	×
Lapatinib	×	✓	×	×	×	×	×	×
Paclitaxel (Albumin Bound)	×	✓	✓	✓	×	×	×	×
Eribulin	×	×	✓	×	×	×	×	×
Pirarubicin	×	×	✓	✓	×	×	×	×

TABLE 3 | Medicines in the list and guidelines for the treatment of esophageal cancer.

Medicines	Essential medicines list (2018 edition)	Standard for diagnosis and treatment of esophageal cancer (2018 edition)	Guidelines for diagnosis and treatment of esophageal cancer (2022 edition)	The Chinese guidelines for radiotherapy of esophageal cancer (2019 edition)
Paclitaxel	✓	✓	✓	✓
Fluorouracil	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓
Carboplatin	✓	✓	×	✓
Capecitabine	✓	✓	×	✓
Oxaliplatin	✓	✓	✓	✓
Calcium folinate	✓	✓	✓	✓
Trastuzumab	✓	×	✓	✓
Tigio	×	✓	×	✓
Epirubicin	×	✓	×	×
Nedaplatin	×	×	×	✓
Changchun Ruibin	×	×	×	✓
Etoposide	✓	×	×	×
Pingyangmycin	✓	×	×	×
Docetaxel	×	✓	✓	✓
Irinotecan	×	✓	✓	✓
Pembrolizumab	×	×	✓	×
Nivolumab	×	×	✓	×
Camrelizumab	×	×	✓	×

The two guidelines recommend 4 first-line medicines, including 1 essential medicine for the treatment of liver cancer. The matching degree is 25.00%. Two guidelines published after 2018 are available for comparison: standard for the diagnosis and treatment of primary hepatic carcinoma (2019 edition) and the guideline for the radiotherapy of hepatocellular carcinoma in China (2020 edition). The two guidelines recommend 6 first-line medicines, including 1 essential medicine for the treatment of liver cancer. The matching degree is 16.67% (**Table 1**).

Breast Cancer

China ranks top in the incidence of female malignant tumors with a prevalence of about 3% for breast cancer (23). There are 16 breast cancer medicines on the essential medicines list (2018 edition). After screening, three guidelines published in 2018 and before are available for comparison: Chinese Advanced Breast Cancer Consensus Guideline (CABC 2015), Guidelines for breast cancer diagnosis and treatment (2017 edition) and breast cancer diagnosis and treatment guideline (2018.V1). The three guidelines recommend 27 first-line medicines, including 13 essential medicine for the treatment of breast cancer. The matching degree is 48.15%. Four guidelines published after 2018 are available for comparison: Chinese Advanced Breast Cancer Consensus Guideline 2020 (CABC3), breast cancer diagnosis and treatment guideline (2022), Guidelines for clinical diagnosis and treatment of advanced breast cancer in China (2020 edition), and the Guidelines for breast cancer diagnosis and treatment (2019 edition). The four guidelines recommend 21 first-line medicines, including 12 essential medicine for the treatment of breast cancer. The matching degree is 57.14% (**Table 2**).

Esophageal Cancer

Esophageal cancer is a high-risk malignancy in China. Its incidence and mortality are sixth and fourth respectively (24). There are 10 types of medicines for the treatment of esophageal cancer in the essential medicines list (2018 edition). After screening, one guideline published in 2018 is available for comparison: Standard for diagnosis and treatment of esophageal cancer (2018 edition). The guideline recommend 11 first-line medicines, including 7 essential medicine for the treatment of esophageal cancer. The matching degree is 63.64%. Two guidelines published after 2018 are available for comparison: the guidelines for diagnosis and treatment of esophageal cancer (2022 edition) and the Chinese guidelines for radiotherapy of esophageal cancer (2019 edition). The two guidelines recommend 16 medicines, including 8 essential medicine for the treatment of esophageal cancer. The matching degree is 50.00% (**Table 3**).

Lung Cancer

Lung cancer has the highest incidence and mortality rate among malignant tumors in China (25). The national essential medicines list (2018 Edition) contains 13 types of essential medicines for the treatment of lung cancer. After screening, three guidelines published in 2018 and before are available for comparison: Expert Consensus on Diagnosis and Treatment of Advanced Primary Lung Cancer in China (2016 Edition), Guidelines for diagnosis and treatment of primary lung cancer (2018 edition) and Primary Lung Cancer Diagnosis and Treatment Standards (2018 edition). The guidelines recommend 21 first-line medicines, including 8 essential medicine for the treatment of lung cancer. The

TABLE 4 | Medicines in the list and guidelines for the treatment of lung cancer.

Medicines	Essential medicines list (2018 edition)	Expert Consensus on Diagnosis and Treatment of Advanced Primary Lung Cancer in China (2016 edition)	Guidelines for diagnosis and treatment of primary lung cancer (2018 edition)	Primary Lung Cancer Diagnosis and Treatment Standards (2018 edition)	Chinese medical association guideline for clinical diagnosis and treatment of lung cancer (2019 edition)	Clinacal practice guideline for stage IV primary lung cancer in China (2021 version)	Guidelines for diagnosis and treatment of primary lung cancer (2022 edition)
Gemcitabine	✓	✓	✓	✓	✓	✓	✓
Etoposide	✓	✓	✓	✓	✓	✓	✓
Paclitaxel	✓	✓	✓	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓	✓	✓	✓
carboplatin	✓	✓	✓	✓	✓	✓	✓
Gefitinib	✓	✓	✓	✓	✓	✓	✓
Ektinib	✓	✗	✓	✓	✓	✓	✓
Pemetrexed	✓	✓	✓	✓	✓	✓	✓
Erlotinib	✗	✓	✓	✓	✓	✓	✓
Afatinib	✗	✓	✓	✓	✓	✓	✓
Daktinib	✗	✗	✗	✗	✓	✓	✓
Ositinib	✗	✗	✓	✗	✓	✓	✓
Aletinib	✗	✗	✗	✗	✓	✓	✓
Kezotinib	✗	✓	✓	✓	✓	✓	✓
Bevacizumab	✗	✓	✓	✓	✓	✓	✗
Pabolizumab	✗	✗	✗	✗	✓	✓	✓
Albumin paclitaxel	✗	✓	✗	✗	✓	✓	✓
Carrelizumab	✗	✗	✗	✗	✗	✓	✓
Changchun Ruibin	✗	✓	✓	✓	✓	✓	✓
Docetaxel	✗	✓	✓	✓	✓	✓	✓
Irinotecan	✗	✓	✓	✓	✓	✓	✓
Atzumab	✗	✗	✗	✗	✗	✓	✗
Lobaplatin	✗	✗	✓	✗	✓	✗	✓
Nedaplatin	✗	✗	✓	✓	✓	✗	✓
cyclophosphamide	✓	✗	✗	✗	✗	✗	✗
vincristine	✓	✗	✗	✗	✗	✗	✗
Ifosfamide	✓	✗	✗	✗	✗	✗	✗
methotrexate	✓	✗	✗	✗	✗	✗	✗
Doxorubicin	✓	✗	✗	✗	✗	✗	✗
Tigio	✗	✓	✗	✗	✗	✗	✗
Topotecan	✗	✗	✓	✗	✗	✗	✗
Tislelizumab	✗	✗	✗	✗	✗	✗	✓
Sintilimab	✗	✗	✗	✗	✗	✗	✓
Atezolizumab	✗	✗	✗	✗	✗	✗	✓
Ceritinib	✗	✗	✗	✗	✗	✗	✓

TABLE 5 | Medicines in the list and guidelines for the treatment of colorectal cancer.

Medicines	Essential medicines list (2018 edition)	China Colorectal Cancer Diagnosis and Treatment Standards (2017 edition)	Guidelines for the diagnosis and treatment of colorectal cancer (2018.V1)	guidelines for the diagnosis and treatment of colorectal cancer (2019 edition)	Chinese protocol of diagnosis and treatment of colorectal cancer (2020 edition)
Fluorouracil	✓	✓	✓	✓	✓
Oxaliplatin	✓	✓	✓	✓	✓
Capecitabine	✓	✓	✓	✓	✓
Cetuximab	×	✓	✓	✓	✓
Bevacizumab	×	✓	✓	✓	✓
vincristine	✓	×	×	×	×
Calcium folinate	✓	✓	×	×	×
Irinotecan	×	✓	✓	✓	✓
Aldehyde hydrofolate	×	✓	×	×	✓
Letitrexed	×	×	✓	✓	✓
Regofini	×	✓	✓	✓	✓
Furaquintinib	×	×	×	✓	✓

matching degree is 38.10%. Three guidelines published after 2018 are available for comparison: the clinical practice guideline for stage IV primary lung cancer in China (2021 version), the Chinese medical association guideline for clinical diagnosis and treatment of lung cancer (2019 edition), and the Guidelines for diagnosis and treatment of primary lung cancer (2022 edition). The three guidelines recommend 28 medicines, including 8 essential medicine for the treatment of lung cancer. The matching degree is 28.57% (**Table 4**).

Colorectal Cancer

The incidence and mortality of colorectal cancer have been on the rise in China. China's 2018 cancer statistics revealed that the incidence and mortality of colorectal cancer in China ranked third and fifth among all malignant tumors, respectively (26). On the essential medicines list (2018 edition), there are 5 types of medicines for the treatment of colorectal cancer. After screening, two guidelines published in 2018 and before are available for comparison: China Colorectal Cancer Diagnosis and Treatment Standards (2017 edition) and Guidelines for the diagnosis and treatment of colorectal cancer (2018.V1). The guidelines recommend 10 first-line medicines, including 4 essential medicine for the treatment of colorectal cancer. The matching degree is 40.00%. Two guidelines published after 2018 are available for comparison: the Chinese protocol of diagnosis and treatment of colorectal cancer (2020 edition) and the guidelines for the diagnosis and treatment of colorectal cancer (2019 edition). The two guidelines recommend 10 medicines, including 3 essential medicine for the treatment of colorectal cancer. The matching degree is 30% (**Table 5**).

Gastric Cancer

The incidence of stomach cancer in China is second only to lung cancer, while mortality ranks third (27). There are 8 kinds of essential medicines for the treatment of gastric cancer in the national essential medicines list (2018 edition). After screening, two guidelines published in 2018 are available for comparison: Standard for diagnosis and treatment of gastric cancer (2018 edition) and Guidelines for diagnosis and treatment of gastric cancer (2018 edition). The guidelines recommend 13 first-line medicines, including 7 essential medicine for the treatment of gastric cancer. The matching degree is 53.85%. One guideline published after 2018 is available for comparison: the guidelines for the diagnosis and treatment of gastric cancer (2022 edition). The guideline recommend 13 medicines, including 7 essential medicine for the treatment of gastric cancer. The matching degree is 53.85% (**Table 6**).

Leukemia

Leukemia is one of the most common malignant blood system tumors, and its mortality rate is high. The 2016 annual report on cancer registration in China revealed that leukemia incidence ranked 13th and mortality ranked 10th in the national cancer registration areas (28). There are 17 medicines for the treatment of leukemia in the essential medicines list (2018 edition), but the Compound Huangdai tablets and methylprednisolone are not classified as oncology drugs. After screening, two guidelines published in 2018 are available for comparison: Guidelines for the diagnosis and treatment of acute promyelocytic leukemia in China (2018 edition) and Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma in China (2018 edition). The guidelines recommend 15 first-line medicines, including 10 essential medicine for the treatment of leukemia. The matching degree is 66.67%. Two guidelines published after 2018 is available for comparison: guidelines for the diagnosis and treatment of chronic lymphocytic leukemia-small lymphocytic lymphoma (2022 edition) and guidelines for the diagnosis and treatment of chronic myeloid leukemia (2022 edition). The guidelines recommend 15 medicines, including 4 essential medicine for the treatment of gastric cancer. The matching degree is 26.67% (**Table 7**).

TABLE 6 | Medicines in the list and guidelines for the treatment of gastric cancer.

Medicines	Essential medicines list (2018 edition)	Standard for the diagnosis and treatment of gastric cancer (2018 edition)	Guidelines for diagnosis and treatment of gastric cancer (2018 edition)	the guidelines for the diagnosis and treatment of gastric cancer (2022 edition)
Fluorouracil	✓	✓	✓	✓
Calcium folinate	✓	×	×	✓
Capecitabine	✓	✓	✓	✓
Cisplatin	✓	✓	✓	✓
Carboplatin	✓	×	✓	×
Oxaliplatin	✓	✓	✓	✓
Paclitaxel	✓	✓	✓	✓
Trastuzumab	✓	✓	✓	✓
Tigio	×	✓	✓	✓
Epirubicin	×	✓	✓	✓
Docetaxel	×	✓	✓	✓
Albumin paclitaxel	×	✓	×	✓
Irinotecan	×	✓	✓	✓
Simustine	✓	×	×	×
Apatinib	×	✓	✓	✓

DISCUSSION

The degree of matching between the seven cancer essential medicines listed above and the medicines recommended by the guidelines is shown in **Table 8**. It is evident that the degree of matching between the essential medicines for the majority of diseases and those recommended by the guidelines is low, ranging from 30 to 60%. The matching degree between the essential medicines list and the guidelines needs to be further improved.

The poor match of the Essential Medicines List with guidelines published in 2018 and earlier suggests that the current version of the Essential Medicines List was not constructed with sufficient attention to the guidelines. The mismatch between the essential medicines list and treatment guidelines will significantly impede the clinical medication by doctors. On the one hand, on 11 October 2019, the general office of the State Council issued opinions on further ensuring the supply and price of medicines in shortage, making it clear that the proportion of essential medicine varieties provided by primary medical and health institutions, secondary public hospitals, and tertiary public hospitals should not be <90, 80, and 60%, respectively. Therefore, hospitals must prioritize the availability of essential medicines and the clinical use of the essential medicines to satisfy the assessment requirements of essential medicines. On the other hand, considering the clinical medication effect, doctors must replace essential medicines with those with better therapeutic effects, as recommended by the guidelines. Nie Ruifang (29) reported that the lack of clinical demand is the primary reason why secondary and tertiary medical institutions lack new oncology essential medicines. Consequently, if the list of essential medicines does not match the treatment guidelines, it will be impossible to achieve the optimal clinical treatment effect under the condition of meeting the essential medicines examination standards. Therefore, we suggest that the essential medicines list should be formulated based on the therapeutic medicines recommended in treatment guidelines (8), and should include high-quality medicines and clinical needs recommended in the high-quality guidelines. Moreover, medicines recommended in the treatment guidelines but not in the essential medicines list should be considered for priority inclusion in the essential medicines list, while those in the essential medicines list but not recommended in clinical guidelines or with many clinical applications should be transferred in a timely manner. A perfect transfer in and transfer out mechanism need to be developed, and strategies to improve the matching degree between essential medicines list and clinical guidelines.

Although it was put forward in the opinions on improving the national essential medicine system (GBF [2018] No. 88) issued by the general office of the State Council on September 19, 2018, and the measures for the administration of the National Essential medicine list (Revised Draft) (hereinafter referred to as the draft) issued by the Department of drug policy and essential drug system of the National Health Commission on November 15, 2021, it has not yet been implemented. "The national essential medicine list conforms to regular evaluation and dynamic management, and the adjustment cycle should not exceed 3 years. If necessary, the adjustment can be organized in time". However, the study indicated that the low degree of matching between various oncology essential medicines and the medicines recommended by the guidelines may be due to the lengthy update cycle of the essential medicines list. It can be seen from the results of the matching degree analysis (**Table 8**) that the matching degree of the list with the guidelines published after 2018 is mostly lower than the matching degree of the list with the guidelines published in 2018 and before. Medicines with superior clinical efficacy (**Table 9**) that have

TABLE 7 | Medicines in the list and guidelines for the treatment of leukemia.

Medicines	Essential medicines list (2018 edition)	Guidelines for the diagnosis and treatment of acute promyelocytic leukemia in China (2018 edition)	The guidelines for the diagnosis and treatment of chronic lymphocytic leukemia / small lymphocytic lymphoma in China (2018 edition)	Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia-small lymphocytic lymphoma (2022 edition)	Guidelines for the diagnosis and treatment of chronic myelogenous leukemia (2022 edition)
Arsenite	✓	✓	✕	✕	✕
Hydroxyurea	✓	✓	✕	✕	✕
Cytarabine	✓	✓	✕	✕	✕
cyclophosphamide	✓	✕	✓	✓	✕
Compound Huangdai tablets	✓	✓	✕	✕	✕
Fludarabine	✕	✕	✓	✓	✕
Rituximab	✓	✕	✓	✓	✕
Bendamostine	✕	✕	✓	✓	✕
Nitrogen mustard phenylbutyrate	✕	✕	✓	✓	✕
Ibutinib	✕	✕	✓	✓	✕
Methylprednisolone	✓	✕	✓	✓	✕
Oxaliplatin	✓	✕	✓	✕	✕
Retinoic acid	✓	✕	✕	✕	✕
Daunorubicin	✓	✓	✕	✕	✕
vincristine	✓	✕	✕	✕	✕
Mercaptopurine	✓	✕	✕	✕	✕
Homoharringtonine	✓	✓	✕	✕	✕
methotrexate	✓	✕	✕	✕	✕
Doxorubicin	✓	✕	✕	✕	✕
Asparaginase	✓	✕	✕	✕	✕
Imatinib	✓	✕	✕	✕	✓
Bai Xiaoan	✓	✕	✕	✕	✕
Lenalidomide	✕	✕	✓	✕	✕
zanubrutinib	✕	✕	✕	✓	✕
Orelabrutinib	✕	✕	✕	✓	✕
Venetoclax	✕	✕	✕	✓	✕
obinutuzumab	✕	✕	✕	✓	✕
Nilotinib	✕	✕	✕	✕	✓
Dasatinib	✕	✕	✕	✕	✓
Flumatinib	✕	✕	✕	✕	✓

TABLE 8 | Matching degree of essential medicines list and guidelines for different diseases.

Disease	Matching degree between essential medicines list and guidelines published in 2018 and before	Matching situation	Matching degree between essential medicines list and guidelines published after 2018	Matching situation
Liver cancer	25.00%	Extremely mismatched	16.67%	Extremely mismatched
Breast cancer	48.15%	Mismatched	57.14%	Mismatched
Esophageal cancer	63.64%	More matched	50.00%	Mismatched
Lung cancer	38.10%	Mismatched	28.57%	Extremely mismatched
Colorectal cancer	40.00%	Mismatched	30.00%	Extremely mismatched
Gastric cancer	53.85%	More matched	53.85%	More matched
Leukemia	66.67%	More matched	26.67%	More matched

TABLE 9 | Oncology meidicines marketed in China in 2019 and later in the above table.

Medicine	Time to market
Donafenib	June 2021
Atezolizumab	February 2020
Eribulin	July 2019
Dacomitinib	June 2019
Atezolizumab	February 2020
Tislelizumab	December 2019
Atezolizumab	February 2020
Zanubrutinib	June 2020
Orelabrutinib	December 2020
Venetoclax	December 2020
Obinutuzumab	June 2021
Flumatinib	November 2019

been on the market after the release of the 2018 edition of the Essential Medicines List have not been included in the Essential Medicines List, thus failing to meet clinical drug needs. In light of this, the current three-year regular adjustment and timely adjustment of the directory adjustment management mechanism needs to be further improved. When the essential medicines list is adjusted again, consideration can be given to updating the newly marketed medicines recommended by the guidelines to the list.

The above analysis showed that, in China, there are many guideline formulated by associations, such as the Chinese Medical Doctor Association and the Chinese Medical Association. In recent years, China has made great efforts in formulating and standardizing the guidelines. For example, the healthy China action (2019–2030) released in 2019 clearly mentioned the development of screening, early diagnosis and early treatment guidelines for key cancers such as gastric cancer, esophageal cancer, colorectal cancer, lung cancer, cervical cancer and breast cancer, which have a high incidence rate and mature screening methods and technical schemes, Recently, the general office of the National Health Commission issued the notice on printing and distributing the diagnosis and treatment guidelines for tumor and blood disease related diseases (2022 version), and formulated the diagnosis and treatment guidelines for 21 tumor and blood disease related diseases, including primary lung cancer and gastric cancer. In addition, the draft also proposes that the transfer in and transfer out of essential drugs should refer to the clinical diagnosis and treatment guidelines. In the future, it can further clarify how to quantify the reference guidelines when adjusting the essential medicines list, so as to improve the matching degree between the essential medicines list and the guidelines and better adapt essential mediciines to the needs of clinical medication.Therefore, we think the government should organize and establish departments to formulate scientific and authoritative standard national guidelines, preliminarily evaluate, modify, and improve the guidelines before publication (30). Such departments can also update published guidelines regularly (generally 2–5 years), to provide accurate clinical guidance (31).

In previous analyses, it was found that the essential medicines list and the treatment guidelines for diseases in China are not updated simultaneously. This implies that newly recommended medicines by the guidelines are not included in the essential medicines list. For example, the two medicines for the treatment of non-small cell lung cancer recommended by the lung cancer diagnosis and treatment guidelines, daktinib and ositinib, were approved in 2019, but they have not been in included in the essential medicines list (2018 Edition). This limits the supply of these medicines and affect patient treatment. It should be noted that the rate at which guidelines for some diseases are update is lower compared with that of the essential medicines list. Consequently, doctors still use old guidelines and prescriptions for clinical diagnosis and treatment., and the medicines newly included in the essential medicines list can not be used effectively. The lag of guideline update will affect the clinical medication of doctors and can not provide effective clinical guidance for doctors. Therefore, the national essential medicines list and other treatment guidelines should be updated simultaneously, in China. Moreover, the update cycle of the two should be shortened to comply with the changing medical field to improve consistency between guidelines and list.

The limitations of this study is that it is the first time to analyze the consistency between the essential medicines list and treatment guidelines, there is no literature to refer to the method.

Therefore, there may be some disputes in the calculation of the matching degree between the essential medicines list and treatment guidelines.

CONCLUSION

This is the first study to analyze the relationship between treatment guidelines and the essential medicines list in China. In addition, the quality of essential medicines was evaluated from the perspective of the consistency between the essential medicines list and the treatment guidelines for the first time. This analysis shows that, although China has made great efforts in updating and standardizing treatment guidelines in recent years, as evidenced by establishment of such as, "adjustment cycle in principle shall not exceed 3 years" and "timely adjustment", the matching degree between oncology drugs on the national essential medicines list (2018 edition) and the oncology drugs recommended in treatment guidelines is still low. Therefore, the adjustment mechanism for essential medicines list and matching degree between the list and the guidelines should me improved to promote the utilization of essential medicines.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

JY and LC designed the whole study and contributed to the original draft of the study. CL, XZ, and YC collected and analyzed data and took the responsibility for review and editing. All authors contributed to the article and approved the submitted version.

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Economic Value of Fosaprepitant-Containing Regimen in the Prevention of Chemotherapy-Induced Nausea and Vomiting in China: Cost-Effectiveness and Budget Impact Analysis

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Objective: The purpose of this study was to evaluate the cost-effectiveness and budget impact of fosaprepitant (FosAPR)-containing regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) among patients receiving high emetogenic chemotherapy (HEC) from the Chinese payer's perspective.

Methods: A decision tree model was established to measure the 5-day costs and health outcomes between the APR-containing regimen (aprepitant, granisetron, and dexamethasone) and FosAPR-containing regimen (fosaprepitant, granisetron, and dexamethasone). Clinical data were derived from a randomized, double-blind controlled trial on Chinese inpatients who received HEC. Quality-adjusted life-years (QALYs) were used to estimate the utility outcomes and the incremental cost-effectiveness ratio (ICER) was calculated to assess the economics of FosAPR. A static budget impact model was developed to assess the impact of FosAPR as a new addition to the National Reimbursement Drug List (NRDL) on the medical insurance fund within 3 years in Nanjing, China.

Results: Compared with APR, FosAPR had a mean health-care savings of ¥121.56 but got a reduction of 0.0001815 QALY, resulting in an ICER of ¥669926.19 per QALY. Deterministic sensitivity analysis revealed that the cost of APR was the most influential factor to the ICER. The cost of FosAPR and the complete control rate of the delayed period also had a high impact on the results. According to the probabilistic analysis, the acceptability of FosAPR was more than 80% when the Chinese willingness-to-pay (WTP) was ¥215,999. FosAPR would lead to a 3-year medical insurance payment increase of ¥1.84 million compared with ¥1.49 million before FosAPR entered NRDL in Nanjing. The total budget increased with a cumulative cost of ¥694,829 and covered an additional 341 patients who benefited from FosAPR in Nanjing. Deterministic sensitivity analysis showed that the model of budget impact analysis was stable.

Conclusion: FosAPR had a similar treatment effect to APR but was cost-effective in China at the current WTP threshold. The total budget of medical insurance payments of Nanjing slightly increased year by year after the inclusion of FosAPR. Its inclusion in the NRDL would be acceptable and also expand the coverage of patients who benefited from FosAPR.

Keywords: cost-effectiveness, budget impact analysis, antiemetic, chemotherapy-induced nausea and vomiting, fosaprepitant

INTRODUCTION

Cancer is now a global concern and a heavy burden on the health systems of all countries in the world. According to the "Global Cancer Statistics" published by the American Cancer Society, there were 18.1 million new cases of cancer worldwide and 9.6 million cases of cancer deaths in 2018 (1). While in 2020, the number of new cancer cases rose to 19.3 million and almost 10.0 million cancer deaths around the world (2). In recent years, new treatment methods for malignant tumors, such as immunotherapy, targeted therapy, and genetic therapy, have developed rapidly. However, as one of the commonly used treatments for cancer, chemotherapy is still one of the most effective methods. Drugs of chemotherapy are generally cytotoxic, most of which lack targeting for tumor cells. They may also harm the normal cells of the body, leading to more adverse drug reactions. Digestive system reaction, alopecia, bone marrow suppression, liver, and kidney function damage are common toxic and side effects of chemotherapy. Meanwhile, some cytotoxic drugs have specific side effects. For example, doxorubicin has cardiotoxicity, which may cause damage to myocardial cells, and even lead to heart failure in severe cases. Different chemotherapy strategies had different adverse drug reactions (ADR).

Of all the adverse reactions, chemotherapy-induced nausea and vomiting (CINV) is one of the most common side effects of chemotherapy. It makes patients suffer from low-quality lives and has a large negative impact on patient compliance. Also, it can decline patients' performance status and even make them withdraw from the chemotherapy (3–5). A clinical study by Zhang and Li (6) showed a low rate of antiemetic guideline compliance in chemotherapy patients, implying that medical care still had a lot of shortcomings in this field. Based on the risk of emetic and percentage of incidence of vomiting, it was widely accepted that we divided anti-tumor drugs into four grades: (1) high, with over 90% risk of vomiting; (2) moderate, with 30–90% risks; (3) low, with 10–30% risks; and (4) minimal, with below 10% risks of vomiting (7). The risk here is the incidence of vomiting without preventive treatment. Generally speaking, the emetic of platinum-based chemotherapy regimens is considered at moderate and high grades. In light of the time of occurrence, CINV can be divided into three phases, acute phase (0–24 h), delayed phase (25 h), and anticipatory CINV. Anticipatory CINV occurred more frequently in patients who experienced CINV in previous chemotherapy. Previous literature indicated that the incidence of emesis in the delayed phase was correlated with, but not dependent on that in the acute phase (8). In addition, there are many patient-related risk factors for CINV. Systematic reviews and guidelines identified that history of nausea or vomiting, female sex, younger age, and expectancy of CINV could all influence or even increase the incidence of CINV in patients (9–13). As a result, it is important to improve the quality of care for the patients who received high-emetic chemotherapy (HEC) carefully from various aspects.

One of the effective preventions of nausea and vomiting is to give prior antiemetic drugs before and during chemotherapy. 5-hydroxytryptamine (5-HT_3), substance P (SP), dopamine, acetylcholine, and histamine are neurotransmitters closely related to CINV. In recent years, 5-HT_3 was considered to play an important role in preventing CINV, especially in the acute phase. Furthermore, substance P is a regulatory polypeptide that can bind to neurokinin (NK) receptors and emerges as the dominant driver of the CINV in the delayed phase. The anti-inflammatory effects of glucocorticoids are also used clinically to prevent the occurrence of delayed CINV. Therefore, 5-HT_3 receptor antagonists (5-HT_3 RA), NK-1 receptor antagonists (NK-1 RA), glucocorticoids, general antiemetic drugs proton-pump receptor inhibitors (PPI), and H_2 receptor antagonists are several types of drugs, which are conventionally used to prevent nausea and vomiting. Ondansetron, granisetron, palonosetron, dexamethasone, aprepitant (APR), etc. are all commonly used antiemetic drugs. For moderate or high risks of vomiting, a co-prescription of two or three antiemetic medications would be frequently given as the guideline-recommended.

Aprepitant is a type of NK-1 RA, it can selectively inhibit the link between the substance P and NK-1 receptors, thus blocking the pathway to vomiting. Some clinical trials and observational studies revealed that aprepitant could statistically significantly improve the prevention of emesis compared to the control regimen and this effect was also observed in children (8, 14–16), which showed its outstanding antiemetic function. However, to completely control the CINV, aprepitant needs to be used 48 h after the chemotherapy is dosed, accompanied by much inconvenience. As a result, fosaprepitant (FosAPR) was synthesized to solve the inexpediency of aprepitant. Fosaprepitant is a prodrug of aprepitant, which can convert into aprepitant after absorption. Its bioavailability is almost 100% which is much higher than aprepitant. Secondly, fosaprepitant is easy to use and has the characteristics of a quick effect. Its intravenous infusion can be completed in 30 min before the start of chemotherapy and can rapidly converse to active compounds in the liver (17).

Even though appropriate antiemetic precautions could stop ∼70–80% of CINV episodes (18), the status quo of the CINV is not optimistic. There are more than 30% of patients still suffering from nausea and vomiting after receiving antiemetic treatment (4). Therefore, rescue treatments are badly required when CINV occurs. The basic principle of rescue treatments is to recheck the antiemetic regimens and give different types of antiemetic drugs as appropriate. As for the rescue drugs, except for 5-HT_3 RA, guidelines and expert consensus recommended treatments including promethazine, metoclopramide, olanzapine, lorazepam, haloperidol, scopolamine, omeprazole, etc.

Since 2007, studies have been conducted in seven countries to evaluate the economic value of prophylactic antiemetic regimens (19–24). Most of them showed favorable results with APR. For instance, in 2019, Kashiwa et al. demonstrated that the economic efficiency of the addition of FosAPR to prophylactic antiemetic therapy for outpatient HEC was not cost-effective, although the addition of APR was cost-effective in the context of the Japanese healthcare system (25). However, due to huge differences in different healthcare systems, the economic value of a pharmaceutical product may vary by country. A study in the United States found that APR had little cost-effectiveness benefit.

Based on the Institute for Clinical and Economic Review (ICER) Value Framework 2.0, the economic efficiency and affordability of health technology should be simultaneously considered for inclusion in the reimbursement list (26). Moreover, whether a new drug can be afforded by public health insurance funds is the key issue for its value evidence. Since 2019, enterprises must submit the economic evidence from Cost-effectiveness Analysis (CEA) and Budget Impact Analysis (BIA) to the National Healthcare Security Administration (NHSA) for inclusion in the National Reimbursement Drug List (NRDL) of China.

However, the comprehensive economic assessment of FosAPR-containing regimen therapy for cancer patients in China remains unknown. Especially, there is a lack of comparison between FosAPR and APR. This study aimed to evaluate the cost-effectiveness and budget impact of the FosAPR-containing regimen from the perspective of Chinese payers for patients who received HEC in the context of the Chinese healthcare setting. The BIA of FosAPR was crucial to provide modeling estimates to support evidence-based decision-making for drug reimbursement. It could also be used for budget or resource planning to ensure that the medical insurance funding was affordable if FosAPR would be included in the NRDL.

METHODS

Cost-Effectiveness Analysis

Overview

A decision model which has three stages and two phases was established to describe the therapy process (**Figure 1**). Complete control (CC), incomplete control (IC), and incomplete response (IR) were set to represent three clinical outcomes the patients went through in the acute phase (0–24 h) and delayed phase (25–120 h). CC means no nausea, no vomiting, and no rescue therapy, IC means some emesis but no use of rescue therapy, and IR means nausea and vomiting while getting some use of rescue therapy. The covering time of research was 5 days including the administration of chemotherapy and the preventive antiemetic drug. Microsoft Office Excel 2007 was used to conduct the analysis.

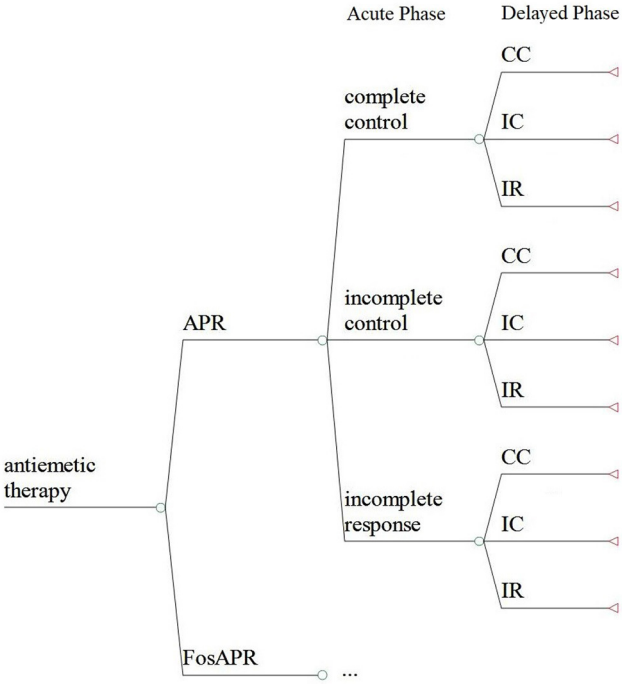

FIGURE 1 | The decision model of the cost-effectiveness analysis. FosAPR, fosaprepitant; APR, aprepitant; CC, complete control; IC, incomplete control; IR, incomplete response.

Clinical Data

The clinical data were stemmed from a randomized, double-blind phase 3 clinical trial, a multicentre study that compared the safety and efficacy of FosAPR with APR in Chinese cancer patients (27). Cancer patients to be enrolled were required to be between 18 and 75 years old receiving high-risk emetic chemotherapy and had a good physical condition, with an Eastern Cooperative Oncology Group (ECOG) performance status score between 0 and 2. In addition, the patient's expected survival time should have been longer than 3 months. A total of 645 patients in 21 centers in China who received chemotherapy including high-risk emetogenic drugs were included in this trial. In this study, patients were divided into APR (n = 317) or FosAPR (n = 328) group randomly. There was no significant difference in demographic data between the two groups. The baseline characteristics of the patients in this study are shown in **Table 1**. Because the clinical data was selected from the published report of clinical trial, ethical approval was not required for the study on participants in accordance with the local legislation and institutional requirements.

A triple therapy regimen (FosAPR (150 mg IV d1) or APR (125 mg orally d1; 80 mg orally d2–d3) plus granisetron and dexamethasone) was used to prevent vomiting. Olanzapine tablets (5 mg orally once) and metoclopramide injection (10 mg IM once) were used as rescue drugs in the research. The complete response rate (CRR) and complete control rate (CCR) in both phases were elicited from the trial report (**Table 2**). The incidences of rescue treatment were 6.40 and 2.84% in FosAPR group and APR group, respectively (27).

Costs and Utility

Costs were estimated from the perspective of the Chinese healthcare system and presented in CNY. Only direct medical costs are incorporated in this study, including drug therapy, rescue therapy, hospitalization, and drug administration. Antiemetic treatment drugs and rescue drugs were described above. The costs of hospitalization consisted of blood routine, blood biochemistry, prescription preparation, and basic consumables. Due to the chemotherapy, all patients were the inpatients, so the hospitalization costs of the two groups were equal in this research. The unit prices of drugs and medical examinations were derived from the surveys that were conducted in local hospitals (e.g., The Affiliated Bayi Hospital of Nanjing University of Chinese Medicine and Nanjing Drum Tower Hospital). The report of the WHO Macroeconomic Committee recommends 1–3 times gross domestic product (GDP) per capita as the threshold for judging the cost-effectiveness of drug. Triple Chinese 2020 GDP per capita (¥215,999) was set to be the willingness-to-pay (WTP) threshold. However, the impact of adverse drug reactions (ADR) was not considered in this study. Also, the discount rate was not considered in the simulation as the trial only lasted for 5 days.

The utility value of three health states of CINV in the Chinese population has not been reported in a clinical trial or published literature before. Referring to the previous studies (25, 28, 29), we separately set the three utility values as 0.9, 0.7, and 0.3. The costs and utility values are summarized in **Table 3**.

Health outcomes were measured by quality-adjusted life years (QALYs). The sum of the 5-day QALYs was calculated as follows:

$$\text{5-day QALY} = (U_{\text{Acute}} * 1 \text{ day} + U_{\text{Delayed}} * 4 \text{ days})/365 \text{ days}$$

The 5-day QALYs of the acute and delayed phases are presented in **Table 4**. To evaluate the cost-effectiveness of FosAPR compared with APR, the incremental cost-effectiveness ratio (ICER) was calculated and was used to compare with the WTP threshold. If the ICER value is less than the WTP threshold, it means that FosAPR is cost-effective compared to APR. Otherwise, it is not economical.

$$ICER = (Cost_{\text{FosAPR}} - Cost_{\text{APR}})/(QALY_{\text{FosAPR}} - QALY_{\text{APR}})$$

Sensitivity Analysis

For testing the uncertainty and robustness of the model, we conducted deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). CCR of FosAPR and APR in acute and delayed phases, cost of antiemetic drugs, utilities of three health states, and incidences of rescue were considered as the influencing factors of the outcomes. The range of CCR in the sensitivity analysis was 95% confidence interval (CI), while the fluctuation of costs and incidences of rescue was set to be ±25%. The range of utility value was plus or minus 0.1 of its baseline value. Tornado diagram was drawn to show the sensitivity of the influencing factors. In PSA, the distributions of cost and utility were gamma and beta distribution, respectively. CCR, CRR, and incidences of rescue were all in normal distribution. Microsoft Office Excel 2007 was used to perform a Monte-Carlo simulation of 1,000 samples and a scatter plot was made to demonstrate the variation in data. The cost-effectiveness acceptability curve was also generated according to the results of the simulation. The

TABLE 1 | The baseline characteristics of patients in the study.

	FosAPR group ($n = 328$)	APR group ($n = 317$)
Age, median (range)	55 (20–79)	53 (18–74)
Sex (%)		
Male	163(49.70%)	163(51.42%)
Female	165(50.30%)	154(48.58%)
ECOG (%)		
0	64(19.57%)	64(20.19%)
1	251(76.76%)	238(75.08%)
2	12(3.67%)	15(4.73%)
Cisplatin-contained (%)	263(80.2%)	234(73.8%)

ECOG, Eastern Cooperative Oncology Group performance status score. One data missing in the FosAPR group.

TABLE 2 | Health state probabilities of the clinical trial.

Response (%)	FosAPR regimen ($n = 328$)		APR regimen ($n = 317$)	
	Acute phase	Delayed phase	Acute phase	Delayed phase
Complete control	84.45	72.56	87.38	74.45
Incomplete control	11.28	18.60	8.52	18.93
Incomplete response	4.27	8.84	4.10	6.62

FosAPR: fosaprepitant; APR: aprepitant.

TABLE 3 | Costs and utility values in the study.

Type of value	Value	Range	Distribution	References
Cost (¥)				
Drugs in FosAPR	512.48	±25%	Gamma	Local charge
Drugs in APR	634.88	±25%	Gamma	Local charge
Inpatient	469.34	–	Gamma	Local charge
Rescue therapy	23.61	–	Gamma	Local charge
Utility				
CC	0.9	±0.1	Beta	(23, 26, 27)
IC	0.7	±0.1	Beta	(23, 26, 27)
IR	0.3	±0.1	Beta	(23, 26, 27)

FosAPR: fosaprepitant; APR: aprepitant; CC: complete control; IC: incomplete control; IR: incomplete response.

TABLE 4 | Utility values of outcomes in acute and delayed phases.

Health state in the acute phase (0–24 h)	Health state in the delayed phase (25–120 h)	Base-case 5-day QALY
CC	CC	0.0123
	IC	0.0101
	IR	0.0047
IC	CC	0.0118
	IC	0.0096
	IR	0.0041
IR	CC	0.0104
	IC	0.0082
	IR	0.0027

QALY, quality-adjusted life year; CC, complete control; IC, incomplete control; IR, incomplete response.

curve illustrated the probability of FosAPR being cost-effective at different WTP thresholds.

Budget Impact Analysis

Overview

According to the practical principles of BIA published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and relevant guidelines, a static budget impact model was developed to assess the impact of inclusion of FosAPR in the NRDL on the health insurance budget of Nanjing in 2022–2024 (30, 31). Microsoft Excel 2007 was used to build the BIA model of FosAPR. Deterministic sensitivity analysis was performed on the base-case BIA results to test the uncertainty of model parameters.

Target Population

The target population was tumor patients treated with HEC regimens in Nanjing, China. The total population was elicited from the Nanjing Statistical Yearbook 2020 released by the Nanjing Municipal Bureau of Statistics (32). At the end of 2019, the total population of Nanjing was 8.5 million. The incidence of cancer in China is about 201 per 100,000 people (33). Due to the lack of relevant epidemiological data in China, it was not possible to calculate the total number of patients receiving HEC. Consulting the research of Restelli et al. (34) in Italy, patients who suffered from lung cancer, head and neck cancer, gastric cancer, testicular cancer, and bladder cancer were selected as the population of HEC. By calculation, there were about 5,793 cancer patients receiving HEC regimens in Nanjing. The morbidities of five cancers are shown in **Table 5**.

TABLE 5 | Morbidities of five cancers.

Tumor types	Morbidity	Reference
Lung cancer	36.09/100,000	(35)
Head and neck cancer	4.32/100,000	(36)
Gastric cancer	21.98/100,000	(35)
Testicular cancer	0.3/100,000	(37)
Bladder cancer	5.46/100,000	(35)

Market Share

In China, 5-HT3 receptor antagonists occupied the majority of the antiemetic drugs market. The market share of antiemetics for CINV in 2021 was obtained from Jiangsu Institute of Medicine Information, which is a large database with medicine procurement records covering 35 secondary and tertiary hospitals and 27 primary health institutions in Nanjing, China. Nanjing is the capital of Jiangsu Province, which is located in the southeast coast of China, with a population of over 9 million (in 2020) residing across 11 municipal districts. The total gross domestic product (GDP) of this city was 1,481.8 billion CNY (∼US$228.8 billion) in 2020, which represents the middle-and-upper level of economic development in Eastern China. Due to its superior geographical position, the 62 sampled healthcare institutions in Nanjing usually provide medical services to the residents of 3 provinces and 1 municipality (Jiangsu Province, Zhejiang Province, Anhui Province, and Shanghai Municipality) in China. Therefore, the data from the drug market in Nanjing was regional representative. The market share of antiemetics for CINV in Nanjing in 2021 was still dominated by 5-HT3 receptor antagonists, with dolasetron, tropisetron, ondansetron, palonosetron, and azasetron as the top five. The market share was 32.03, 24.75, 16.43, 14.60, and 6.85%, followed by Granisetron and APR, which accounted for 4.96 and 0.39%, respectively. The brand-name APR was produced by Merck and was approved for import registration in July 2013 in China. But the brand name FosAPR was not listed. In October 2019, generic FosAPR injections produced by Chia Tai Tianqing Pharmaceutical Co., Ltd., and Hausen Pharmaceutical Co., Ltd. were successively approved for marketing in China. Therefore, we set the market share of this drug to 0% in 2021. Ramosetron and netupitant and palonosetron capsules were not considered for the BIA for they have not been included in the local health insurance drug list of Nanjing. Based on market research, database, and literature (38), FosAPR would compete with 5-HT3 receptor antagonists and APR in the antiemetic drug market of CINV after being included in the NRDL. There was no difference in the ratio of market share decline of all seven competing products. The market share of each 5-HT3 receptor antagonist and NK-1 RA (APR) was set to decline by a linear ratio of 2% every year (39). For example, the market share of Dorasetron in 2021 is 24.75%. After a linear decrease of 2%, the market share is expected to be 24.75%* (1–0.02) = 24.25% in 2022 and 24.75%* (1–0.02) ^2 = 23.77% in 2023. The changes of the market share of each drug within 3 years after the entry of FosAPR into the health insurance drug list are shown in **Table 6**.

Costs of Antiemetic Therapies

Only drug costs were incorporated into the budget. The cost of consumables and administration such as intravenous injection could be ignored compared with drug costs. Generally, all patients with HEC regimens need to be hospitalized for drug delivery, so the cost of hospitalization and adjuvant drugs were consistent. To simplify the results and facilitate comparison,

these costs were not included in the analysis. The unit prices of drugs were originated from the survey of the drug purchase prices in Nanjing. The Chinese Society of Clinical Oncology (CSCO) Guidelines for Prevention and Treatment of Nausea and Vomiting Caused by Anti-tumor Therapies 2019 was referred to make the dosing plan (40). The administration schemes and the prices of a single course of therapies are shown in **Table 7**.

Palonosetron, granisetron, and FosAPR were available in two specifications, so the average cost per course was used. FosAPR and APR must be used in combination with palonosetron (0.25 mg, day 1) and dexamethasone tablets (6 mg, day 1; 3.75 mg, days 2–3). 5-HT3 receptor antagonists should be combined with dexamethasone injection (10 mg, per day 1). The cost of dexamethasone was too low to take into account. The treatment cycle was calculated to be about 6 cycles by the weighted average of the first-line chemotherapy regimens for the cancers included in the study (41–47). Accordingly, the study assumed that antiemetic drugs were administered 6 times within a year. Based on the individual out-of-pocket (OOP) standard of medical insurance in Nanjing (48), the OOP ratio of all kinds of antiemetic drugs varied from 0.1 to 0.5. The proportion of reimbursement was about 80% defined by the Nanjing Medical Insurance Bureau. Take ondansetron as an example, its OOP ratio in Nanjing for urban employee was 0.1 and its annual cost was ¥407.88. The cost covered by medical insurance would be 407.88*(1–0.1) *80% = 293.67 CNY. Assume that FosAPR was covered by health insurance, with an OOP ratio of 0.5 and an estimated 80% of reimbursement similar to APR. The final single course cost, annual cost, and cost covered by health insurance of each antiemetic drug are summarized in **Table 8**.

Research Perspective

The proportions of reimbursement were not uniform in China, and different proportions of reimbursement may have a different effect on the results of BIA. The BIA was based on the health insurance reimbursement policy in the urban area of Nanjing. All the patients in the study were assumed to be urban employees in Nanjing. To facilitate the calculation and the comparison, only the medical costs of antiemetic drugs were included, and the cost of adjunctive drugs and hospitalization were excluded.

RESULTS

Cost-Effectiveness Analysis

Base-Case Analysis

The total costs of FosAPR and APR regimens were ¥983.33 and 1,104.89, respectively. While the two regimens obtained a benefit of 0.0110993 and 0.0112807 QALY. Compared with APR, FosAPR had a mean health-care savings of ¥121.56, but APR exceeded 0.0001815 QALY to FosAPR, resulting in ICER of ¥669,926.19 per QALY (**Table 9**). Although the cost-effectiveness ratios of the two antiemetic regimens were both smaller than the WTP threshold, the ICER was much higher than the WTP threshold, which meant that FosAPR was cost-effective compared with APR in the context of the Chinese healthcare system.

TABLE 6 | Market share changes of antiemetics within 3 years.

Year	Dorasetron	Tropisetron	Ondansetron	Palonosetron	Azasetron	Granisetron	APR	FosAPR
2021	24.75%	14.60%	32.03%	16.43%	6.85%	4.96%	0.39%	0.00%
2022	24.25%	14.31%	31.39%	16.10%	6.71%	4.86%	0.38%	2.00%
2023	23.77%	14.02%	30.76%	15.78%	6.58%	4.76%	0.37%	3.96%
2024	23.29%	13.74%	30.14%	15.46%	6.45%	4.67%	0.36%	5.88%

APR, aprepitant; FosAPR, fosaprepitant.

TABLE 7 | Daily administration schemes and prices of a single course for prevention of CINV.

Drugs	Strength	Unit price (¥)	Dosing	Total cost
Dorasetron	12.5 mg/injection	144.50	12.5 mg, day1, IV	144.50
Tropisetron	5 mg/injection	37.72	5 mg, day1, IV	37.72
Ondansetron	8 mg/injection	33.99	8–16 mg, day1, IV	67.98
Palonosetron	0.25 mg/injection	53.80	0.25 mg, day1, IV	53.80
	0.5 mg/tablet	154.40	0.5 mg, day1, PO	154.40
Azasetron	10 mg/injection	39.70	10 mg, day1, IV	39.70
Granisetron	3 mg/injection	7.90	3 mg, day1, IV	7.90
	1 mg/tablet	10.58	2 mg, day1, PO	21.16
APR	125 mg,80 mg/tablet	191.67	125 mg, day1; 80 mg, day2-3, PO	575.00
FosAPR	150 mg/injection	450.00	150 mg, IV, day1	450.00
	150 mg/injection	458.00	150 mg, IV, day1	458.00

IV, intravenous injection; PO, oral; APR, aprepitant; FosAPR, fosaprepitant.

TABLE 8 | Single course cost, annual cost, and cost covered by medical insurance of antiemetic drugs.

Drugs	Single course cost	Annual cost	Cost covered by medical insurance
Dorasetron	144.50	867	346.80
Tropisetron	37.72	226.32	162.95
Ondansetron	67.98	407.88	293.67
Palonosetron	104.10	624.6	199.87
Azasetron	39.70	238.2	171.50
Granisetron	14.53	87.18	62.77
APR	628.80	3,772.8	1,560.77
FosAPR	507.80	3,046.8	1,270.37

APR, aprepitant; FosAPR, fosaprepitant.

TABLE 9 | Base-case results of FosAPR and APR in CEA.

	Cost (¥)	QALY	CER	ICER
FosAPR	983.33	0.0110993	88,594.19	–
APR	1,104.89	0.0112807	97,945.06	–
Incremental	−121.56	−0.0001815		669,926.19

FosAPR, fosaprepitant; APR, aprepitant; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Sensitivity Analysis

One-way sensitivity analysis results demonstrated that the costs of two antiemetic drugs were the most influential factors in the outcomes, especially the cost of APR (**Figure 2**). If the price of APR is reduced more than ¥85 or FosAPR increases its price, then the APR group might be cost-effective. Otherwise, FosAPR was a more recommended option when choosing antiemetic drugs before performing high-emetic chemotherapy.

PSA scatter plot showed that most scatter were in the third quadrant, which meant FosAPR was more economical compared with APR. At the same time, more than two-thirds of the scatters were below the WTP threshold line, implying that people's acceptance of FosAPR was far higher than that of APR at the current WTP threshold (**Figure 3**). As well as the acceptance curve displayed, the probability that FosAPR could be cost-effective was over 80% when the WTP threshold was ¥215,999. As the WTP threshold rose, the probability of cost-effectiveness gradually decreased (**Figure 4**). The curve implied that the higher the threshold, the higher the tendency of patients to choose APR. The outcomes of PSA both prompted that FosAPR was economical in China.

Budget Impact Analysis

Base-Case Analysis

After the inclusion of FosAPR in the NRDL, it is expected that the target population in Nanjing using FosAPR will increase by 116, 229, and 341 in 2022–2024, respectively, and the total medicare payments will increase from ¥1.49 million in 2021 to ¥1.84 million in 2024, indicating a certain rise in the amount of medical insurance payment. The incremental BI of 3 years would be 117,361, 232,376 and 345,090, respectively, accounting for 0.073, 0.135, and 0.188 of the total expenditure of that year. The cumulative total cost of the medical insurance payments in 3 years reached ¥694,828 (**Table 10**).

Sensitivity Analysis

To test the robustness of the model, a deterministic sensitivity analysis was conducted on the drug prices, the ratio of market share decline, the health insurance OOP ratio, and the health insurance reimbursement rate of FosAPR. The range of each parameter was set between ±20%. The results of sensitivity analysis showed that the influence of the parameters on the results within the fluctuation of ±20% was similar to that of the base-case results, which meant the results of the BIA were stable. As shown in **Figure 5**, the price of FosAPR, the OOP ratio, and the proportion of reimbursement had a great impact on the results. Reducing the price or proportion of reimbursement, or increasing the OOP ratio of FosAPR could make the total payment decline significantly. The cumulative difference could reach ¥298,959 when the parameters fluctuated between ±20%. The high price of FosAPR might contribute to this result. On the premise of the OOP ratio and reimbursement ratio set in this study, if the drug price of FosAPR was <¥32, it was possible to make the medical insurance payments equal to that in 2021. The ratio of market share decline had a certain influence on the result. When the ratio varied between 1.6 and 2.4%, the accumulated cost difference could reach ¥137,017 compared with the base-case result.

DISCUSSION

There were only a few published health technology assessment programs about FosAPR globally. To our knowledge, this is the first study to calculate the economic value of FosAPR for preventing CINV in patients who received moderate to high emetic chemotherapy from the perspective of the Chinese healthcare system for the affordability of health insurance funding. In detail, this study evaluated the cost-effectiveness of the FosAPR-containing regimen vs. the APR-containing regimen and conducted a budget impact analysis of the inclusion of FosAPR into the NRDL of China based on phase 3 clinical trial and real-world statistics.

In the cost-effectiveness analysis, although the APR-containing regimen had a higher cost than FosAPR, it gained a better outcome of QALY in patients. However, by calculating the ICER of two antiemetic drugs, we could not observe the pharmacoeconomic advantage of APR. As the cost of inpatient and other drugs in the antiemetic regimens were the same for both groups, the high drug price of APR might be the dominant factor that affected its economics. Despite the differences in the incidences of ADR, the disparities in administrations of rescue were minimal. The sensitivity analyses were conducted and confirmed the robustness of the model. With the expiration of the APR patent and the successive appearance on the market of its generic drugs, its cost-effectiveness might gradually emerge. Otherwise, if the price of APR remained high, for FosAPR, the probability of being more cost-effective in the

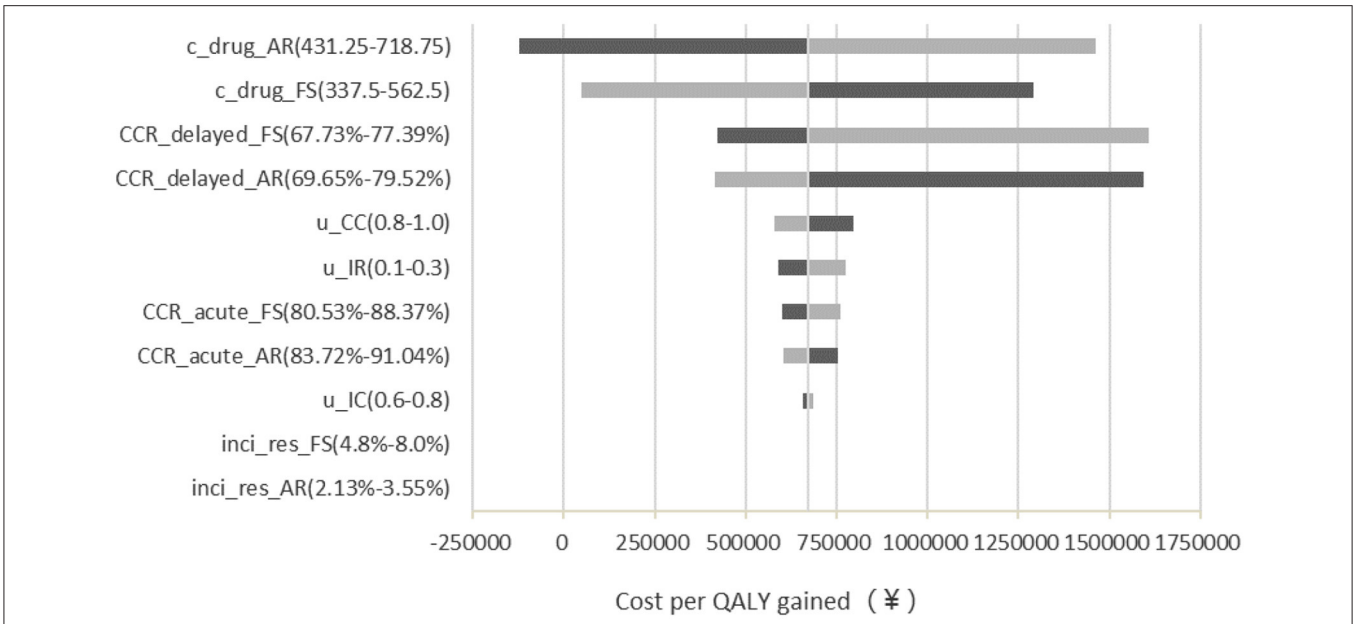

FIGURE 2 | Deterministic sensitivity analysis tornado diagram of FosAPR vs. APR in CEA. c, cost; CCR, complete control ratio; u, utility; FS, fosaprepitant; AR, aprepitant; inci_res, incidence of rescue therapy.

acceptability curves would still be greater than that of APR in the Chinese background set by our study. In the European countries, Restelli et al. (34) constructed a Markov model to incorporate netupitant, aprepitant, and fosaprepitant into the cost-utility and budget impact analyses from the perspective of the Italian National Health Service (NHS). The results of the study illustrated that the netupitant-containing regimen was the most cost-effective. Besides, the cost-utility analysis conducted by Kashiwa and Matsushita (25) compared APR and FosAPR with a standard regimen based on data from two different trials, respectively, which revealed the cost-effectiveness of the addition of APR. Contrary to these studies, FosAPR showed an economic advantage in the context of the Chinese healthcare system. We speculated that it might be related to the following reasons. First, clinical data referred in studies were different in population and study design, which resulted in different response rates of patients. In Kashiwa's study, the economic results compared the addition of APR or FosAPR relatively with the standard regimen, forming an indirect comparison between APR and FosAPR. However, the clinical trial incorporated in this study was a randomized, parallel-group study in the Chinese population (27). Based on the trial, the conclusion of the cost-effectiveness of the FosAPR-containing regimen took the APR-containing regimen as the control group. Second, the health care program combined medical components in various combinations. There are huge differences in medical components between different countries, which led to cost differences. Third, from the perspective of Japanese payers, the price of FosAPR was higher than APR ($129.67 vs. 103.76). The total costs of FosAPR- or APR-containing regimen were $208.87 and 173.89, respectively, making the addition of FosAPR not cost-effective eventually. In China, the price negotiation between NHSA and drug manufacturers had significantly reduced the price of FosAPR (¥512.48 of FosAPR vs. ¥634.88 of APR), leading to its increase in cost-effectiveness.

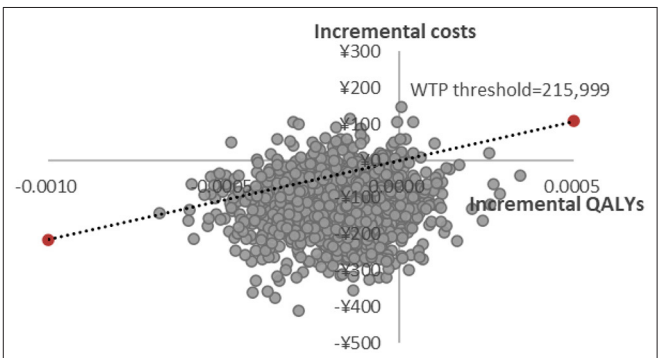

FIGURE 3 | Probabilistic sensitivity analysis of FosAPR vs. APR. WTP, willingness-to-pay; QALY, quality-adjusted life year.

As for the budget impact analysis, it might slightly increase the health insurance budget expenditure (1.49 million in 2021 to 1.84 million in 2024) and have a certain impact on the burden of the medical insurance fund if FosAPR was included in the NRDL of China. It could be related to the following factors. Firstly, the price of FosAPR was high, which was one of the most important reasons. The costs of other antiemetics were <¥200 every single course. In addition, FosAPR needed to be combined with palonosetron for therapy, whose single course cost was more than ¥500. Therefore, the increase in market share after the addition of FosAPR in NRDL would inevitably lead to an increase in medical expenditure. However, the incremental

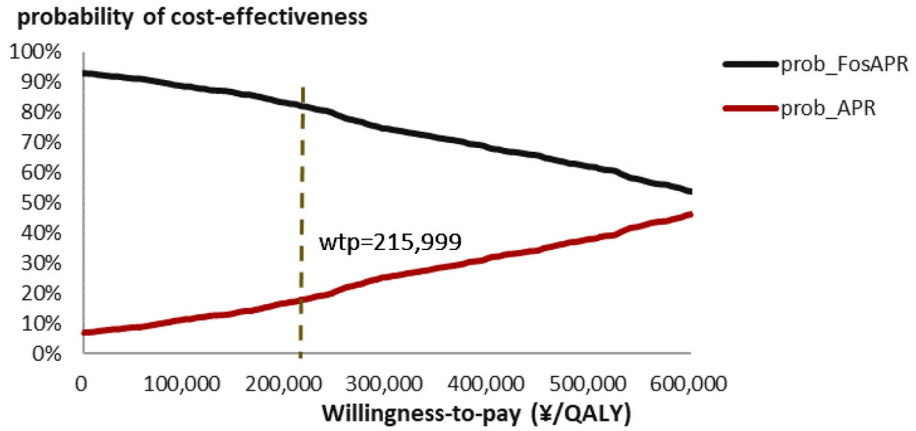

FIGURE 4 | Cost-effectiveness acceptability curve of FosAPR. WTP, willingness-to-pay; QALY, quality-adjusted life year; prob, probability of cost-effectiveness.

budget was no more than 20% of the total amount of health insurance that covered antiemetic drugs every year. According to the Statistical Bulletin on the Development of Medical Security in 2020 (49), announced by the Nanjing Medical Security Bureau on 21 July 2021, the total expenditure of health insurance funds was ¥258,22 million. The cumulated incremental budget only accounted for a tiny proportion (0.003%) of the total expenditure, which may lead to a minor impact on the overall budget fund. Besides, the application of antiemetic drugs could reduce the mounting cost pressure on oncology to some extent. Secondly, the expected market share in 3 years of FosAPR in the model was much larger than those in actual status. According to the baseline proportion of drug purchases in Nanjing, the application of NK-1 RA in the market has not been widely promoted, so the promotion speed of NK-1 RA in the market was lower than our assumption. Therefore, the actual market share of FosAPR 3 years after its inclusion in the NRDL might be much smaller than the estimated share in the study. From the sensitivity analysis, we could see that if the ratio of market share decline dropped from 2 to 1.6%, the insurance budget and the cumulative costs would reduce accordingly compared with the base-case result. In other words, as the market promotion of FosAPR in real world could be smaller than our assumption, the actual impact on the insurance budget would be little after its inclusion in the NRDL. The results of BIA were based on the assumptions of the study and the estimates of the market, so the calculated health insurance expenditure of Nanjing might be overestimated, which was also one of the limitations of this BIA.

According to the guidelines and published pieces of literature (41–47), we found that chemotherapy was still one of the most effective and widely recommended methods for treatment in each period of cancer. Therefore, in this study, the incidence rate of five types of cancer in China was used to calculate the target population for receiving HEC. Similarly, in another Italian study that focused on the budget impact analysis of netupitant and palonosetron, the incidence rates of five types of cancer were also used to calculate the population for receiving HEC (34).

TABLE 10 | Total medical insurance payments of FosAPR before and after inclusion (CNY).

Year	Pre-inclusion	Post-inclusion	Difference	Cumulation
2022	1,491,153	1,608,514	117,361	117,361
2023	1,491,153	1,723,529	232,376	349,738
2024	1,491,153	1,836,243	345,090	694,828

However, with the development of new means of treatment, immunotherapy, targeted therapy, and genetic therapy were also used for some cancer patients with genetic mutations, making the proportion of patients receiving chemotherapy decrease. Therefore, the target population for receiving HEC was inevitably overestimated in the study. In general, the lack of rate of local HEC usage in China could lead to calculation errors in the target population, affecting the BIA results to some extent. In addition, due to the different medical insurance reimbursement policies across the country, this study only selected Nanjing urban medical insurance reimbursement policy as the reference for budget analysis, which might cause deviation in the results if the results were extended to the whole nation. This study also had some limitations in CEA. Firstly, we did not consider outpatients' situations because of the shortages in outpatients' research, which posed a certain obstacle to providing evidence for the medication chosen for outpatients. Secondly, we only brought direct medical costs in the CEA study, neglecting the indirect medical cost impacts on patients in the real world. In the real world, the hidden costs of chemotherapy were relatively exorbitant. Thirdly, the utility values of the three stages were not rigorous enough to reflect their true influence on QALYs.

The major strengths of this study are revealed in several ways. Firstly, our study filled the gap in the economic evaluation of antiemetic medicine. Secondly, it provided strong evidence for better drug choices for patients, and doctors, and for better planning of the NRDL.

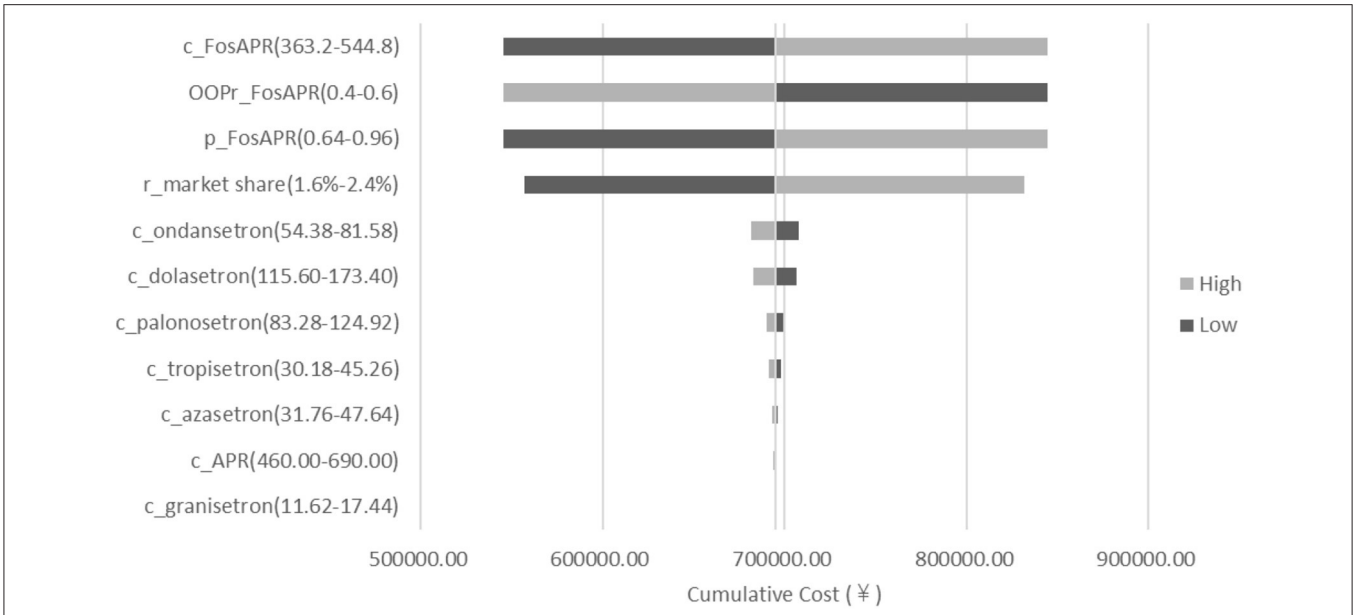

FIGURE 5 | Deterministic sensitivity analysis tornado diagram of FosAPR in BIA. c, cost; p, proportion of reimbursement; OOPr, out-of-pocket ratio; r_market share, ratio of market share decline.

CONCLUSION

FosAPR had a non-inferior effect with APR and was cost-effective compared to APR at the current Chinese WTP threshold. The outcomes of the clinical trial and pharmacoeconomic evaluation both supported that FosAPR would be a better choice than APR to prevent CINV for patients who received emetic chemotherapy. In general, we could predict from the BIA results that the addition of FosAPR in the NRDL may mildly increase the burden of the public health insurance fund but also increase the coverage of patients who benefitted from FosAPR. The incremental BI of predicted years was relatively acceptable for the medical insurance fund. When considering whether the drug is included in the NRDL, the medical insurance payers should make a comprehensive investigation to negotiate the drug price, improve the economy of FosAPR, and the affordability of the medical insurance fund as much as possible.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions 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 from the patients/participants or patients/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

NZ and XL designed the whole study. XX, YB, KX, and ZZ were responsible for collecting and analyzing data. XX and ZZ conducted the models of the study. XX and YB contributed to the original draft of the study. ZZ, NZ, and XL took the responsibility for review and editing. All authors contributed to the article and approved the submitted version.

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Degarelix vs. leuprorelin for the treatment of prostate cancer in China: A cost-utility analysis

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Objective: To explore the cost-effectiveness of degarelix acetate for injection (degarelix) compared to leuprorelin in prostate cancer (Pca) castration treatment from Chinese healthcare system perspective.

Methods: A Markov model, adapted from the one established in Finland was conducted for the cost-effectiveness analysis of degarelix and leuprorelin for Pca treatment. The main data were derived from global phase III clinical trials of degarelix (CS21), published study and expert surveys. Outcomes, utility and costs of prostate cancer patients were calculated on a 30-year time horizon. The CS21 study based population of intention-to-treat (ITT) population and three scenarios were modeled. Taking three times of the Gross domestic product (GDP) per capita (242,928 yuan, 2021) as the acceptable threshold for cost-effectiveness. One-way and probabilistic sensitivity analyses were performed on key parameters, including transition probabilities, costs, utility, and discount rate to test the robustness of the model.

Results: Base case analysis for ITT population revealed that total costs of degarelix and leuprorelin were 566,226 yuan and 489,693 yuan, while the total quality-adjusted life years (QALYs) were 5.19 and 4.51 during the 30-year time horizon, resulting an incremental cost effectiveness ratio (ICER) of 112,674 yuan/QALY which was 1.39 times the GDP per capita, lower than willingness-to-pay level of three times the GDP per capita. The results for scenario analyses revealed that compared to leuprorelin, degarelix for Pca treatment in China was cost-effective. One-way sensitivity analysis showed that the model was most sensitive to price of 80 mg degarelix, utility of 1st-line therapy, hazard ratio of PSA recurrence, price of 3.75 mg leuprorelin, response rate of docetaxel per cycle, and discount rate of cost. In probabilistic sensitivity analysis, compared to leuprorelin, the probability of degarelix to be cost-effective was 53 and 81% for willingness-to-pay threshold of one and three times the GDP per capita.

Conclusion: Compared to leuprorelin, degarelix for prostate cancer treatment is cost-effective. Moreover, scenario, one-way, and probabilistic sensitivity analyses revealed that the model was robust.

KEYWORDS

degarelix, leuprorelin, prostate cancer, cost-utility analysis, Chinese healthcare system

Introduction

Prostate cancer (Pca) is an epithelial malignant tumor of the prostate. According to the 2016 WHO "Pathology and Genetics Tumors of the Urinary System and Male Genital Organs," the pathological types of prostate cancer include the most common adenocarcinoma (acinar adenocarcinoma), intraductal carcinoma, urothelial carcinoma, and squamous cell carcinoma among others (1).

Prostate cancer is one of the most common malignancies of the male genitourinary system. Its risk factors include race, age, and heredity (2). According to GLOBCAN released by WHO in 2018, globally, Pca was the second most common male malignant tumor, second only to lung cancer. Incidence rates of prostate cancer exhibit significant geographical and racial differences. The United States, Northern and Western Europe, Australia as well as New Zealand are high-incidence areas, with a maximum incidence rate of 86.4/100,000, while Asia and North Africa are relatively low-incidence areas with a minimum incidence rate of 5/100,000 (3). Prostate cancer is particularly common in developed countries, with about 249,000 new cases reported in the United States in 2021, accounting for 13.1% of all new cancer cases (4). A study published in 2016 assessed the incidence and mortality rates of prostate cancer in major countries and regions around the world. Based on age-standardized rate per 100,000 analysis, France (123.3/100,000), Sweden (107.6/100,000), Australia (108.2/100,000), the United States (106.8/100,000) and other developed countries had higher prostate cancer incidences than India (7.1/100,000), Thailand (8.7/100,000) and other Asian countries (5). Data from the National Cancer Center shows that since 2008, prostate cancer is the most prevalent tumor of the male urinary system in China. In 2016, its incidence rate was 11.12/100,000, ranking sixth with regard to male malignant tumors, while its mortality rate was 4.85/100,000, ranking seventh among all male malignant tumors (6).

Prostate cancer treatment is associated with a heavy financial burden globally. In Italy, the direct medical costs of Pca ranged from € 196 million to € 228 million per year, accounting for 0.2% of the national health service expenditure in 2016, while in Canada, the total cost of metastatic castration-resistant Pca was $193,604,000, and the total cost of medical castration and bone-targeted therapy to maintain castration testosterone levels was $416,284,000 (7). In China, prostate cancer-associated disease burden exhibited an increasing trend. From 1990 to 2013, the disability adjusted of life years (DALYs), the years of life lost (YLL), and the years lost due to disability (YLD) as a result of prostate cancer increased by 30.66, 25.51 and 51.5 thousand persons per year, with an annual growth rate of 1.05, 1.04 and 1.07% (8).

Androgen-deprivation therapy (ADT) as a primary systemic therapy in advanced prostate cancer patients, or as a neoadjuvant/adjuvant therapy in combination with radiotherapy for localized or locally advanced prostate cancer, includes castration and antiandrogen therapy. Castration therapy can be divided into surgical castration (bilateral orchiectomy) and medical castration, including luteinizing hormone-releasing hormone (LHRH, also known as gonadotropin-releasing hormone or GnRH) agonists or antagonists (6). Degarelix, which was approved in 2018 by National Medical Products Administration, was the first and only gonadotropin-releasing hormone (GnRH) antagonist marketed in China for prostate cancer treatment. International multicenter phase III clinical trials (CS21 and CS21A) (9, 10) and Chinese phase III clinical trials (PANDA) (11) showed that during prostate cancer treatment, compared to the widely used GnRH agonists, degarelix could rapidly reduce testosterone levels to the target level by day 3, significantly improving the survival outcomes of patients without PSA recurrence, and its safety was good.

Therefore, we choose leuprorelin, the most widely used GnRH agonist as reference to explore the cost-effectiveness of degarelix. The cost-effectiveness of degarelix has been proved in UK and US (12, 13) and there are no cost-utility analyses of degarelix in China. We aim to explore the cost-effectiveness of degarelix in China from the Chinese healthcare system perspective.

Methods and materials

Model structure and settings

Adaptation of the cost-utility model

This study was an adaptation of the Finnish model into Chinese environment national treatment practices and costs (14).

The Finnish model was a Markov process model to perform a cost–utility analysis of degarelix as castration treatment for patients with prostate cancer compared to standard treatment with LHRH agonists with anti-androgen flare protection. In this study, the basic structure of the model remained unchanged, and the corresponding disease conversion performed according to actual treatment situations and actual medical expenses data in China.

Model structure adaptation

With regard to prostate cancer treatment in China, the overall disease treatment process was different from the Finnish model. After anti-androgen withdrawal, 35% of patients would skip chemotherapy and accept abiraterone treatment (thick arrow). Therefore, during model adaptation, the transfer path from anti-androgen withdrawal to abiraterone was added to the disease conversion part. The modified structure diagram was

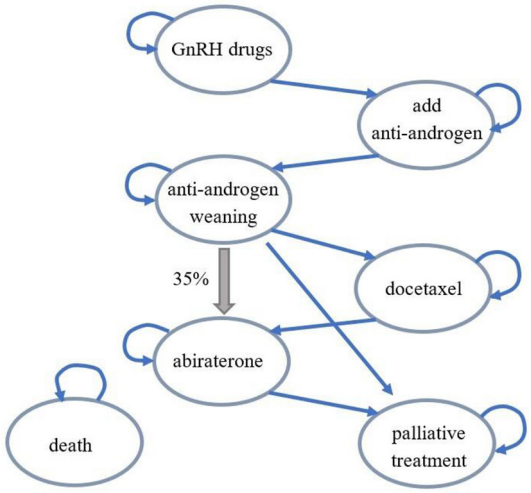

FIGURE 1
Structural diagram of the Chinese adaptation model.

as shown in Figure 1, and the disease state transitions were correspondingly added based on this structure diagram in the Chinese adaptation model. Each disease state in the model could progress to death state, and these transition arrows were not represented in the structure diagram to maintain aesthetics.

Comparator

Leuprorelin, the most widely used GnRH agonist in China, was selected as the reference. Leuprorelin acetate microsphere for injection (Etanercept, 3.75 mg) has been approved in China for nearly 30 years and is the main choice for androgen deprivation therapy. Degarelix is the only GnRH antagonist used for prostate cancer treatment, and the clinical Phase 3 trial (CS21) (9) evaluating the clinical efficacy and safety of degarelix had been completed with leuprorelin in combination with anti-androgen therapy (28 days) as the reference. 7.5 mg leuprorelin was selected as the reference in CS21 trial while this study chose 3.75 mg leuprorelin as the reference. The reasons for choosing 3.75 mg leuprorelin are as follows: (1) For leuprorelin, which has not yet been marketed in China with a specification of 7.5 mg, the most common specification in the market is 3.75mg; (2) The recommended usage and dosage in the drug instruction and CSCO Guideline for Diagnosis and Treatment of Prostate Cancer 2021 of the China Society of Clinical Oncology is 3.75 mg/4-week; (3) The HTA Review Report by All Wales Therapeutics and Toxicology Center (AWTTC) and study of degarelix conclude that there is no evidence of difference in the therapeutic efficacy of leuprorelin at doses of 7.5 and 3.75 mg (15, 16). Therefore, it is reasonable to use CS21 test data for the economic evaluation of leuprorelin with a lower dose of 3.75 mg.

TABLE 1 The basic settings of the model.

Parameters	Values
Perspective	Chinese healthcare system
Targeted population	Intention to treat analysis (ITT), PSA >20 ng/ml
Comparator	Leuprorelin (3.75 mg) + anti-androgen bicalutamide (28 days)
Cycle	28 days
Time horizon	30 years
Discount rate	5%
Starting age	68 years old

Simulated population

The population modeled was designed to reflect the participant population of the CS21 Phase III clinical trial (CS21) (9). The inclusion criteria of simulated population are as follows: (1) Men aged ≥18 years; (2) Histologically-confirmed adenocarcinoma of the prostate (any stage) for which endocrine treatment was indicated (except neoadjuvant hormonal therapy); (3) Increased PSA level despite previous treatment with curative intent; (4) Serum testosterone level of >1.5 ng/ml; (5) PSA level of ≥2 ng/ml; (6) ECOG score of ≤2. The exclusion criteria are as follows: (1) Candidate for curative therapy; (2) Previously or currently accepted hormonal management of prostate cancer (neoadjuvant or adjuvant hormonal therapy for localized treatment of curative intent was permitted if ≤6 months' duration and discontinued >6 months before study inclusion).

In addition to changes in model structure, domestic experts believe that survival time of domestic prostate cancer patients is not as long as that of European patients. The age of onset for domestic patients is lower than that of European patients (14, 17, 18). Therefore, the time horizon in the original Finnish model was set to 30 years, and the starting age of treatment changed from 72 to 68. The basic settings and some characteristics of the simulated population of the model were as shown in Table 1.

Treatment regimens

The first-line treatment regimens included in this study were degarelix acetate for injection and leuprorelin acetate microspheres for injection with anti-androgen flare protection. Specifications and drug regimens for each drug were:

Degarelix acetate for injection: 80 mg or 120 mg*2 sticks, according to the recommended dose of the drug insert (19), every 28 days as a medication cycle (Table 2).

TABLE 2 Medication regimen of degarelix acetate for injection.

Starting dosage	Maintenance dosage
240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/ml	80 mg given as one subcutaneous injection at a concentration of 20 mg/ml

The first maintenance dose should be given 28 days after the starting dose. Degarelix does not cause a surge in testosterone and does not require concomitant antiandrogen therapy for initial treatment.

Leuprorelin acetate microspheres: 3.75 mg, according to recommended dose in drug instructions and Guidelines of the Chinese Society of Clinical Oncology (CSCO) Prostatic Cancer 2021 (20), adults are subcutaneously administered with leuprorelin acetate (3.75 mg) every 4 weeks. Co-administration of anti-androgen drugs (28 days) with the first dose of leuprorelin should be done to avoid or reduce the testosterone "scintillation" effect.

Model parameters

Efficacy

Clinical efficacy

Hazard ratios for PSA recurrence in the therapy with degarelix and leuprorelin were obtained from an open-label, multicenter, randomized, parallel-group study (CS21 trial). The global study involved prostate cancer patients and it evaluated the safety and efficacy of degarelix vs. leuprorelin (9).

The probability of a patient entering second-line therapy from first-line therapy was calculated based on the probability of progression on first-line therapy (PSA recurrence) and the probability of receiving various second-line therapy regimens after progression on first-line therapy. Regarding the progression probability of first-line therapy, since the period of the CS21 clinical trial was 12 months, clinical data for the 30-year study period of the model cannot be obtained. Therefore, we used the survival curve to simulate the survival data of patients outside the clinical trial period to obtain long-term efficacy data. Because the PSA recurrence in CS21 trial (9) was defined as two consecutive rises in PSA levels of 50% compared with nadir, and >5 ng/ml in two consecutive measurements at least 2 weeks apart. The Weibull, Loglogistic, Lognormal, Exponential, and Gompertz distributions were used to simulate and extrapolate the Kaplan–Meier curves of PSA progress of degarelix and leuprorelin. It was determined that PSA progress curve of leuprorelin group in Degenerate with the best fitting degree was the Loglogistic distribution curve according to the red pool information criterion (AIC). The survival function $S(t) = 1/(1 + \lambda t^{\gamma})$ was Log-logistic distribution (S is the survival rate and t is the time), where γ and λ were shape and scale parameters of the Log-logistic function, t was time, and $S(t)$ was the probability that a patient did not have PSA progression by time t.

On this basis, we calculated the progression probability of first-line therapy for each cycle of patients in degarelix and leuprorelin groups. Corresponding probabilities for each cycle in the model were different (Figure 2).

Second-line therapy involved the anti-androgen addition, anti-androgen withdrawal, docetaxel, and abiraterone. Response rates for each therapy were presented in Table 3 (14).

Mortality

The probability of transition from health state to death in the model was calculated from age-specific basal mortality and relative hazard ratio of the Chinese population by Logistic curve. Age-specific mortality rates of the Chinese population were obtained from the sixth census data (21). Mortality hazard ratio of PSA progression/metastatic was obtained from time-varying univariate and multivariate survival analyses of the relationship between PSA progression and survival in a previous study and the hazard ratio was 2.39 (22).

Cost

From the Chinese healthcare system perspective, we only considered direct medical costs, which were divided into the costs of: the drug, second-line treatment, treatment management, and adverse event treatment. Drug prices were the median prices of the latest ongoing bids, while treatment management and adverse event costs were mainly obtained from expert surveys. Due to large differences in medical care patterns in different regions and between urban and rural areas in China, as well as the fact that prostate cancer treatment is mainly concentrated in hospitals in large cities, the cost data for this study were mainly obtained from expert surveys of tertiary hospitals in first and second-tier cities. In this study, 16 experts at urology departments of tertiary hospitals in Beijing, Shanghai, Guangzhou, Chengdu and Xi'an were invited for questionnaire survey. Before conducting the survey, a deputy director expert in Beijing was invited to conduct a preliminary survey on question setting of the questionnaire. Then, after modifications had been made according to the opinions of the expert, interviews with other experts were conducted. The obtained data were sorted, analyzed and the mean calculated, which would be substituted into the model for corresponding calculations.

Prices of degarelix and leuprorelin

Degarelix prices in this study included the price of the first cycle high-dose and the price of the subsequent injection of

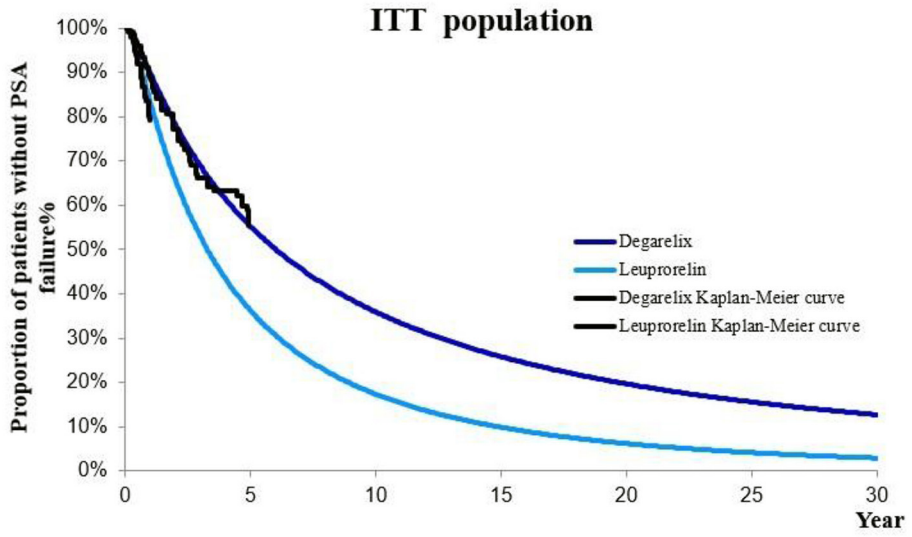

FIGURE 2
Kaplan–Meier curve of PSA progression in degarelix and leuprorelin groups (ITT population).

TABLE 3 The response rates of second-line treatment.

Type of treatment	Mean duration of response (months)	Proportion of patients %	
		Response rate per cycle	Non-response rate per cycle
Add anti-androgens	6	0.83	0.17
Antiandrogen withdrawal	6	0.83	0.17
Docetaxel	12	0.91	0.09
Abiraterone	6.45	0.84	0.16

TABLE 4 The price and dosage of each drug.

Drug	Price (yuan)	Dosage
Degarelix (120 mg*2 in the first cycle)	8,900	1
Degarelix (80 mg*1 in subsequent cycle)	3,200	Per cycle
Leuprorelin	1,389.29	Per cycle

each cycle, which were obtained from the winning bid database. The domestically marketed products of leuprorelin include the original drugs (Enantone, Takeda, 1,599.4 yuan/piece) and two generic drugs (Livzon 1,295.9 yuan/piece and Boente 1,272.58 yuan/piece). Therefore, the price was the average price of the original drugs and generic drugs (1,389.29 yuan/piece), which were obtained from the bid-winning database. Drug prices and dosages were as presented in Table 4.

Costs of disease management and other drugs

During prostate cancer treatment, in addition to the cost of degarelix and the corresponding reference substance, there are costs of disease management and other therapies. Drug costs were obtained from the latest implementation median price of the bid-winning data website in 2021, while the costs of medical resource consumption and disease management were obtained from expert survey (Table 5).

Costs of adverse event treatment

Adverse events in this study included cardiovascular events, musculoskeletal events, and spinal cord compression (SCC). Cardiovascular events were divided into fatal and non-fatal types; musculoskeletal events were divided into three types: mild, moderate, and severe, while spinal cord compression treatments were surgery and chemotherapy. All treatment costs were obtained from expert surveys (Table 6).

Utility

Utility data in this study were obtained from the original Finnish model, which were from the study of Bayoumi et al. (23). Utility values of each disease state used in the model were as shown in Table 7.

Based on the utility value for each health state, during drug treatment, we considered adverse event-associated changes in utility values for patients. We assumed that changes in utility values caused by each adverse event in degarelix and leuprorelin groups were equal, as shown in Table 8 (24, 25).

TABLE 5 Other treatment cost and administration cost.

Parameters type	Parameters	Value	References
Other treatment costs	Anti-androgen - flare cover/daily	¥169.37	Bid-winning data website
	Second-line enzalutamide 160mg/day (40 mg*4 capsules)	¥216.67	Bid-winning data website
	Docetaxel (20 mg)/daily	¥245.66	Bid-winning data website
	Abiraterone (250 mg)/daily	¥40.162	Bid-winning data website
	Dexamethasone (5 mg)/daily	¥0.07	Bid-winning data website
	Continued treatment after the failure of abiraterone/cycle	¥25,200.00	Expert survey
	Supportive care/cycle	¥7,500.92	Expert survey
	Palliative care/cycle	¥5,804.82	Expert survey
Administration Cost	GP consultation fee/each time	¥28.25	Expert survey
	Bone scan/each time	¥563.75	Expert survey
	CT scan/each time	¥457.50	Expert survey
	MRI/each time	¥1,440.00	Expert survey
	Blood test/each time	¥369.38	Expert survey

*Drug price.
≠Drug cost.
¥ Chinese currency.

TABLE 6 Cost of adverse event management.

Types of adverse event		Category	Value
Spinal cord compression		Radiotherapy cost (per patient)	¥30,000.00
		Surgery fee (per patient)	¥40,000.00
Musculoskeletal events	Severe	Joint disorders	¥27,142.86
		Fracture	¥21,500.00
		Other musculoskeletal events	¥24,000.00
	Moderate	Joint disorders	¥16,276.50
		Fracture	¥15,276.72
		Other musculoskeletal events	¥17,776.50
	Mild	Joint disorders	¥14,528.25
		Fracture	¥7,417.14
		Other musculoskeletal events	¥8,278.25
Cardiovascular events	Fatal		¥28,723.96
	Non-fatal		¥18,369.28

¥ Chinese currency.

Base case analysis

Base case analysis results were expressed as incremental cost-effectiveness ratio (ICER) in ITT population, which was calculated as incremental costs/incremental QALYs. Based on the China Guidelines for Pharmacoeconomic Evaluations (26) recommendations, we used three times the GDP per capita as the threshold of Willingness to pay (WTP). If the ICER < the threshold of WTP, then, we can consider that the treatment strategy is cost effective. The GDP per capita was 80,976 yuan in China in 2021 (27).

Scenario analyses

Scenario analyses were also conducted for different price of drug, time horizon, and dosage of drug to evaluate the economics of degarelix and leuprorelin for prostate cancer treatment.

One-way sensitivity analysis

One-way sensitivity analysis was performed to examine the impact of variation in individual parameters on robustness

TABLE 7 Utility values for each disease state.

Entry	Value
Utility of first-line treatment	0.90
Utility of anti-androgen addition	0.80
Utility of anti-androgen withdrawal	0.80
Utility of chemotherapy and abiraterone	0.69
Utility of supportive and palliative care	0.40

TABLE 8 Utility of adverse events.

Adverse events	Value
Severe SCC (non ambulant)	−0.20
Mild SCC (ambulant)	−0.37
Severe musculoskeletal events	−0.37
Moderate musculoskeletal events - applied as decrement	−0.26
Mild musculoskeletal events - applied as decrement	−0.12
Cardiovascular events	−0.73

of base-case results. The analysis was performed on model parameters such as hazard ratio of first-line treatment, response rate of second-line treatment, utility value of health states, cost and dosage of treatment drug, cost of second-line treatment drug, cost of treatment management, cost of best supportive care, and discount rate. Apart from reported varies in original parameters, without the source of parameters ranges, costs parameters varied between −20 and +20%, while efficacy parameters varied between −10 and +10%. Findings from one-way sensitivity analysis were measured by ICER, and the calculation formula was:

$$\mathrm{ICER} = (\mathrm{Cost}_{\text{degarelix arm}} - \mathrm{Cost}_{\text{leuprorelin arm}})/(\mathrm{QALYs}_{\text{degarelix arm}} - \mathrm{QALYs}_{\text{leuprorelin arm}}).$$

If ICER are all less than zero, then, the intervention program is an absolute superiority program.

Probabilistic sensitivity analysis

To verify the influence of parameter uncertainty as a whole on model results, probability sensitivity analysis was performed on the range of model parameters and their distribution characteristics, including hazard ratio of first-line treatment, response rate of second-line treatment, utility value of health state, cost and dosage of treatment drug, cost of second-line treatment drug, cost of treatment management, cost of best supportive care, and discount rate. Probabilistic sensitivity analysis was conducted by simultaneously varying all parameters within set different distributions in 5,000 Monte Carlo simulation iterations to illustrate the results of uncertain analysis and build a cost-effectiveness acceptability curve.

Results

Base case analysis

Using a 30-year time horizon Markov model (Table 9), the total costs for degarelix and leuprorelin groups were 566,266 yuan and 489,693 yuan, while total QALYs were 5.19 and 4.51, respectively. Compared to leuprorelin, incremental cost-effectiveness ratio of degarelix in prostate cancer treatment was 112,674 yuan/QALY, which was 1.39 times GDP per capita, lower than three times China GDP per capita in 2021. Therefore, degarelix was more economical for prostate cancer treatment than leuprorelin.

Scenario analyses

Scenario analyses simulated the cost-effectiveness of degarelix in the treatment of prostate cancer under three scenarios. Results of crowd scenario analyses were showed in Table 10. (1) Scenario 1: under the threshold of 1 time the GDP per capita, when the price of degarelix (80 mg) dropped to 2,968.59 yuan, a decrease of 7.23%, degarelix was economical for the treatment of prostate cancer. (2) Scenario 2: when the time horizon was 10 years, the ICER of degarelix for prostate cancer was 135,317 yuan/QALY, 1.67 times the GDP per capita. (3) Scenario 3: when the dose of leuprorelin was adjusted to 7.5 mg per cycle, the same with CS21 trial, the degarelix had a dominant advantage over the leuprorelin in the treatment of prostate cancer. Therefore, compared to leuprorelin, degarelix was more economical for prostate cancer treatment in China.

One-way sensitivity analysis

Three times the GDP per capita was used as the WTP threshold to calculate ICER, then, a storm map was drawn based on one-way sensitivity analysis of degarelix relative to leuprorelin.

Figure 3 shows that when all uncertain factors changed within the specified range. Results of the one-way sensitivity analyses were largely consistent with those of the base-case analysis, with most showing limited variations from main results. Of all uncertainties, the six factors that had the greatest impact on outcomes were price of 80 mg degarelix, utility of 1st-line therapy, hazard ratio of PSA recurrence, price of 3.75 mg leuprorelin, response rate of docetaxel per cycle, and discount rate of cost. The other factors had limited effects. When the drug cost of degarelix 80 mg varied from 2,560 to 3,840 yuan, ICER fluctuated in the range of 28,252 to 197,096.

TABLE 9 Results of base case analysis.

Treatment	Total cost (yuan)	QALYs	Incremental QALYs	ICER (yuan/QALY)	Incremental Net Benefit (INB)
Degarelix	566,226	5.190	0.679	112,674	88,473
Leuprorelin	489,693	4.510			

TABLE 10 Results of crowd scenario analyses.

Scenario	Treatment solutions	Total cost (yuan)	QALYs	Incremental QALYs	ICER (yuan/QALY)	Incremental Net benefit value (INB)
The price of degarelix was decreased by 7.23%	Degarelix	544,696	5.19	0.679	80,976	110,004
	Leuprorelin	489,693	4.51			
The time horizon was adjusted to 10 years	Degarelix	406,735	4.395	0.497	135,317	53,515
	Leuprorelin	339,442	3.898			
The dose of leuprorelin per cycle was adjusted to 7.5mg	Degarelix	566,266	5.19	0.679	Dominant	209,566
	Leuprorelin	610,786	4.51			

Probabilistic sensitivity analysis

Based on 5,000 Monte Carlo simulations, the cost-effectiveness scatterplot and the cost-effectiveness acceptable curve were drawn. From the cost-effect scatter plot (Figure 4), most of the scatter points were in the first quadrant of the coordinate axis, suggesting that degarelix could bring more QALYs, but at the same time, the cost was higher. When WTP was 112,674yuan/QALY, which is the ICER of base case analysis, the probability of degarelix having a cost-utility advantage was 62%. When WTP was one–three times the GDP per capita, most of the scattered points were below the threshold line. The cost-effectiveness acceptable curve (Figure 5) shows that when WTP was one–three times the GDP per capita, in the range of 80,976 to 242,928 yuan/QALY, the probability of degarelix having a cost-utility advantage was 53% and 81%.

Discussion

This is the study that revealing the cost-effectiveness of degarelix in Chinese health system settings. The findings of our CEA modeling comparing degarelix with leuprorelin indicated that at the 30-year time horizon, degarelix was cost effective over leuprorelin as the baseline strategy at the threshold of three times the GDP per capita. One-way sensitivity analysis revealed that six factors that had the greatest impact on outcomes of degarelix compared to leuprorelin were price of 80 mg degarelix, utility of 1st-line therapy, hazard ratio of PSA recurrence, price of 3.75 mg leuprorelin, response rate of docetaxel per cycle, and discount rate of cost. Probabilistic sensitivity analysis showed that compared to leuprorelin, when WTP thresholds were one and three times the GDP per capita in 2021, probabilities of degarelix being cost-effective were 53 and 81%. The sensitivity analysis results revealed that our model was relatively robust. An additional threshold analysis indicated that the list price of degarelix would have to decrease by 7.23%, the cost of degarelix starter injections would be 8,098.11 yuan, and the cost of maintenance injections would be 2,968.59 yuan. The ICER will reach the threshold of 1 time Chinese GDP per capita (80,976 yuan, 2021). Our findings are in line with the previous results done in Pca patients from other national studies (12, 13).

Prostate cancer has a longer natural survival period than most other malignancies. At present, the main treatment methods for prostate cancer in the world mainly include radical surgery, radiation therapy, chemotherapy and endocrine therapy, and the survival time is the main indicator to evaluate the quality of various types of treatment. Endocrine therapy for prostate cancer has a history of more than 70 years. Endocrine therapy has been shown to effectively prolong the survival time of patients. In one study, the median survival time for prostate cancer patients treated with endocrine therapy was 7.81 years (28).

To date, only one research has evaluated the cost-effectiveness of degarelix and leuprorelin in the treatment of patients with Pca in China. Xuan et al. (14) evaluated the

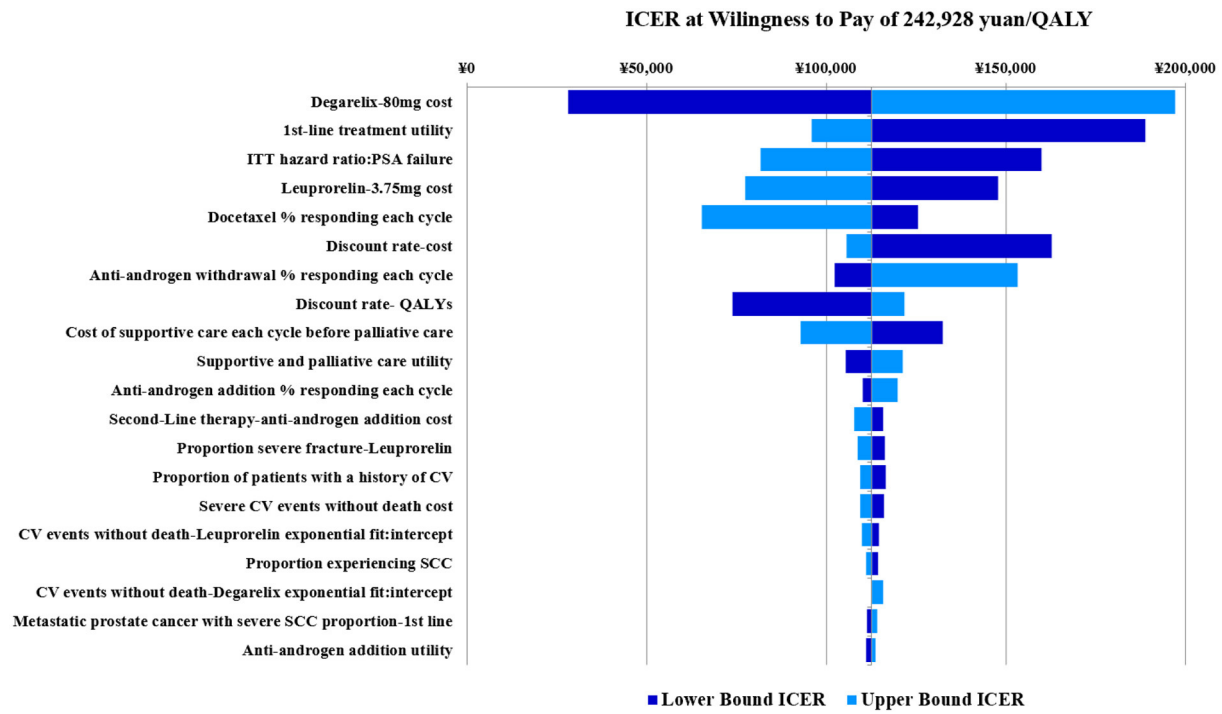

FIGURE 3
Degarelix vs. leuprorelin univariate sensitivity analysis tornado plot (base case analysis ICER= 112,674).

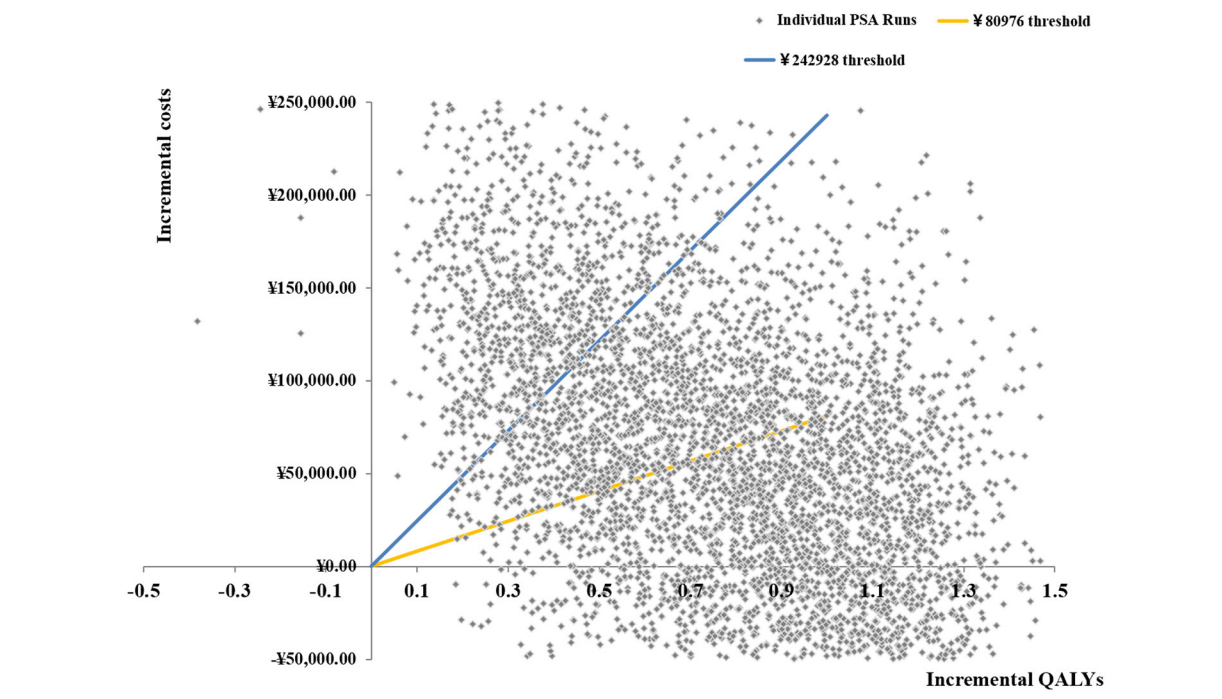

FIGURE 4
Base-case probabilistic sensitivity analysis: scatter plot (5,000 iterations).

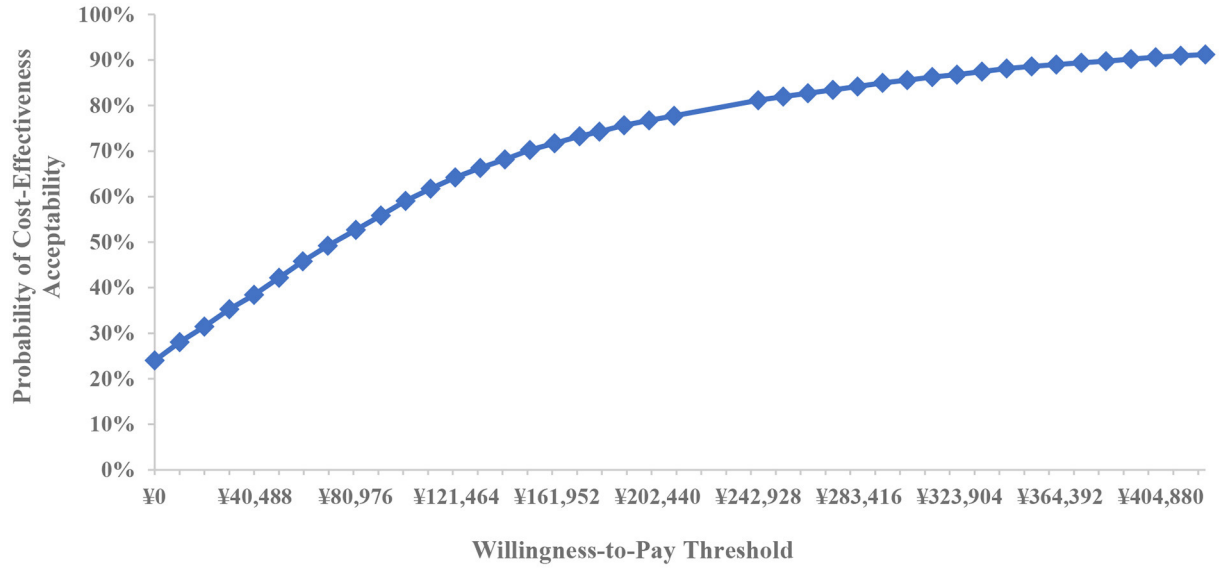

FIGURE 5
Cost-effectiveness acceptable curve.

cost-effectiveness of degarelix, leuprorelin and goserelin from the perspective of Chinese healthcare system in 2018 and the conclusions were consistent with those of this study.

Degarelix is the third generation GnRH antagonist which can competitively block the GnRH receptor, resulting in a rapid, but reversible, decrease in LH, FSH and testosterone without any flare (29, 30). A meta-analysis study revealed that incidence rates of adverse reactions of degarelix were significantly lower than GnRH agonists, such as back pain, weight gain and cardiovascular events (31). And two initial studies that demonstrated this association analyzed data from the Surveillance Epidemiology and End Results-Medicare linked database and identified an increased risk of incident coronary heart disease, myocardial infarction, and cardiovascular death among men with prostate cancer treated with a GnRH agonist (32, 33). Therefore, degarelix can bring more clinical benefits to patients with Pca and the cost-effectiveness analysis is important for patients, clinicians and payers.

The major change in the process of adapting the Finnish model to China was the treatment cost. We obtained information and prices on clinical visits, medication, and health resource utilization in different disease states of prostate cancer by surveying urologists across the country. Drug prices were mainly obtained *via* the bid-winning data network. For instance, the price of abiraterone was the median of bid-winning prices of provinces and cities in the bid-winning data network. The number of visits, medical resource utilization, and cost per time of prostate cancer patients at each disease state were obtained from experts. Thus, the cost data in this study are subject to personal limitations.

The utility value in this study is obtained from the original Finnish model, which is the data of the European population. Due to limitations of domestic utility research, availability of utility data for each disease state of prostate cancer population is poor. Therefore, the original data was used in this study.

This study has several limitations. First the treatment management and adverse reaction costs in the model came from surveys of experts, which had a certain subjectivity. But treatment management and adverse reaction costs have great difference between hospitals, and no adequate cost data could be obtained from literature searches. On the other hand, prostate cancer treatment is mainly concentrated in hospitals in large cities, the cost data for this study were mainly obtained from expert surveys of tertiary hospitals in first and second-tier cities, which can match the real world level. Therefore, expert surveys were the best approaches for obtaining data. Second, regarding the probability of metastasis, due to a lack of data on response rates of prostate cancer patients in second-line treatment and best supportive care in China, data were obtained from international clinical trials. There may be cases where treatment effects of patients in mainland China differ from the results in clinical trials. However, there was no substitute for data that fully meets the modeling needs. If clinical data from patients in mainland China are available in future, we will replace the data in the existing model. Third there were no published studies on health preferences of various treatment regimens for Chinese prostate cancer patients, therefore, health utility values in the model were all taken from existing literature on international clinical trials. Since health utility values were greatly affected by country and race, if health utility values

for Chinese prostate cancer patients under different treatment regimens can be directly obtained in future, we will replace the health utility value parameters in the existing model.

Conclusion

This study used the Markov model to simulate the cost-effectiveness of degarelix vs. leuprorelin for prostate cancer treatment. During the 30-year simulation period, the study showed that compared to leuprorelin, degarelix had a cost-effective advantage in castration treatment of Chinese prostate cancer patients.

Data availability statement

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

Author contributions

JY and LZ designed the whole study. CL, XZ, LC, and RD collected and analyzed data. LC and RD conducted the models of the study. CL and XZ contributed to the original draft of the study and took the responsibility for review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Trends in accessibility of negotiated targeted anti-cancer medicines in Nanjing, China: An interrupted time series analysis

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Background: In order to establish a long-term strategy for bearing the costs of anti-cancer drugs, the state had organized five rounds of national-level pricing negotiations and introduced the National Health Insurance Coverage (NHIC) policy since 2016. In addition, the National Healthcare Security Administration (NHSA) introduced the volume-based purchasing (VBP) pilot program to Nanjing in September 2019. Taking non-small cell lung cancer as an example, the aim of the study was to verify whether national pricing negotiations, the NHIC policy and the VBP pilot program had a positive impact on the accessibility of three targeted anti-cancer drugs.

Methods: Based on the hospital procurement data, interrupted time series (ITS) design was used to analyze the effect of the health policy on the accessibility and affordability of gefitinib, bevacizumab and recombinant human endostatin from January 2013 to December 2020 in Nanjing, China.

Results: The DDDs of the three drugs increased significantly after the policy implementation ($P < 0.001$, $P < 0.001$, $P = 0.008$). The trend of DDDc showed a significant decrease ($P < 0.001$, $P < 0.001$, $P < 0.001$). The mean availability of these drugs before the national pricing negotiation was <30% in the surveyed hospitals, and increased significantly to 60.33% after 2020 ($P < 0.001$, $P = 0.001$, $P < 0.001$). The affordability of these drugs has also increased every year after the implementation of the insurance coverage policy. The financial burden is higher for the rural patients compared with the urban patients, although the gap is narrowing.

Conclusion: The accessibility of targeted anti-cancer drugs has increased significantly after the implementation of centralized prices, the NHIC policy and the VBP pilot program, and has shown sustained long-term growth. Multi-pronged supplementary measures and policy approaches by multiple

stakeholders will facilitate equitable access to effective and affordable anti-cancer drugs.

KEYWORDS

accessibility, pricing negotiation, targeted anti-cancer medicines, interrupted time series, policy intervention

Background

Current status of cancer

A globally aging population and rapid industrialization, along with risk factors such as chronic diseases, super bacteria, unhealthy lifestyles and environmental pollution, have markedly increased the global incidence of cancer worldwide. From 2006 to 2016 (1), the number of cancer patients increased by 38%, and the number of deaths increased by 17.8% across 195 countries and territories around the world, and cancer-related morbidity and mortality continue to rise (2, 3). The top 3 cancers in terms of incidence rates are lung cancer, stomach cancer and colorectal cancer, whereas lung cancer, liver cancer and stomach cancer rank foremost in terms of mortality rates (4). The accompanying surge in cancer treatment-related costs exerts a considerable burden on society and families (5, 6). Data from the National Cancer Center shows that in recent years, the annual cancer-related medical expenses in China have exceeded 220 billion yuan, and the out-of-pocket (OOP) expenses comprise more than half of the total family income (7, 8).

Targeted anti-cancer drugs

In recent years, molecular targeted drugs and other innovative anti-cancer therapies have significantly prolonged the survival of cancer patients (9), alleviated pain and improved quality of life (10), thereby reducing the psychological pressure on family and community (11). However, due to the high costs of pharmaceutical research and development (12), patent protection of new drugs, limited national medical security capacity, skewed regional economic development, and differences in the diagnostic and treatment facilities of medical institutions, the availability of targeted anti-cancer drugs is severely restricted (13, 14). A famous Chinese movie named "Dying to Survive" was released in 2018, which described a story of cancer patients who could not afford the high cost of anticancer medicines and had to purchase illegal generic drugs from India (15).

Counter-measures

In accordance with the principle of "government-led, policy linkage and continuous regulation," the National Health Commission of China (NHC), in coordination with relevant departments, has adopted measures such as "group purchase" to exchange price for quantity, rational drug use, medical insurance payment, and R&D innovation on the basis of reducing the tax rate (16). The aim is to establish a long-term strategy to bear the costs of anti-cancer drugs. Since 2016, the state has organized the first round of national-level pricing negotiations and the National Health Insurance Coverage (NHIC) policy (17). In May 2016, the NHC announced the results of the first negotiation, and the prices of the targeted anti-cancer drugs icotinib and gefitinib used for the treatment of advanced non-small-cell lung cancer were reduced by 55% (18). In July 2017, the Ministry of Human Resources and Social Security of the People's Republic of China organized the second negotiation and introduced pharmacoeconomic evaluation as a negotiation tool for the first time (19). Eighteen drugs (including bevacizumab and recombinant human endostatin) were included in type B medicine list for national basic medical insurance, with an average price reduction of 44% (19). In October 2018, 17 drugs newly included in the medical insurance type B reimbursement catalog were announced in the third pricing negotiation (20), and their prices were reduced from 31 to 80%, thus greatly relieving the burden on patients (20). Ten innovative drugs that entered the Chinese market before 2018 were subjected to negotiations in November 2019 (21). New reforms were introduced by the NHIC in 2020 on account of the growing innovations in the development of anti-cancer drugs.

The centralization of the procurement of prescription drugs is being used in an increasing number of countries (22), and has the advantages of reducing drug prices, controlling drug expenditure, and improving drug accessibility by creating economies of scale (23). On 14th November 2018, the NHSA introduced the implementation of a new VBP pilot (i.e., the "4+7" pilot) program in 4 municipalities (Beijing, Shanghai, Tianjin, and Chongqing) and 7 sub-provincial cities (Guangzhou, Shenyang, Chengdu, Dalian, Xiamen, Xi'an, and Shenzhen) and the program was officially launched in March 2019 with the principle of combining tendering and procurement to achieve "volume-for-price" (24, 25). Since the

pilot program was launched, the prices of 25 centrally purchased high-quality generic drugs including two targeted anti-cancer drugs, gefitinib and imatinib mesylate, have seen a significant reduction of 52% on average, with a maximum unit price reduction of 96% (24, 26). As for policy sustainability, four rounds of VBP have been successively implemented nationwide (27). In December 2019, the government announced that it would further expand the "4+7" pilot cities, and Nanjing was also included (28). Within 4 months of the launch of the pilot program in Nanjing, US$ 20 million was saved for the benefit of ordinary people, with a 59% reduction in the average price of 25 centrally purchased drugs (28).

The effect of the NHIC policy

The NHIC policy was implemented in order to improve the accessibility and affordability of targeted anti-cancer drugs. Studies conducted outside China have shown that health insurance policies improve the willingness of patients to receive and continue treatment (29), reduce the economic burden (30, 31)and mortality rate of patients (32, 33), and increase the chances of receiving treatment by 25–35% (34). In addition, domestic studies have also confirmed that health insurance coverage increases the utilization of health services and lowers the economic burden of disease (16, 35). The current focus is on analyzing the change in the proportion of medical insurance and out-of-pocket payments, and the impact of lowered drug prices on the cost burden (36, 37). Diao et al. evaluated the impact of the provincial government health insurance program in Hangzhou and found that it improved the availability and affordability of 6 targeted anti-cancer drugs. Nevertheless, the financial burden remained high, especially for the rural low-income residents (38). Another group evaluated the price and availability of 15 innovative anti-cancer drugs included in the type B medicine list for national basic medical insurance in 2017 and found that the mean availability rate ranged from 27.44 to 47.33%, and the rate of price reduction was between 34 and 65% (16).

Nevertheless, it is challenging to introduce drugs covered by medical insurance into routine clinical practice due to the scope of drug reimbursement, the assessment of the proportion of drugs, the differences between the national and local insurance policies, and that between various hospitals. Therefore, it is critical to evaluate the implementation of the aforementioned policies to improve access to targeted anti-cancer drugs. Lung cancer is the most prevalent malignancy in China and is associated with high mortality rates (39). Gefitinib, bevacizumab and recombinant human endostatin are the first-line treatment drugs for non-small cell lung cancer (NSCLC) with somatic epidermal growth factor receptor (EGFR) mutations in China, and were included in the first and second batches of the price-negotiated anti-cancer drugs (40, 41). However, there is little evidence regarding the changes in the utilization, price, availability and affordability of these drugs for the treatment of NSCLC. The aim of the study was to verify whether the aforementioned policies have a positive impact on the accessibility of these targeted anti-cancer drugs in Nanjing, China.

Methods

Study design

The procurement of gefitinib, bevacizumab and recombinant human endostatin by various hospitals in Nanjing from January 2013 to December 2020 was analyzed using the interrupted time series (ITS) design. The primary reasons that we chose these three drugs included three aspects. First of all, lung cancer is the most prevalent malignancy in China and is associated with high mortality rates. And, gefitinib, bevacizumab and recombinant human endostatin are the first-line treatment drugs for NSCLC with somatic EGFR mutations in China. In the next place, these three drugs were included in the first and second batches of the price-negotiated anti-cancer drugs, and were approved earlier in China. This ensures sufficient observation period before and after the policy. The last reason, the data retrieved from the Nanjing Regional Hospital Drug Analysis System database is sufficient.

Setting

Nanjing is located on the southeast coast of China, which is the capital of Jiangsu Province. In 2021, Nanjing has a population of over 9 million people in 11 municipal districts. The total gross domestic product (GDP) of Nanjing was 248.1 billion US$ (42), making it the city with the middle- and upper-level economic development area in Eastern China.

Data source

The monthly purchasing data was retrieved from the Nanjing Regional Hospital Drug Analysis System database, which was jointly established with the support of Jiangsu Provincial Science and Technology Department and Provincial Health Commission. Totally, the 8 secondary hospitals and 23 tertiary hospitals in Nanjing were included in the study. The sampled hospitals were accounting for 24.24% of secondary hospitals and 82.14% of tertiary hospitals in Nanjing, respectively. Primary hospitals were excluded since they are not qualified to prescribe targeted anti-cancer drugs.

TABLE 1 Descriptive information and multiple interventions of gefitinib, bevacizumab, and recombinant human endostatin.

Generic Name	Approval date in China	National pricing negotiations	Marketing Authorization Holder	Dosage Form	DDD (mg)	PAPs before pricing negotiation	The first policy intervention point	The second policy intervention point
Gefitinib (branded drug)	2004	2016.7	AstraZeneca AB	Tablet	250	Free after payment of 8 months	2016.7	2020.1
Gefitinib (generic drug)	2017	—	Qilu	Tablet	250	—	—	2020.1 (the VBP pilot program)
Bevacizumab	2010	2017.9	Roche	Injection	25	Free after payment of 4 months	2017.9	2020.1 (renewal)
Recombinant human endostatin	2006	2017.9	Simcere	Injection	8.5	—	2017.9	2020.1 (renewal)

Data cleaning and filtering

The Data Cleaning workflow is comprised of three steps. The initial basic action was to ingest the monthly sales data from the various data sources and identify the sampled hospitals. For the sake of improving the data quality and the analysis outcomes, the next step was filling the missing values. Afterwards, the last step was Data Verification. To ensure reliability, Data Verification was completed independently by two research assistants.

Statistical analysis

Utilization

The monthly DDDs were calculated by dividing the monthly sales data in volume by DDD, defined as the daily amounts based on dosage regimen recommended in the manufacturer's instructions as approved by National Medical Products Administration (NMPA) (43). Higher DDDs indicated greater frequency of usage.

$$DDDs = sales\ data\ in\ volume/DDD.$$

Price

The daily cost of drugs was measured in terms of DDDc as below:

$$DDDc = expenditures/DDDs.$$

Availability

The availability of medicine was calculated as the percentage of the surveyed hospitals that stocked the drugs within the time period.

Very low: <30%, hardly available in the surveyed hospitals.
Low: 30–49%, available in few hospitals.
Fairly high: 50–79%, available in many hospitals.
High: ≥80%, available in most hospitals.

Affordability

As per the methodology of WHO/Health Action International (HAI), the affordability of each drug was calculated as the number of days' wages needed by the lowest-paid unskilled government worker to purchase a course of treatment based on standard treatment regimens. Treatment course requiring more than 1 day's wages is considered unaffordable (44). Data on the per capita annual disposable income from 2012 to 2020 was obtained from the Nanjing Statistical Yearbook. Given the long-term treatment and heavy financial burden of targeted anti-cancer drugs, the expenditure was also assessed in terms of the median progression-free survival (mPFS) that was evaluated based on the treatment guidelines.

The OOP expenditure for the medicines per patient=the total cost of medicine × (1– the proportion of reimbursement).

Availability of patients = OOP expenditure for the medicine for achieving mPFS /per capita annual disposable income.

Pharmaceutical-sponsored patient-assistance programs (PAPs) have been established to improve the access of low-income and uninsured patients to cancer drugs and decrease the economic burden. Patients who have purchased a prescribed course of treatment can apply for the free drug program through the hospital. Gefitinib and bevacizumab are included in the PAPs (Table 1). If the outcome of availability is <1, the drug is generally affordable for patients, and if the outcome of availability is >1, the drug is non-affordable for patients.

ITS regression analysis was used to evaluate the changes in the utilization of negotiated targeted anti-cancer drugs

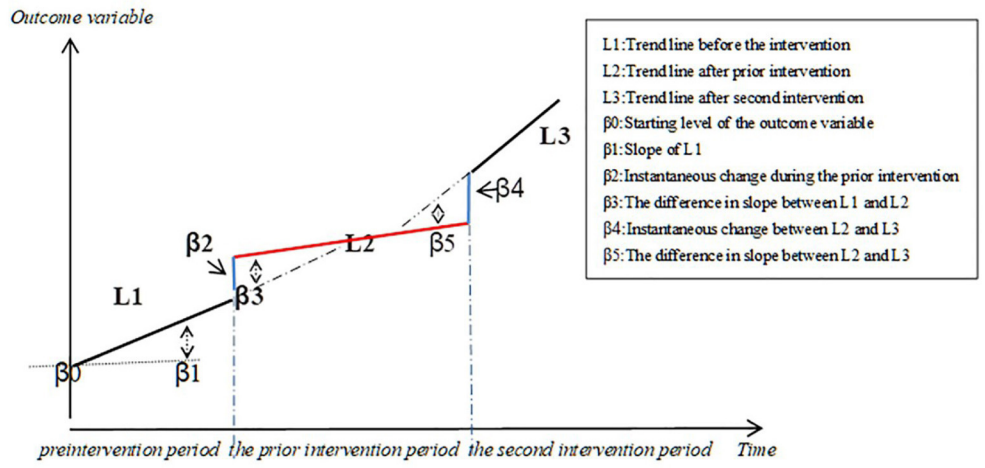

FIGURE 1
Graphic illustration of the ITS model and the trend lines for data points before and after policy implementation.

over a 96 month-period based on DDDs, DDDc, the level of availability, and affordability. The regression equation is as follows (Figure 1):

the single-treatment period analysis:

$$Yt = \beta 0 + \beta 1^{*} time + \beta 2^{*} intervention + \beta 3^{*} posttime + \varepsilon t$$

multiple treatment periods analysis:

$$Yt = \beta 0 + \beta 1^{*} time + \beta 2^{*} intervention + \beta 3^{*} posttime + \beta 4^{*} intervention2 + \beta 5^{*} secondtime + \varepsilon t$$

Y_t is the aggregated outcome variable measured at each equally spaced time point t (45), *time* is the time since the start of the study, *intervention* is a dummy (indicator) variable representing the intervention (preintervention periods 0, otherwise 1), *posttime* is the time after intervention number variable, *intervention 2* is the second intervention indicator variable, *secondtime* is the count change of the second intervention time. β0 represents the intercept and starting level of the outcome variable, β1 is the slope or trajectory of the outcome variable until the introduction of the prior intervention, β2 is the change in the level of the outcome that occurs in the period immediately following the introduction of the first intervention (compared with the preintervention period), β3 is the difference between preintervention and the prior intervention slopes of the outcome (46), β4 is the change in the level of the outcome that occurs in the period immediately following the introduction of the second intervention (compared with the prior intervention period), and β5 is the difference between the prior intervention and the second intervention slopes of the outcome. εt is the residual at time t, which represents the variation of the outcome variable not explained by the model (47).

We collected data of multiple interventions to estimate the post-intervention trends separately following the first and second policy intervention periods in the study. The first policy intervention point was the time at which the first or second batch of national-level pricing negotiations began. Gefitinib was included in the first batch of price-negotiated anti-cancer drugs in July 2016, and bevacizumab and recombinant human endostatin were included in the second batch in September 2017. As previously mentioned, Nanjing was included in January 2020 to expand the scope of the VBP pilot. Gefitinib (generic drug) was one of 25 centrally purchased drugs. To verify whether the VBP pilot program had a positive impact on the accessibility to gefitinib, we set the second policy intervention point of gefitinib (branded drug and generic drug) as January 2020. In addition, the second round of national-level pricing negotiations for bevacizumab and recombinant human endostatin were included in type B medicine list for national basic medical insurance from September 2017 to December 2019. These two drugs were once again covered by pricing negotiations and national basic medical insurance from January 2020 to December 2021(48). In general, further price reductions are expected during drug procurement renewals. Hence, we set January 2020 as the second policy intervention point for bevacizumab and recombinant human endostatin (Table 1).

The interrupted linear regression model requires that the outcome variable has a linear trend over time before and after the policy intervention and that the series has no autocorrelation. The Durbin-Watson (D-W) method was used to test for the existence of 1st order autocorrelation in the time series, with values close to 2 or 4 indicating no autocorrelation. The

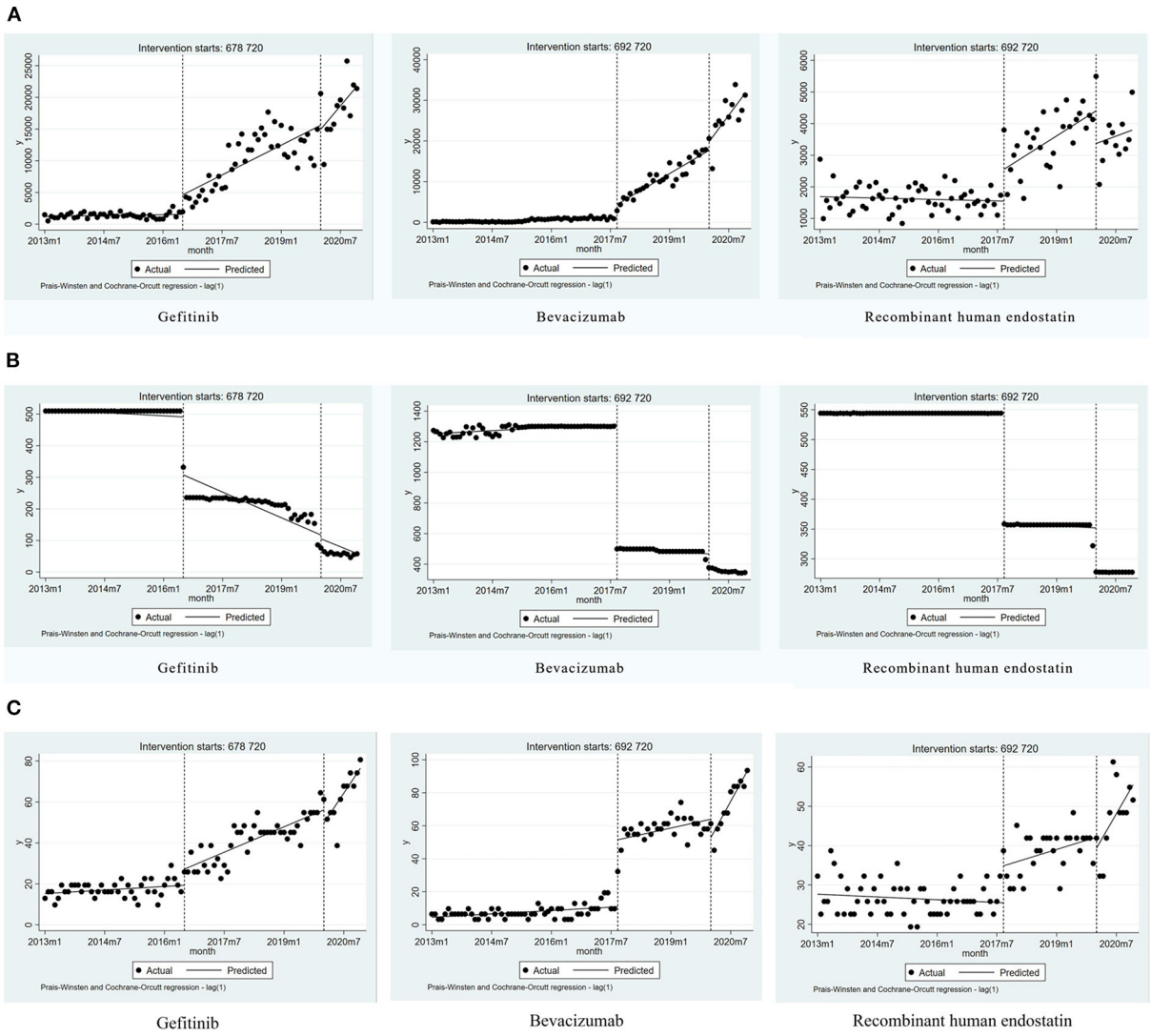

FIGURE 2
Results of the regression analysis of the monthly DDDs, the monthly DDDc, and the availability of study drugs before and after policy implementation. **(A)** The monthly DDDs of gefitinib, bevacizumab, and recombinant human endostatin. **(B)** The monthly DDDc of gefitinib, bevacizumab, and recombinant human endostatin. **(C)** The availability of gefitinib, bevacizumab, and recombinant human endostatin.

generalized least square estimator (GLSE) was used to correct any autocorrelation. The databases and plots were constructed using Excel 2020, and STATA v.16 software was used for statistical analysis. The test level was two-sided test $\alpha = 0.05$.

Results

ITS analysis of changes in the trend of utilization

Gefitinib was included in the list of insured drugs in July 2016, and bevacizumab and recombinant human endostatin were included in September 2017. The time interval for all drugs was divided into two parts. The DDDs of all three drugs increased significantly after policy implementation ($P < 0.001$, $P < 0.001$, $P = 0.008$). The scatter plots of the observed monthly DDDs are shown in Figure 2. After setting January 2020 as the second policy intervention time, there was no significant difference between the monthly trend after the second intervention point and the monthly trend after the first intervention point for gefitinib ($P = 0.416$) and recombinant human endostatin ($P = 0.750$). However, the trend for bevacizumab increased by 397 per month after the second intervention point ($P = 0.046$, *95%CI* = 10.57, 1,209.81) (Table 2).

TABLE 2 Estimates from the multiple-treatment period's analysis of the impact of health policies on the monthly DDDs, the monthly DDDc, and the availability of the three medicines.

Variable	DDDs			DDDc			Availability		
	β	***P***	***95%CI***	*β*	***P***	***95%CI***	*β*	***P***	***95%CI***
Gefitinib									
Baseline level	1,212.15	0.000	898.95 to 1,525.25	511.60	0.000	508.69 to 514.52	15.23	0.000	12.90 to 17.56
Baseline trend	7.68	0.352	−8.64 to 24.00	−0.13	0.256	−0.35 to 0.09	0.10	0.126	−0.03 to 0.22
Level change	3,086.64	0.000	1,415.19 to 4,757.32	−241.34	0.000	−274.29 to −208.38	7.91	0.006	2.35 to 13.46
Trend change	253.64	0.000	173.87 to 333.41	−2.16	0.000	−3.08 to −1.23	0.59	0.000	0.37 to 0.82
The second level change	−647.57	0.848	−7,330.31 to 6,035.17	−94.37	0.000	−116.72 to −72.02	−6.37	0.282	−18.05 to 5.32
The second trend change	355.01	0.416	−509.00 to 1,219.13	−0.10	0.929	−2.44 to 2.23	1.74	0.009	0.44 to 3.03
Bevacizumab									
Baseline level	−100.65	0.039	−196.10 to −5.20	1252.86	0.000	1,236.90 to 1,268.82	4.51	0.000	2.97 to 6.04
Baseline trend	21.96	0.000	18.60 to 25.33	1.11	0.000	0.74 to 1.48	0.11	0.001	0.05 to 0.18
Level change	3,252.26	0.000	2,568.05 to 3,936.48	−807.23	0.000	−817.31 to −797.15	40.63	0.000	32.32 to 48.93
Trend change	453.68	0.000	403.75 to 503.61	−2.54	0.000	−3.52 to −1.57	0.33	0.152	−0.12 to 0.79
The second level change	2,128.29	0.331	−2,195.59 to 6,452.17	−90.07	0.000	−109.41 to −70.72	−11.15	0.063	−22.93 to 0.63
The second trend change	610.19	0.046	10.57 to 1,209.81	−2.17	0.026	−4.08 to −0.26	3.23	0.000	1.85 to 4.61
Recombinant human endostatin									
Baseline level	1,688.95	0.000	1,487.84 to 1,890.07	544.09	0.000	543.95 to 544.24	27.66	0.000	24.50 to 30.82
Baseline trend	−2.48	0.394	−8.22 to 3.27	0.00	0.241	−0.00 to 0.01	−0.04	0.386	−0.13 to 0.05
Level change	1,006.54	0.000	534.99 to 1,478.09	−184.65	0.000	−188.76 to −180.55	9.40	0.000	4.20 to 14.53
Trend change	68.38	0.000	42.79 to 93.97	−0.28	0.244	−0.74 to 0.19	0.30	0.035	0.02 to 0.58
The second level change	−1,031.83	0.080	−2,190.06 to 126.40	−74.41	0.000	−83.49 to −65.33	−2.79	0.523	−11.41 to 5.84
The second trend change	−27.40	0.750	−198.04 to 143.24	0.29	0.206	−0.15 to 0.75	1.20	0.018	0.21 to 2.20

ITS analysis of changes in the daily cost

Due to the impact of the national pricing negotiations on targeted anti-cancer drugs, the monthly DDDc decreased significantly for gefitinib, bevacizumab, and recombinant human endostatin ($P < 0.001$, $P < 0.001$, $P < 0.001$). After setting January 2020 as the second policy intervention time, we found that the price reduction trend was not significantly different for gefitinib ($P = 0.929$) and recombinant human endostatin ($P = 0.206$). However, after the second policy implementation, there was a decrease in the trend for bevacizumab [$P = 0.026$, 95%CI = (−4.08, −0.26)] (Figure 2, Table 2). The price reduction rate was 71% for bevacizumab, 67% for gefitinib, and 49% for recombinant human endostatin.

ITS analysis of changes in the availability

Eight secondary hospitals and 23 tertiary hospitals in Nanjing were included in the study. The availability of gefitinib, bevacizumab, and recombinant human endostatin increased significantly after the implementation of the NHIC policy ($P < 0.001$, $P = 0.001$, $P < 0.001$). The implementation of the second health policy was associated with a significant increase in the trend for gefitinib [$P = 0.009$, 95%CI = (0.44, 3.03)], bevacizumab [$P < 0.001$, 95% CI = (1.85, 4.61)] and recombinant human endostatin [$P = 0.018$, 95%CI = (0.21, 2.20)] (Figure 2, Table 2). The mean availability of these drugs before the national pricing negotiation was <30% in the surveyed hospitals, and increased to 60.33% after 2020, indicating that the drugs were available at many hospitals.

Changes in affordability

Before the NHIC policy implementation, only generic gefitinib was affordable to urban patients, and neither urban nor rural patients could afford the other targeted drugs. As shown in Table 3, the affordability of the drugs included in this study was 0.49 to 4.42 times the per capita annual disposable income for urban patients, and 1.16–11.31 times that for rural patients prior to policy implementation. After insurance coverage, the affordability was 0.2–0.33 times the per capita annual disposable income for urban patients, and 0.52–0.77 times that for rural patients in 2017. Due to the reduction of prices and the improvement of capita per-capita annual disposable income levels, the affordability of these drugs has increased every year after the implementation of the insurance policy (Table 3). The

TABLE 3 The change in patient affordability for mPFS treatment courses before and after the pricing negotiations.

Variable	Specification	DDD (mg)	Treatment course based on mPFS (M)	Year	Affordability before policy		Affordability after policy			
					Patient without PAP	Patient with PAP				
Gefitinib (branded drug)	2,500 mg	250	4.6	2016	*U*:1.43; *R*:3.37	*U*:1.43; *R*:3.37				
				2017			*U*:0.30; *R*:0.77			
				2018				*U*:0.27; *R*:0.63		
				2019					*U*:0.25; *R*:0.58	
				2020						*U*:0.17; *R*:0.38
Gefitinib (generic drug)	2,500 mg	250	4.6	2017	*U*:0.49; *R*:1.16					
				2018			*U*:0.20; *R*:0.52			
				2019				*U*:0.06; *R*:0.14		
				2020					*U*:0.03; *R*:0.06	
Bevacizumab	100 mg/4 ml	25	6.1	2017	*U*:4.42; *R*:11.31	*U*:2.90; *R*:7.41				
				2018			*U*:0.31; *R*:0.73			
				2019				*U*:0.29; *R*:0.67		
				2020					*U*:0.21; *R*:0.47	
Recombinant human endostatin	15 mg/2.4 × 105 U/3 ml	8.5	6	2017	*U*:1.82; *R*:4.64					
				2018			*U*:0.33; *R*:0.77			
				2019				*U*:0.30; *R*:0.71		
				2020					*U*:0.22; *R*:0.51	

The per capita annual disposable income:2016 CNY 49,998 in the urban area and CNY 21,156 in the rural area; in 2017 CNY 54,528 in the urban area and CNY 21,333 in the rural area; in 2018 CNY 59,308 in the urban area and CNY 25,263 in the rural area;2019 CNY 64,372 in the urban area and CNY 27,636 in the rural area;2020 CNY 67,553 in the urban area and CNY 29,621 in the rural area.
U, Urban; R, Rural; M, Months.

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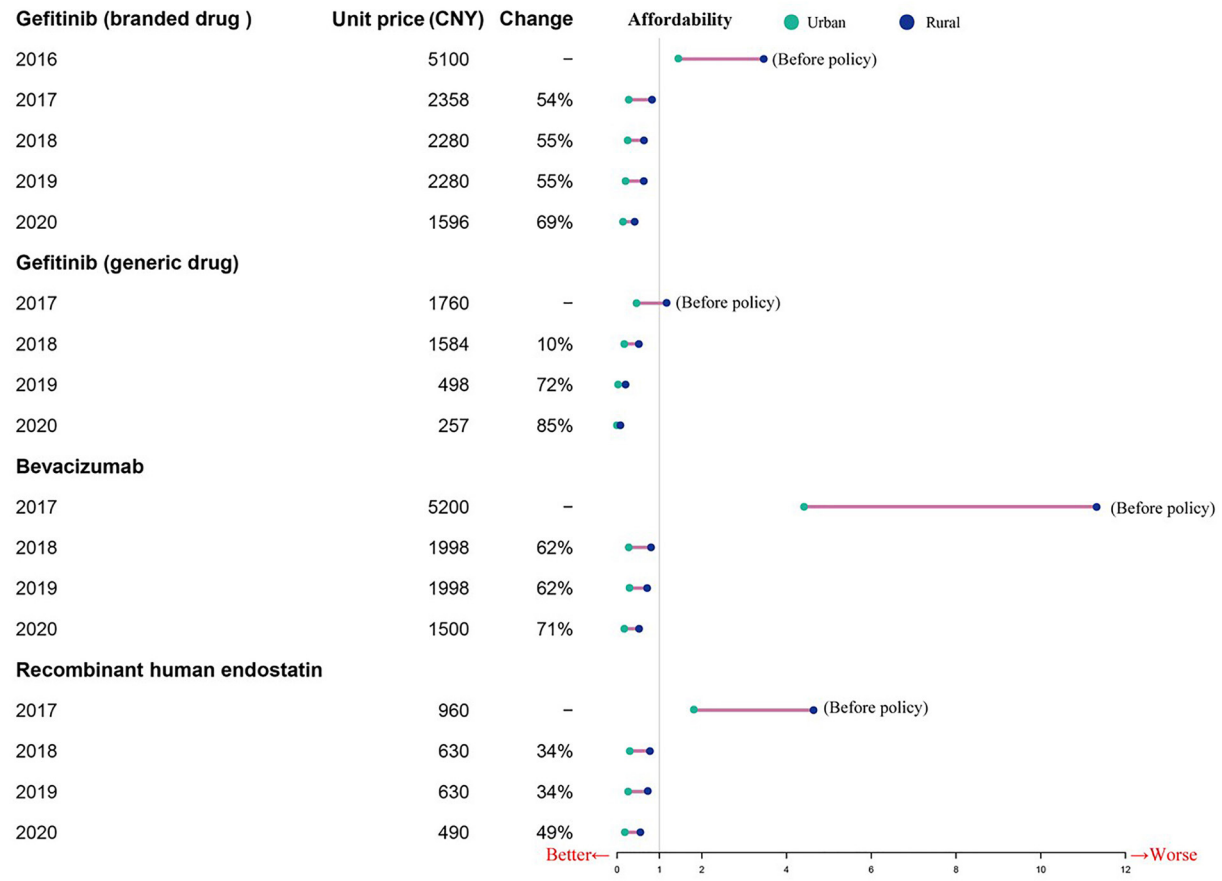

FIGURE 3
Change in affordability for mPFS treatment courses between urban areas and rural areas.

financial burden is higher for the rural patients compared to the urban patients, although the gap is narrowing (Figure 3).

Discussion

The utilization of targeted anti-cancer drugs has increased significantly

Given the high morbidity and mortality of lung cancer in China (49), the consumption of targeted drugs is substantial. We used an interrupted time-series design to conduct segmented regression analyses of the changes in the utilization of three targeted drugs commonly used to treat lung cancer. The national pricing negotiations and health insurance reimbursement policy and have significantly increased the utilization of gefitinib, bevacizumab, and recombinant human endostatin, and the trend was consistent throughout the observation period after the intervention (38). Multiple interventions were further used to estimate the post-intervention trends after the implementation of the national negotiation policy (50).

The monthly trends after the second intervention were not significantly different for gefitinib and recombinant human endostatin, indicating that the revised prices had a lasting positive impact on long-term utilization. However, the trend for bevacizumab was significantly different after the second intervention in January 2020. This change in the trend can be attributed to health insurance reimbursement and the renewal of negotiations in Nanjing, which further boosted its use. In addition, policy implementation resulted in an instantaneous upward effect, indicating that price is one of the key factors affecting the utilization of targeted anti-cancer drugs. Another possible explanation is that the risk associated with targeted anti-cancer drugs has reduced significantly, which is more conducive to clinical use. As the capital of Jiangsu province, the medical and health resources are mainly concentrated in Nanjing. In recent years, with improvement in traffic conditions, the medical institutions in Nanjing can provide health services for the patients from the surrounding cities or rural areas, such as some

cities in Anhui province. It could lead to the steady increase in the volume of patient visits. According to the Nanjing Health Statistics Yearbook, from 2013 to 2020, the incidence of cancer patients with at least one hospital visit increased year by year. Therefore, the usage of three negotiated targeted anti-cancer medicines could be influenced by the number of patient visits during the study period. However, due to lack of control group in this study, we could not perform a qualitative analysis on the impact of patient visits.

The price of the drugs included in this study has declined markedly

The cost of developing innovative anti-cancer drugs has soared in recent years. In order to recover costs and generate profits during the lifetime of the drug patent, pharmaceutical companies have to raise prices. To reduce the burden of health insurance and ensure significant profits for pharmaceutical companies, the government has launched the centralized strategic pricing negotiation policy through bulk sales. The national pricing negotiation policy and the VBP pilot program effectively lowered drug prices and relieved the economic pressure on the beneficiaries of insurance schemes.

Our study shows that the national pricing negotiation has successfully reduced the price of three negotiated targeted anti-cancer drugs. The daily cost of these drugs declined by over 49% after negotiation. A previous study showed that the prices of the three targeted drugs have dropped significantly after the first round of national drug pricing negotiation, with an average reduction of 58.6% (51). Three negotiations that were conducted from 2017 to 2019 for 150 drugs (including 57 targeted anti-cancer drugs), slashed the average daily cost by 54% (17). A nationwide study showed that compared with unregulated antineoplastics, the prices of regulated antineoplastic medications decreased after setting price caps (52). In the United States, Medicare is the most prominent financier for targeted anti-cancer drugs, followed by state Medicaid programs and commercial insurers (53). However, researchers at the University of Texas MD Anderson Cancer Center found that the high drug prices during and after their launch have contributed to increased spending (54). In addition, the price of new anti-cancer drugs has increased over time. Our results show that national pricing negotiation and health insurance reimbursement can successfully achieve OOP control.

In general, with the launch of generic drugs, the price and accessibility of branded drugs may decrease. According to the database of the Nanjing Regional Hospital Drug Analysis System, domestic generic gefitinib and bevacizumab launched in February 2017 and March 2020, respectively, while there was no generic drug for recombinant human endostatin. Our data was retrieved from January 2013 to December 2020. Therefore, whether the launch of generic drugs affects the price and accessibility, our study mainly focuses on the impact of generic gefitinib on branded gefitinib. From Figure 2, we can intuitively see that after generic gefitinib launched in February 2017, the trend of the monthly DDDs, the monthly DDDc, and the availability did not change much, and basically remained at the same level. Therefore, it is temporarily impossible to conclude the impact of the launching of generic drugs on the price and accessibility of branded drugs from the data in this paper.

Positive effects of pricing negotiation, the VBP pilot program and the NHIC policy on drug availability

Implementing the NHIC policy is an important step in guiding the procurement and availability of essential anti-cancer drugs for the public sector. Our findings indicate that the mean availability of the targeted anti-cancer drugs was <30% in Nanjing City prior to the national pricing negotiations. The drugs were available at few hospitals, which were only at full cost as an OOP expense and unavailable in the rest hospitals due to unreliable supply. However, the availability of these drugs increased significantly to 60.33% in 2020 after the implementation of the aforementioned policies and has shown sustained growth in the long term. Some studies have reported greater availability of anti-cancer drugs in private hospitals (71%) compared to public hospitals (43%) (55, 56). Possible reasons for the low availability 7 of drugs in public hospitals include inaccurate estimation of the demand, poorly managed supply chain systems, an underfunded public health sector, or lack of commercial motivation (57). Thus, pricing negotiation can help control pharmaceutical spending for hospitals, which highlights the need to streamline drug procurement, distribution, and supply.

The affordability of patients has improved

Anti-cancer treatments were not affordable for most families, which often led to treatment abandonment (5–8, 54). A retrospective observational study focusing on the utilization of targeted therapies in Taiwan showed that targeted therapies were representing a substantial economic burden (58). The number of days a daily wage worker would have to work to afford anti-cancer treatment depends on the treatment protocol, indications, and the economic output per person. There are significant differences in the affordability of anti-cancer drugs worldwide. Based on individual income, the patients in the low- and middle-income countries have lower affordability compared to high-income countries (59, 60).

We found that the affordability of the three anti-cancer drugs has increased every year after the implementation of the aforementioned policies in Nanjing, although there are still considerable differences between urban and rural areas. And, other studies on the price negotiation system of special medical insurance drugs in 6 typical provinces in China found similar positive effects on affordability of expensive targeted anti-cancer drugs (38, 61). The financial burden of rural patients is higher than that of urban patients, although the gap is narrowing. These differences were driven by national drug pricing negotiations, centralizing procurement, the gap in per capita annual disposable income and lower ratios of individual payment needed after the implementation of NHIC policy. Moreover, the affordability of individual patients is transient since multiple clinical examinations, standard tests, and chemotherapy over a long period incur high total costs. Therefore, a supplementary measure should be in place to top up the basic cover offered by the basic social health insurance schemes.

Pricing negotiations, centralizing procurement, and implementation of the NHIC policy can promote the utilization and affordability of anti-cancer drugs. This indicates that the cost of anti-cancer treatments and the affordability of individual patients were the major factors contributing to the inequity. Therefore, the cost and affordability should be taken into consideration when negotiating medicine procurement terms. Consistent with other previous findings, the barriers to the accessibility of negotiated targeted anti-cancer drugs include high prices, limited coverage of public insurance schemes (62), inequality across insurance schemes, regional variations (59), non-availability of the medicine at the facilities, and updated clinical diagnosis and treatment standards (63). This in turn could be due to the differences in the high cost of anti-cancer drugs, the burden of disease, disease priorities, the capacity of the health insurance system, government budget management, regional economic development, and unequal diagnosis and treatment capacities of medical institutions (64, 65).

To the best of our knowledge, this is the first study to measure the accessibility of anti-cancer drugs over an 8-year period after national health policy implementation. We analyzed 96 months of data before and after the policy was implemented to comprehensively assess the long-term influence of government health policy. Furthermore, ITS analysis for single and multiple treatment periods was used to compare the trends in utilization, price, and availability of anti-cancer drugs. We demonstrated the impact of national health policy based on multiple interventions, by estimating post-intervention trends separately following pricing negotiations, NHIC policy and the VBP pilot program. Nonetheless, there were a few limitations in the study. Due to limited data access, only one city was included in our study, and the results may not be generalized to the other regions of China, especially for backward areas. As far as we know, the social security agency of Nanjing had put kinds of negotiated drugs into the scope of Special Medicine Management System since 2017. The management model of medical institutions, responsible physicians, retail pharmacies and infusion centers was implemented in Nanjing city. Gefitinib and recombinant human endostatin were included in the scope of Special Medicine Management System in 2017, and bevacizumab was included in 2018 (66). In addition, private hospitals and retail pharmacies were not included in our study. This could indeed have an impact on the accessibility of drugs in the hospital channel. The inclusion of more purchasing data from different medical institutions may help reduce the selection bias to a certain extent.

Conclusion

Trends in the accessibility of targeted anti-cancer drugs increased significantly after the implementation of the national pricing negotiation, the NHIC policy and the VBP pilot program and showed sustained long-term growth. Lower drug prices relieve the economic pressure on the beneficiaries of the insurance schemes and achieve OOP control. However, the further study aims to generate evidence to inform the government health coverage of negotiated targeted anti-cancer medicines as a more inclusive and equal policy, through each of the needed patients can get access to the anti-cancer medicines regardless of regional variations, types of cancer, or the ability to pay. In the future, multi-pronged supplementary measures and policy approaches by multiple stakeholders (government, financiers, and pharmaceutical companies) such as national price negotiation, PAPs, efficient resource allocation, issuance of compulsory licenses for procurement, and other special marketing arrangements will facilitate equitable access and use of effective and affordable innovative anti-cancer drugs.

Data availability statement

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

Author contributions

XL and YL conceptualized and designed the whole study. YL and HY were responsible for collecting and analyzing data. YL drafted the initial manuscript. KF took the responsibility for editing. All authors contributed to the critical revision of the manuscript and approved the final version.

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Conflict of interest

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

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Cost-utility analysis of centrally inserted totally implanted access port (PORT) vs. peripherally inserted central catheter (PICC) in the oncology chemotherapy

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Background: Peripherally inserted central catheter (PICC) and centrally inserted totally implanted access port (PORT) are two types of intravenous infusion devices that are widely used in clinical practice. PORTs are more expensive to insert than PICCs but have fewer complications. Two cost-utility analyses of PICCs and PORTs in China have been published, but had conflicting findings. This study aimed to compare the cost-utility of PICCs and PORTs.

Methods: We conducted a prospective observational trial including 404 patients with cancer and a cross-sectional study to calculate cost and complications of a PICC and PORT. Utility was measured using the EuroQol five-dimensional questionnaire (EQ-5D-5L). A cost-utility analysis was performed from a healthcare system perspective in China.

Results: The average total cost of PICCs and PORTs were ¥ 4,091.7 and ¥ 4,566.8, which yielded 0.46 and 0.475 quality-adjusted life-years (QALYs) in a 6-month dwell time, respectively. The incremental cost-utility ratio (ICUR) was ¥ 31,670.9 per QALY. A one-way sensitivity analysis showed that the base-case results were robust, and the probabilistic sensitivity analysis showed that at a willingness-to-pay (WTP) threshold of ¥ 80,976 per QALY (China's per capita GDP in 2021) the probability of a PORT being cost-effective was 96%.

Conclusion: PORTs were more cost-effective than PICCs for a 6 and 12-month dwell time. The total cost for a PORT was also less than that of a PICC. PORT is therefore recommended as a medium to long-term intravenous delivery device in clinical practice.

KEYWORDS

central venous catheter, peripherally inserted central catheter (PICC), centrally inserted totally implanted access port (PORT), quality of life, cost-utility analysis, chemotherapy

Introduction

The rate of cancer diagnosis continues to rise in China. In 2017, the total cancer expenditure for Chinese residents reached RMB 304.84 billion, with a per capita treatment cost of RMB 50,000 (1). Chemotherapy is currently one of the most effective methods for treating cancer. However, the repeated venous punctures needed for chemotherapy may lead to vascular injury and most chemotherapy drugs have strong irritant and corrosive effects if extravasated, resulting in side effects such as phlebitis (2). To protect the patient's blood vessels from corrosive chemotherapeutic drugs and reduce their pain, central venous catheters are widely used in clinical practice (3). In addition to delivering chemotherapeutic drugs, central catheters can also be used for bolus or maintenance nutrient solutions, drugs or blood products (4).

Centrally inserted totally implanted access ports (PORT) and peripherally inserted central catheters (PICC) are two widely used medium- and long-term intravenous infusion devices. Both can safely infuse stimulating drugs while protecting the patient's blood vessels (5–7). Many clinical studies have shown that the probability of PICC-related complications is higher than that of PORT-related complications (8–10), in particular with respect to retention time and the increased pain of repeated venous punctures (11). However, since the cost of PORT implantation is twice that of PICC, PICCs are used more often clinically. Comparative cost analyses of these two catheterization techniques have been performed (12–14), but the health outcomes of patients who receive these two types of catheters have not. There are currently two studies in China that have performed a comparative cost-utility analysis for these catheters (15, 16). However, they reported opposite findings, and the cost of PORT insertion has decreased as the centralized purchase catalog continues to be adjusted. The pharmacoeconomic evidence regarding these two techniques must be updated to ensure appropriate clinical and health care decision-making.

This study prospectively collected the complication rates, direct medical costs and health outcomes associated with PICC and PORT used in individual patients. We then calculated the incremental cost-utility ratio (ICUR) of these two placement methods from the perspective of the healthcare system and at a threshold of China's GDP per capita in 2021 in order to measure the economic impact of these catheters.

Materials and methods

Study design and participants

Patients with PICCs and PORTs implanted at a tertiary-referral hospital in Zhejiang from April 6, 2021 to May 6, 2021 were selected for this study. Inclusion criteria were: (1) patients ≥18 years old; (2) oncology patients requiring long-term intravenous infusion; (3) initial PICC or PORT placement; and (4) no contraindications to the implantation of PICC or PORT. Exclusion criteria were: (1) clinically significant upper extremity/central deep venous thrombosis; (2) unable to communicate or suffering from psychiatric disease. This study lasted for 1 year. Demographic and clinical information, costs, health outcomes and patient data such as age, gender and disease diagnosis were collected prospectively from the electronic case system. Complication rates were calculated based on follow-up data. A cost-utility analysis was performed using health economics methods, with the primary endpoint being the removal of the catheter. The PORT and PICC groups were enrolled according to clinical practice, with no alterations in patient care throughout the study. For study purposes, the PICC group was considered the control group and the PORT group was the experimental group.

Ethical approval was granted by the Cancer Hospital of The University of the Chinese Academy of Sciences (IRB-2020-11). Informed consent was obtained from all patients participating in the study.

TABLE 1 Adverse effects.

Adverse effects	PICC ($n = 202$)	PORT ($n = 202$)
Catheter-related thrombosis	5 (2.5%)	1 (0.5%)
Catheter occlusion	12 (5.9%)	8 (4%)
Migration	12 (5.9%)	1 (0.5%)
Infection	5 (2.5%)	5 (2.5%)
Eczema	21 (10.4%)	4 (2%)
Other	4 (2%)	6 (3%)

Data are presented as n (%). PICC, peripherally inserted central catheter; PORT, Centrally inserted totally implanted access port.

Adverse effects

Adverse effects were collected starting the day after catheter placement. The main complications associated with central venous catheterization are shown in Table 1. Patients were followed up 1, 3, 6, and 12 months after PICC or PORT insertion.

Cost

Only direct medical costs were considered from the perspective of the Chinese healthcare system. Cost information was collected in four parts: insertion cost, maintenance cost, complication cost and removal cost. All costs were measured by the Cancer Hospital of The University of Chinese

TABLE 2 Distribution type and input values for the sensitivity analysis.

Groups	Variable	Base-case value (¥)	Range in the sensitivity analysis	Distribution used in the probabilistic sensitivity analysis
PICC	Insertion cost	1,986.22	1,377.5∼2,169.5	Gamma
	Maintenance cost	1,982.85	1,624.13∼2,236.67	Gamma
	Thrombosis cost	2,244.98	1,330.36∼3,159.6	Gamma
	Infection cost	2,158.44	1,245.48∼4,212	Gamma
	Incidence of catheter-related thrombosis	2.50%	2.5∼11%	Beta
	Incidence of catheter occlusion	5.90%	1∼8%	Beta
	Incidence of migration	5.90%	1∼8%	Beta
	Utility	0.92	0.9∼0.94 (95%CI)	Beta
PORT	Insertion cost	3,546.37	2,837.1∼4,255.64	Gamma
	Maintenance cost	923.72	547.5∼1,108	Gamma
	Thrombosis cost	2,244.98	1,330.36∼3,159.6	Gamma
	Infection cost	2,158.44	1,245.48∼4,212	Gamma
	Incidence of catheter-related thrombosis	1.50%	1.5∼8%	Beta
	Incidence of catheter occlusion	4%	0.5∼4.8%	Beta
	The incidence of infection	1.50%	1.5∼8%	Beta
	Utility	0.95	0.94∼0.96 (95%CI)	Beta

PICC, peripherally inserted central catheter; PORT, Centrally inserted totally implanted access port.

TABLE 3 Demographic characteristics.

		All patients			Patients after PSM		
		PICC	PORT	*p*-value	PICC	PORT	*p*-value
		$n = 313$ (%)	$n = 273$ (%)		$n = 202$ (%)	$n = 202$ (%)	
Age		57.54 ± 11.60	57.23 ± 10.84	0.513$^{\alpha}$	57.61 ± 11.02	57.45 ± 10.74	0.802$^{\alpha}$
Sex	Male	184 (58.79)	90 (32.97)	<0.05$^{\beta}$	77 (38.12)	77 (38.12)	>0.05$^{\beta}$
	Female	129 (41.21)	183 (67.03)		125 (61.88)	125 (61.88)	
Diagnosis	GI cancer	56 (17.89)	33 (12.09)	<0.05$^{\beta}$	38 (18.81)	39 (19.3)	0.91$^{\beta}$
	Lung cancer	72 (23.00)	36 (13.19)		44 (21.78)	35 (17.33)	
	Gynecological cancer	39 (12.46)	64 (23.44)		38 (18.81)	26 (12.87)	
	Breast cancer	23 (7.35)	98 (35.90)		22 (10.89)	65 (32.18)	
	Nasopharyngeal carcinoma	47 (15.02)	0 (0)		19 (9.41)	0 (0)	
	Other	76 (24.28)	42 (15.38)		41 (20.3)	37 (18.32)	

PICC, peripherally inserted central catheter; PORT, centrally inserted totally implanted access port; GI, gastrointestinal;**α**, Student t-tests; **β**, X^2-test; PSM, Propensity score matched.

Academy of Sciences. Insertion and removal costs were one-time costs. As the maintenance cycle is different for PICCs and PORTs, with PICCs being maintained once a week and PORTs once a month, the maintenance cost was equal to single maintenance cost × maintenance times. The common management measures for catheter-related complications were obtained by consulting specialists and then calculating the complication cost based on the published prices of drugs and tests at the Cancer Hospital of The University of Chinese Academy of Sciences.

Utility

Utility was assessed by performing a cross-sectional study from April 6, 2021 to May 6, 2021. We chose the EuroQol five-dimensional (EQ-5D-5L) questionnaire to assess patients with PICCs or PORTs. The EQ-5D-5L scale has the highest rate of citation and recommendation in national guidelines, and the 5L questionnaire is more sensitive and accurate than the 3L questionnaire for measuring health status (17–19). Respondent health utility values were calculated according to

TABLE 4 Utility of PICC and PORT.

Group	Number	Mean	SE	*P*-value
PICC	104	0.92	0.0938	$F = 18.211$
PORT	91	0.95	0.0595	$P < 0.01$

PICC, peripherally inserted central catheter; PORT, Centrally inserted totally implanted access port.

the Chinese EQ-5D-5L point system formula (20), with higher scores representing better health-related quality of life.

Cost-utility analysis

In this study, incremental cost-utility-ratio (ICUR) was calculated to compare the cost-utility of PICC and PORT under the threshold of willingness-to-pay (WTP). If the ICUR was less than the WTP, PORT was considered more cost-effective than PICC. If the ICUR was greater than the WTP, PORT was not more cost-effective than PICC.

$$ICER = \frac{COST_{PORT} - COST_{PICC}}{QALY_{PORT} - QALY_{PICC}}$$

Sensitivity analyses

We performed sensitivity analyses to evaluate the uncertainty and robustness of the base-case result. A one-way sensitivity analysis was used to assess the cost of PICC and PORT insertion, maintenance cost, complication rates and health utility values. The range of PICC and PORT costs was obtained from physician surveys, and complication and utility rates were obtained from prior literature. In the probabilistic sensitivity (PSA) analysis, 1000 Monte Carlo simulations were performed based on the distribution of the parameters. The range and distribution of these parameters are shown in Table 2.

Result

Patients

To reduce selection bias and balance patient baseline characteristics, participants were matched 1:1 for age, gender and diagnosis using a propensity match score (PSM) with a caliper value of 0.005 (21). A difference was considered statistically significant if $P < 0.05$ (14). A *t*-test, chi-square test or Fisher's exact test was used to compare the baseline characteristics of the patients matched by PSM. A total of 404 patients were included after PSM matching, 202 patients in each group. Patient baseline characteristics are shown in Table 3.

Cost

There was a significant difference in the dwell time of PICCs vs. PORTs [PICC (143.4 ± 7.5), PORT (337.6 ± 5.4), $P < 0.01$], and the maintenance cycle of PICCs and PORTs was different. PICCs were maintained once a week while PORTs could be maintained once a month. The average daily maintenance costs of PICCs and PORTs were therefore calculated at 6 months and 12 months with tubes, respectively.

Utility

A questionnaire survey was performed on 104 patients with PICCs and 91 patients with PORTs for long-term intravenous drug administration. Utility values were higher in the PORT group (0.95) than in the PICC group (0.93, $p < 0.05$), which was similar to what was reported by a previous study (17). Findings are shown in Table 4.

Cost-utility analyses

Patients who had a PICC for 6 months had a total cost of ¥4,091.7 and 0.46 QALYs, while patients who had a PORT for 6 months incurred a total cost of ¥4,566.8 and 0.475 QALYs. Patients with a PICC for 12 months had a total cost of ¥6,089.6 and 0.92 QALYs, while patients with a PORT for 12 months had a total cost of ¥5,497.5 and 0.95 QALYs. The cost of using a PICC for 12 months was greater than that of a PORT, making PORT the better option with respect to both cost and utility. The results of the economic analysis of using a PICC and PORT for 6 months are shown in Table 5.

Sensitivity analyses

As shown in Figure 1, the one-way sensitivity analysis shows that all uncertainties vary within reasonable limits, with the maintenance cost of using a PICC having the greatest impact on the results of the underlying analyses. The PSA results show that under a WTP = 80,976¥/QALY (China's GDP per capita in 2021) threshold, the probability of a PORT being more economical was 96.2%. The cost-effectiveness acceptability curve shows that the probability of a PORT being economical at WTP = 30,000¥/QALY is 50%, and the probability of PORT being cost-effective when WTP was double GDP per capita was 96% (Figures 2, 3).

TABLE 5 Base-case result.

Group	Cost (¥)	Effect (QALYs)	Incremental cost (¥)	Incremental effect (QALY)	ICUR (¥/QALY)
PICC	4,091.709473	0.46			
PORT	4,566.772369	0.475	475.0628962	0.015	31,670.85975

QALY, quality-adjusted life-year; ICUR, incremental cost-utility ratio.

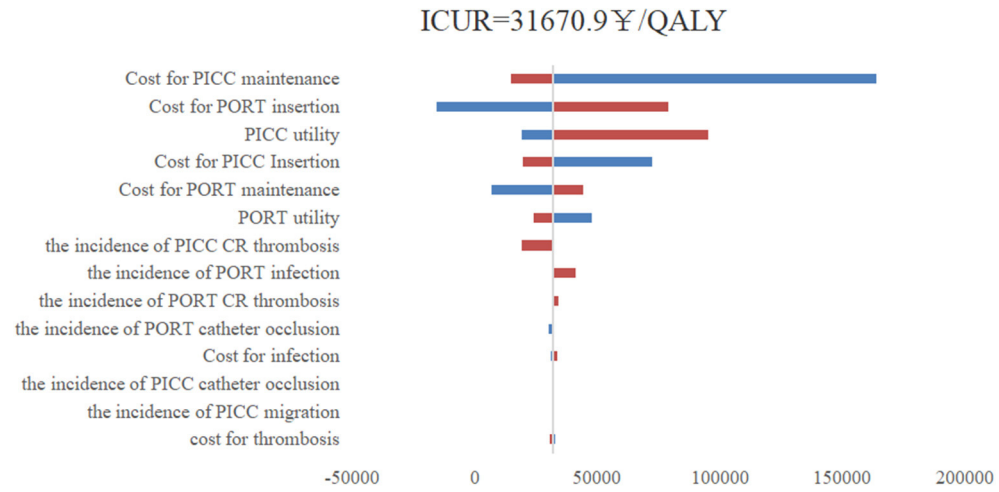

FIGURE 1
One-way sensitive analysis; PICC, peripherally inserted central catheters; PORT, centrally inserted totally implanted access port; QALY, quality-adjusted life -year; ICUR, incremental costutility ratio; CR, catheter-related.

Discussion

This study provides a comparative health economics analysis of the costs and health outcomes of PORTs and PICCs as medium and long-term intravenous access for oncology patients from a healthcare system perspective. Although the total insertion cost of a PORT was higher than that of a PICC, due to the high maintenance cost of PICCs and the high incidence of complications, the ICUR of PICCs vs. PORTs was 31,670.9 ¥/QALY at 6 months of intravenous administration. Under the WTP we set (2021 GDP per capita), the use of a PORT was economical. At 12 months of intravenous administration, PORTs were the overwhelmingly superior solution.

In our one-way sensitivity analyses, the maintenance cost of PICCs had the greatest impact on our results, followed by the insertion cost of a PORT, the utility of using a PICC, the insertion cost of a PICC and the maintenance cost of a PORT. The cost of PICCs and PORTs were the main factors that affected their economic results, in particular the maintenance cost of the intravenous infusion device, which accumulated over time. The insertion cost of the PORT was higher than that of the PICC, but the PICC had a shorter maintenance cycle and costs therefore accrued quickly. PORTs therefore became more economical as the duration of use increased.

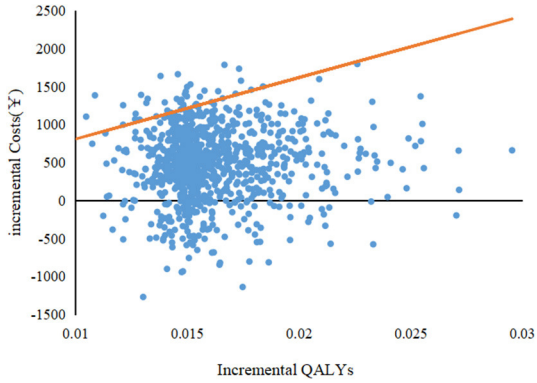

FIGURE 2
Probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

A cost-utility analysis of PORTs and PICCs was previously performed in China. Wang et al. found that the cost-effectiveness ratio of full PICC placement was lower than that of a PORT when the catheter was left in place for ≤12 months (15),

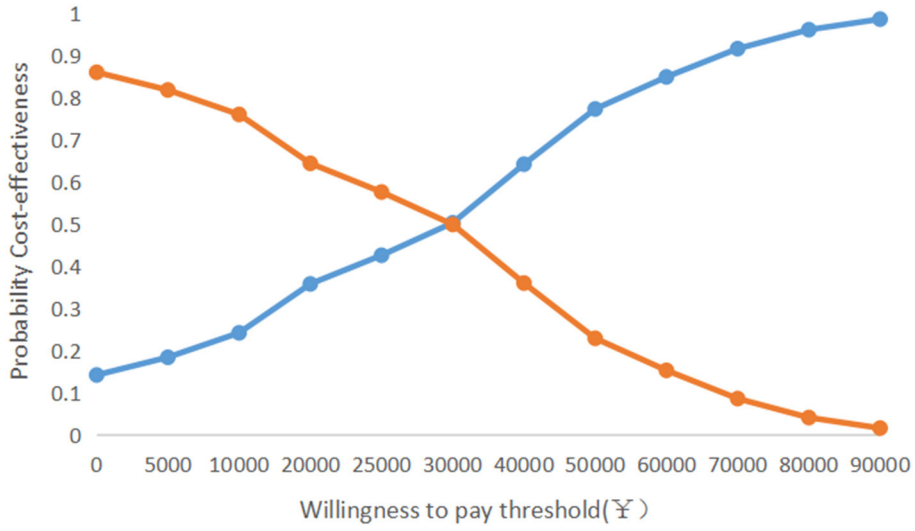

FIGURE 3
Cost-effectiveness acceptability curve.

and that the cost-effectiveness ratio was better over this period. The different results of our work may be due to the significant reduction in the cost of PORTs over time and the different evaluation perspectives (provider perspectives) adopted by the two studies. Our study is consistent with the findings of Litian et al. (16), who used a similar evaluation approach to analyze the costs and health outcomes of the full PICC and PORT retention process from a social perspective. However, the data for that study was derived from a meta-analysis and the PORT had not yet experienced a significant price reduction at the time of publication.

This study has the following limitations. First, at the time that this study was conducted, there was a high rate of withdrawal of PICC patients in the short term due to complications or the end of treatment. This may have affected the collection of complications associated with PICCs at a later stage and led to an artificially low reported incidence of PICC complications. Second, utility was collected via a cross-sectional survey with a small sample size. Assessing the utility of patients who are bedridden or have limited mobility makes it unclear if different intravenous delivery devices will have an appreciable impact on their quality of life. A future multicenter health economics study may yield more accurate results.

Conclusion

This study investigated the economics of two intravenous infusion devices, PICC and PORT, for a 6 and 12-month indwelling time using a cost-utility method based on real-world individual patient data. We found that despite the high cost of a PORT, patients had a higher quality of life and fewer adverse events, making it economical for a 6-month indwelling time. At 12 months the cumulative cost of a PORT was lower than that of a PICC. PORTs also had superior health outputs than PICCs, making it an absolutely superior option. The results of this study provide a theoretical basis for preferentially recommending PORTs as intravenous infusion conduits.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Cancer Hospital of the University of Chinese Academy of Sciences (IRB-2020-11). The patients/participants provided their written informed consent to participate in this study.

Author contributions

The conception and design of this study were primarily conducted by GS. The drafting of the article was mainly the responsibility of XZ. All authors have reviewed the analysis, interpretation of the data, contributed to the drafting of the

manuscript, revised the manuscript for important intellectual content, approved the final version to be published, and agree to be accountable for all the aspects of this study.

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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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Socioeconomic inequality in health care use among cancer patients in China: Evidence from the China health and retirement longitudinal study

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Background: Cancer is a major public health problem worldwide and the leading cause of death in China, with increasing incidence and mortality rates. This study sought to assess socioeconomic-related inequalities in health care use among cancer patients in China and to analyze factors associated with this disparity.

Methods: This study used data collected for the China Health and Retirement Longitudinal Study in 2018. Patients who reported having cancer were included. The annual per capita household expenditure was classified into five groups by the quintile method. We calculated the distribution of actual, need-predicted, and need-standardized health care use across different socioeconomic groups among patients with cancer. The concentration index (CI) was used to evaluate inequalities in health care use. Influencing factors of inequalities were measured with the decomposition method.

Results: A total of 392 people diagnosed with cancer were included in this study. The proportion of cancer patients who utilized outpatient and inpatient services was 23.47% and 40.82%, respectively, and the CIs for actual outpatient and inpatient service use were 0.1419 and 0.1960. The standardized CIs (CI for outpatient visits = 0.1549; CI for inpatient services = 0.1802) were also both positive, indicating that affluent cancer patients used more health services. The annual per capita household expenditure was the greatest factor favoring the better-off, which contributed as much as 78.99% and 83.92% to the inequality in outpatient and inpatient services use, followed by high school education (26.49% for outpatient services) and living in a rural village (34.53% for inpatient services). Urban Employee Basic Medical Insurance exacerbated the inequality in inpatient services (21.97%) while having a negative impact on outpatient visits (−22.19%).

Conclusions: There is a pro-rich inequality in outpatient and inpatient services use among cancer patients in China. A lower socioeconomic status is negatively associated with cancer care use. Hence, more targeted financial protection for poor people would relieve cancer patients of the burden caused by the high cost of cancer care.

KEYWORDS

inequality, health care use, cancer patients, concentration index, China

Introduction

Cancer is a major public health problem globally and has become the leading cause of death and illness in China (1). The International Agency for Research on Cancer estimated that 19.3 million cancer cases were newly diagnosed worldwide and nearly 10.0 million cancer-related deaths occurred in 2020 (2). With a rapidly aging population worldwide and an increase in unhealthy lifestyles, cancer has been identified as the primary cause of death, reducing the survival time of cancer patients (3). An estimated 4.6 million new cancer cases and 3.0 million cancer deaths occurred in China in 2020 (4). China had a slightly lower cancer incidence rate but substantially higher cancer mortality compared to other countries (5).

Developing countries accounted for >56% of the total new annual incidence of cancer patients, with a total cancer-related mortality rate of 64% (6). Lung and bronchus cancer was commonly diagnosed and identified as the leading cancer killer in China, with ∼781,000 new cases and 626,000 deaths every year, followed by stomach, esophageal, liver and colorectum cancers (7). In 2015, the mortality attributed to these five types of cancer accounted for about three-quarters of all cancer mortality (5). In addition, 16.6% of the total disease burden (measured in DALYs) were attributed to cancer in China (8). Meanwhile, studies have found that cancer patients often bear considerable medical expenditure. The overall incidence rate of catastrophic health expenditure in cancer patient families was estimated at 60.0% (9, 10). Patients with cancer from socioeconomically disadvantaged households were particularly financially vulnerable due to the high costs of cancer care, which prevented them from accessing health care. Health care use by cancer patients in lower socioeconomic status groups was limited (11, 12). A systematic review based on cancer inequalities studies has concluded that there were statistically significant socioeconomic inequalities in cancer biological and precision therapy utilization, and a 1.2-fold gap in cancer therapies treatment between cancer patients with the lowest socioeconomic status and the highest socioeconomic status was observed (13). The rich cancer patients tended to use more health care. In addition, health care costs might be particularly challenging for those without health insurance who were more likely to pay greater out-of-pocket costs (14). Hence, the disparity in health care use in China remains a major issue to maximizing total health.

The inequality in health has been a major priority of the health system globally (15). Several studies have contributed an extensive amount of research on the many different dimensions of cancer outcome inequality (16–19), including reporting gradients in cancer incidence, mortality, and survival were associated with deprivation and lower socioeconomic status. However, socioeconomic inequalities in health care use or behavior among cancer patients remain largely unexplored, although this type of inequality has also been observed in some high-income countries, such as South Korea, Australia, and England (20–22).

Previous studies have highlighted systematic differences in cancer care use, with higher incidence rates and inadequate use being more prevalent in lower socioeconomic status groups. Moreover, income substantially affected the use of health care (23). However, existing research has only focused on the association between socioeconomic status and health care use inequalities among cancer patients; to date, the effects of other socioeconomic and need factors remain unclear. Furthermore, no systematic analysis of health care use inequality and influencing factors among cancer patients in China has been published. Hence, this study sought to close these gaps by measuring socioeconomic inequalities in health care use among patients with cancer in China in order to determine which areas will require more attention in the future.

Methods

Study design and data sources

This study was based on data collected from the China Health and Retirement Longitudinal Study in 2018, which was conducted by the China Center for Economic Research of Peking University. The survey used a questionnaire to collect data, such as demographic characteristics, socioeconomic status, social security level, and physical health status of patients. Using a multistage probability-proportional-to-size sampling, a total of 19,507 individuals aged ≥45 years were identified. Patients who were reported as having cancer and had no missing values for dependent variables were considered eligible for inclusion. After excluding those with missing relevant variables, a total of 392 individuals were finally included in this study.

Socioeconomic status

The annual per capita household expenditure was adopted as a proxy for socioeconomic status (24) and used to group individuals into five groups, from the lowest to the highest. The quintile of socioeconomic status categories was determined within each county or district and then pooled across all sampled counties and districts because the level of economic development differed between sampling regions.

Variables

Dependent variables

Two variables of health care use were employed. Patients with cancer were asked if they had visited a public hospital, private hospital, public health center, clinic, or health worker's or

doctor's practice or been visited by a health worker or doctor for outpatient care in the last month (not including for a physical examination) and had they received inpatient care in the past year. The answers to these questions were coded as a dummy variable (0 = no, 1 = yes).

Independent and control variables

The following variables were included to investigate the relationship of socioeconomic status and health care use: gender (male or female), age (45–59, 60–74, or ≥75 years), educational level (primary school or below, middle school, or high school and above), marital status [single (separated/divorced/widowed/never married), married or partnered], employment status (unemployed, employed, or retired), impoverished status (no or yes), region (east, central, west, or northeast), Hukou type (agricultural Hukou or non-agricultural Hukou), region of residence (urban, suburban, or rural), health insurance [no health insurance, Urban Employee Basic Medical Insurance (UEBMI), Urban and Rural Resident Basic Medical Insurance (URRBMI), Urban Resident Basic Medical Insurance (URBMI), New Rural Cooperative Medical Scheme (NRCMS), or another], number of people in the household, physical examination (no or yes), self-reported health status (very good, good, fair, poor, or very poor), disability (no or yes), degree of pain (none, a little, somewhat, quite a bit, or very much), smoking (no or yes), and alcohol consumption (no or yes).

Statistical analysis

Measurement of concentration index

The measurement of the CI proposed by Wagstaff et al. (25, 26) was used to examine the magnitude of socioeconomic inequality according to Equation 1.

$$C = \frac{2}{\mu}\mathrm{cov}(h_i, r_i) \quad (1)$$

where h_i is the measure of actual health service use, μ is its mean and r_i is the relative fractional rank of an individual i in the distribution of the annual per capita household expenditure (i = 1 for the lowest and i = n for the highest).

According to Wagstaff et al. (24), the CI is defined as twice the area between the concentration curve and the line of equality, where a concentration curve plots the cumulative proportion of the use of services (y-axis) against the cumulative percentage of respondents, ranked by the annual per capita household expenditure, beginning with the least affluent and ending with the most affluent (x-axis). The CI ranges from −1 to 1. When the concentration curve lies below the diagonal (45° line), the CI is a positive value, indicating the concentration of health inequality in favor of the rich (pro-rich) (27).

Analysis of decomposition method

The decomposition method proposed by Wagstaff et al. (28) was employed to measure factors associated with inequalities. They demonstrated that the health CI can be decomposed into the contributions of individual factors to income-related health inequality, in which each contribution is the product of the sensitivity of heath with respect to that factor and the degree of income-related inequality in that factor. A decomposition analysis estimates how determinants proportionally contribute to inequality in the use of services. A positive value of contribution to socioeconomic inequality means a positive association with health care use; in other words, the variable increases pro-rich inequality and outpatient or inpatient services is more concentrated in the richer population.

The overall inequality in health services use (C) is written as:

$$C = \sum_j (\beta_j^m \bar{x}_j/\mu)C_j + \sum_k (\gamma_k^m \bar{z}_k/\mu)Ck + GC/\mu \quad (2)$$

where μ is the mean of y, $\bar{x}_j$ is the mean of x_j, C_j and C_k are the CI of need and non-need variables; and GC is the error term of health care.

All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and Stata version 16.0 (Stata Corp., College Station, TX, USA). A two-sided value of 0.05 was considered to be statistically significant.

Results

Social demographic characteristics of cancer patients

A total of 392 cancer-related cases were observed, of which 23.47% had visited for outpatient care during the past month and 40.82% had received inpatient services in the last year. Cancer was most prevalent in male and female individuals aged 60–74 years (50.51%). About 2/3 (62.76%) of patients with cancer reported retirement and unemployment with their cancer diagnosis. Only 16 (4.08%) reported being uninsured. Of note, individuals from socioeconomically disadvantaged households were less likely to seek outpatient and inpatient services compared to better-off individuals. Other descriptive statistics of health care use and cancer patients' characteristics are shown in Table 1.

Distribution of health care use among patients with cancer

Table 2 presents the actual, need-predicted, and need-standardized distribution for outpatient and inpatient services use by cancer patients across socioeconomic status groups. CIs for inequality and concentration curves are also reported.

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TABLE 1 Descriptive characteristics of cancer patients.

	Outpatient visits, *n* (%)		Inpatient services, *n* (%)		Total *N* = 392
	No *n* = 300 (76.53%)	Yes *n* = 92 (23.47%)	No *n* = 232 (59.18%)	Yes *n* = 160 (40.82%)	
Gender					
Male	117 (75.48%)	38 (24.52%)	81 (52.26%)	74 (47.74%)	155 (39.54%)
Female	183 (77.22%)	54 (22.78%)	151 (63.71%)	86 (36.29%)	237 (60.46%)
Age, years					
45–59	111 (78.72%)	30 (21.28%)	93 (65.96%)	48 (34.04%)	141 (35.97%)
60–74	149 (75.25%)	49 (24.75%)	112 (56.57%)	86 (43.43%)	198 (50.51%)
≥75	40 (75.47%)	13 (24.53%)	27 (50.94%)	26 (49.06%)	53 (13.52%)
Educational level					
Primary school or below	204 (77.57%)	59 (22.43%)	153 (58.17%)	110 (41.83%)	263 (67.09%)
Middle school	74 (79.57%)	19 (20.43%)	63 (67.74%)	30 (32.26%)	93 (23.72%)
High school and above	22 (61.11%)	14 (38.89%)	16 (44.44%)	20 (55.56%)	36 (9.18%)
Employment status					
Unemployed	157 (72.35%)	60 (27.65%)	113 (52.07%)	104 (47.93%)	217 (55.36%)
Employed	119 (81.51%)	27 (18.49%)	101 (69.18%)	45 (30.82%)	146 (37.24%)
Retired	24 (82.76%)	5 (17.24%)	18 (62.07%)	11 (37.93%)	29 (7.40%)
Region					
East	113 (76.87%)	34 (23.13%)	95 (64.63%)	52 (35.57%)	147 (37.50%)
Central	89 (76.72%)	27 (23.28%)	64 (55.17%)	52 (44.83%)	116 (29.59%)
West	79 (74.53%)	27 (25.47%)	59 (55.66%)	47 (44.34%)	106 (27.04%)
Northeast	19 (82.61%)	4 (17.39%)	14 (60.87%)	9 (39.13%)	23 (5.87%)
Region of residence					
Urban areas	86 (76.11%)	27 (23.89%)	56 (49.56%)	57 (50.44%)	113 (28.97%)
Suburban areas	27 (75.00%)	9 (25.00%)	21 (58.33%)	15 (41.67%)	36 (9.23%)
Rural village	185 (76.76%)	56 (23.24%)	154 (63.90%)	87 (36.10%)	241 (61.79%)
Socioeconomic status					
Quintile 1 (lowest)	26 (83.87%)	5 (16.13%)	22 (70.97%)	9 (29.03%)	31 (8.01%)
Quintile 2	81 (79.41%)	21 (20.59%)	68 (66.67%)	34 (33.33)	102 (26.36%)
Quintile 3	87 (80.56%)	21 (19.44%)	67 (62.04%)	41 (37.96%)	108 (27.91%)
Quintile 4	71 (71.72%)	28 (28.28%)	46 (46.46%)	53 (53.54%)	99 (25.58%)
Quintile 5 (highest)	32 (68.09%)	15 (31.91%)	25 (53.19%)	22 (46.81%)	47 (12.14%)
Health insurance					
No health insurance	10 (62.50%)	6(37.50%)	12 (75.00%)	4 (25.00)	16 (4.08%)
UEBMI	63 (74.12%)	22 (25.88%)	44 (51.76%)	41 (48.24%)	85 (21.68%)
URRBMI	34 (80.95%)	8 (19.05%)	27 (64.29%)	15 (35.71%)	42 (10.71%)
URBMI	14 (87.50%)	2 (12.50%)	11 (68.75%)	5 (31.25%)	16 (4.08%)
NRCMS	170 (76.23%)	53 (23.77%)	132 (59.19%)	91 (40.81%)	223 (56.89%)
Another†	9 (90.00%)	1 (10.00%)	6 (60.00%)	4 (40.00%)	10 (2.55%)
Self-reported health status					
Very good	14 (87.50%)	2 (12.50%)	12 (75.00%)	4 (25.00%)	16 (4.62%)
Good	20 (86.96%)	3 (13.04%)	17 (73.91%)	6 (26.09%)	23 (6.65%)
Fair	93 (78.15%)	26 (21.85%)	86 (72.27%)	33 (27.73%)	119 (34.39%)
Poor	97 (75.19%)	32 (24.81%)	67 (51.94%)	62 (48.06%)	129 (37.28%)
Very poor	40 (67.80%)	19 (32.20%)	29 (49.15%)	30 (50.85%)	59 (17.05%)

(Continued)

TABLE 1 Continued

	Outpatient visits, *n* (%)		Inpatient services, *n* (%)		Total *N* = 392
	No *n* = 300 (76.53%)	Yes *n* = 92 (23.47%)	No *n* = 232 (59.18%)	Yes *n* = 160 (40.82%)	
Disability					
No	168 (79.25%)	44 (20.75%)	135 (63.68%)	77 (36.32%)	212 (54.08%)
Yes	132 (73.33%)	48 (26.67%)	97 (53.89%)	83 (46.11%)	180 (45.92%)
Pain degree					
None	106 (82.81%)	22 (17.19%)	87 (67.97%)	41 (32.03%)	128 (32.65%)
A little	85 (77.27%)	25 (22.73%)	63 (57.27%)	47 (42.73%)	110 (28.06%)
Somewhat	44 (69.84%)	19 (30.16%)	35 (55.56%)	28 (44.44%)	63 (16.07%)
Quite a bit	29 (74.36%)	10 (25.64%)	19 (48.72%)	20 (51.28%)	39 (9.95%)
Very much	36 (69.23%)	16 (30.77%)	28 (53.85%)	24 (46.15%)	52 (13.27%)
Smoking					
No	193 (78.46%)	53 (21.54%)	157 (63.82%)	89 (36.18%)	246 (62.76%)
Yes	107 (73.29%)	39 (26.71%)	75 (51.37%)	71 (48.63%)	146 (37.24%)

†represents Government Employee Health Insurance.
UEBMI, Urban Employee Basic Medical Insurance; URRBMI, Urban and Rural Resident Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance; NRCMS, New Rural Cooperative Medical Scheme.

TABLE 2 Distribution of actual, need-expected, and need-standardized use of outpatient and inpatient services among cancer patients across different socioeconomic status groups.

Socioeconomic status	Outpatient visits use			Inpatient services use		
	Actual	Need-Expected	Need-Standardized	Actual use	Need-Expected	Need-Standardized
Quintile 1 (lowest)/%	20.47	22.28	19.85	29.92	36.56	31.16
Quintile 2/%	18.33	21.73	18.26	35.00	38.26	34.54
Quintile 3/%	27.63	21.39	27.90	47.37	39.15	46.02
Quintile 4/%	29.63	21.61	29.68	48.15	40.26	45.69
Quintile 5 (highest)/%	24.00	19.27	26.39	52.00	33.55	56.25
All/%	23.39	21.66	23.39	39.18	37.80	39.18
CI	0.1419**	−0.0140	0.1549**	0.1960**	0.0164	0.1802**

CI, concentration index.
*$p < 0.05$, **$p < 0.001$.

The CIs for actual outpatient and inpatient services use were both positive, and the values of the indices for inpatient services were much higher than those for outpatient visits (CI for outpatient visits = 0.1419, $p < 0.05$; CI for inpatient services = 0.1960, $p < 0.05$). With regard to need-expected use, the CI was not statistically significant in both outpatient and inpatient services, and proportionality was not rejected in either case (CI for outpatient visits = −0.0140, $p > 0.05$; CI for inpatient services = 0.0164, $p > 0.05$).

This study also revealed a 1.2-fold gap in outpatient visits use and a 1.3-fold gap in inpatient services use between the lowest income quintile and the highest income quintile after adjustment due to health needs. Indeed, after controlling for the distribution of needs, a significant pro-rich degree of inequality emerged (CI for outpatient visits = 0.1549, $p < 0.05$; CI for inpatient services = 0.1802, $p < 0.05$). As shown in Figures 1, 2, the concentration curves of actual and standardized outpatient and inpatient service use were all below the line of equality.

Decomposition of inequality in cancer care use

Table 3 depicts the decomposition results and the contributions of various factors influencing the inequalities in cancer care use.

Regardless of outpatient and inpatient services use, socioeconomic status made the greatest pro-rich contributions—that is, 78.99% and 83.92%, respectively, —followed by high school education (26.48%

for outpatient services) and living in a rural village (34.53% for inpatient services). UEBMI made a great contribution to the pro-rich inequality in inpatient services (21.97%) while having a negative impact on outpatient visits (−22.19%). NRCMS had the opposite effect, but its contribution was relatively small. Among the need variables, a "health-poor" status (11.85%) and smoking (19.89%) had a positive contribution to the pro-rich inequality, while a "health-fair" status reduced the pro-rich inequality (−17.69% for outpatient services). The other variables provided relatively minor contributions to the inequity, as shown in Table 3.

Discussion

Variations in the use of health care among cancer patients have attracted increased attention from both researchers and policymakers in related areas. To our knowledge, this is the first study to examine the association between socioeconomic status and health care use across different socioeconomic populations in China. Our study analyzed the distribution of the use of outpatient visits and inpatient services among patients with cancer from a perspective of equity. The analysis carried out here highlighted that cancer patients from higher socioeconomic status groups were more likely to use health care than those who were worse off. It was also evident that, after controlling for age, gender, and other need variables, there was a clear socioeconomic gradient in health care use. In addition, socioeconomic status and health insurance interacted to influence the risk of inequality in decomposition models.

In our study, the CIs for outpatient and inpatient services use were all positive, indicating that there was statistically significant inequality in the use of health care among cancer patients, in line with previous studies from South Korea and Australia (20, 21). Richer cancer patients appeared to be much more likely to use health care. In addition, this study revealed a greater extent of inequality compared to other research. A possible explanation may be that our study included individuals aged ≥45 years, and most incidence and deaths of cancer occurred in this age range (5). The health condition of these cancer patients might deteriorate due to inadequate sources of income (29), with the financial burden of age-related health rising (30). Compared to the entire population with cancer, the distribution of health care utilization among middle-aged and elderly cancer patients was more unequal.

Our study showed that higher inequality was generally in inpatient services in China. It could be explained by the fact that hospitalization costs were very high. Medical expenses (including medicines and treatments) and non-medical costs (including transportation, caregiver costs, lost productivity, and loss/reduction of household income) in inpatient services were higher than those in outpatient visits, which exacerbated the burden on health care use (31–33). Hence, cancer patients

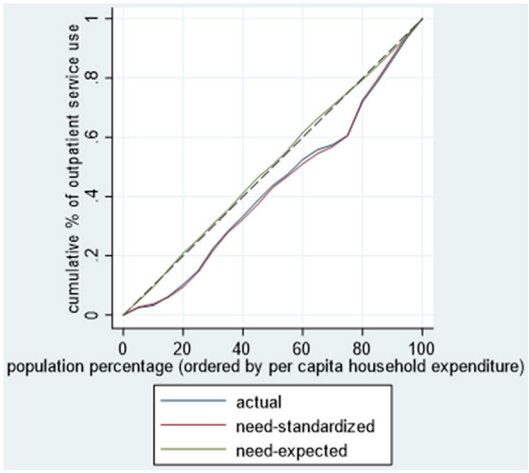

FIGURE 1
Concentration curve for use of outpatient visits among cancer patients.

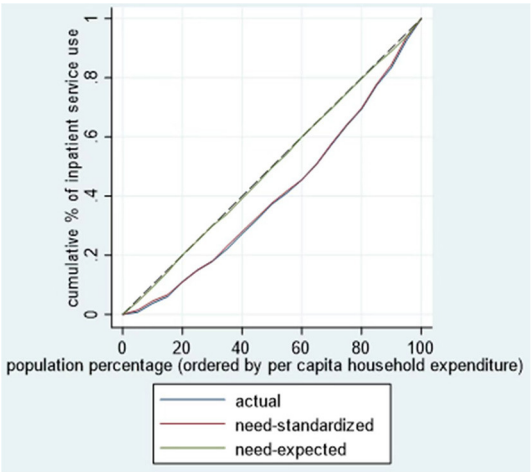

FIGURE 2
Concentration curve for use of inpatient services among cancer patients.

from socioeconomically disadvantaged households could not afford the high medical costs; actually, they tended to abandon medical services or sought cheaper outpatient services instead of inpatient services (34). Meanwhile, a lower socioeconomic status was related to a shorter survival time in cancer patients (11). Cancer patients with a higher socioeconomic status survived long enough to use additional inpatient services. Given this, inequalities in the utilization of inpatient services among cancer patients warrant more attention than disparities in outpatient visits.

We found that inequalities in health care among cancer patients remain largely determined by patients' financial

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TABLE 3 Decomposition of socioeconomic-related inequalities in the use of outpatient and inpatient services among cancer patients.

Variable	Outpatient visits use			Inpatient services use		
	Elasticity	CI	Contribution to CI (%)	Elasticity	CI	Contribution to CI (%)
Gender (ref = male) female	0.7990	−0.0246	−13.86	−0.1245	−0.0246	1.56
Age (ref = 45–60, years)						
60–75	0.1147	−0.0466	−3.77	0.0717	−0.0466	−1.71
≥75	0.0122	0.1163	1.00	0.0027	0.1163	0.16
Educational level (ref = primary school or below)						
Middle school	0.0126	0.1238	1.10	−0.1067	0.1239	−6.75
High school and above	0.1010	0.3724	26.49	0.0411	0.3723	7.79
Marital status [ref = single (separated/divorced/widowed/never married)] married or partnered	0.4027	0.0048	1.35	0.3012	0.0048	0.73
Employment status (ref = unemployed)						
Employed	−0.0196	−0.0133	18.36	−0.1097	−0.1329	7.44
Retired	−0.0396	0.3182	−8.88	−0.0437	0.3180	−7.08
Impoverished (ref = no) yes	0.0009	−0.0841	−0.05	0.0023	−0.0841	−0.10
Region (ref = east)						
Central	−0.0043	0.0388	−0.12	0.0514	0.0388	1.02
West	0.0208	−0.0472	−0.69	0.0419	−0.0472	−1.01
Northeast	0.0064	0.1224	0.55	0.0002	0.1224	0.01
Hukou type (ref = agricultural Hukou)						
Non-agricultural Hukou	0.0248	0.3021	5.28	−0.1673	0.3021	−25.78
Region of residence (ref = urban area)						
Suburban area	−0.0370	0.1825	−4.76	−0.0546	0.1825	−5.09
Rural village	0.0557	−0.1594	−6.26	−0.4246	−0.1594	34.53
The annual per capita household expenditure	1.9040	0.0589	78.99	2.7940	0.0589	83.92
Health insurance (ref = no health insurance)						
UEBMI	−0.1004	0.3137	−22.19	0.1373	0.3137	21.97
URRBMI	−0.0632	−0.1331	5.92	0.0449	−0.1331	−3.05
URBMI	−0.0210	0.1766	−2.62	−0.0063	0.1766	−0.57
NRCMS	−0.0494	−0.1120	3.90	0.1477	−0.1120	−8.44
Another	−0.0174	0.1862	−2.29	0.0074	0.1862	0.71
Number of people in the household	−0.1996	−0.0615	8.66	−0.0444	−0.0615	1.39
Physical examination (ref = no) yes	0.0817	0.1248	7.18	0.2452	0.1248	15.61
Self-Reported health status (ref = very good)						
Good	0.0239	−0.0764	−1.29	−0.0003	−0.0761	0.01
Fair	0.2856	−0.0879	−17.69	−0.0369	−0.0879	1.65
Poor	0.2502	0.0673	11.85	0.1367	0.0672	4.69
Very poor	0.1416	0.1069	10.66	0.0352	0.1069	1.92
Disability (ref = no) yes	0.0580	−0.0736	−3.00	0.1935	−0.0735	−7.25
Pain degree (ref = none)						
A little	0.0624	0.0247	1.01	0.1520	0.0248	1.92
Somewhat	0.1211	−0.0033	−0.28	0.0867	−0.0033	−0.14
Quite a bit	0.0228	0.0989	1.59	0.0561	0.0987	2.82
Very much	0.0744	−0.2036	−10.68	0.0486	−0.2036	−5.05
Smoking (ref = no) yes	0.2150	0.1312	19.89	0.1193	0.1312	7.99
Alcohol consumption (ref = no) yes	−0.0140	0.1157	−1.14	−0.0249	0.1157	1.47

capability in China. The key role of socioeconomic status in health care use was consistent with studies in other countries. Results of an Italy survey of individuals aged >50 years also indicated that income was a positive and significant determinant of use in preventive cancer care use (35). One possible explanation for this may be that, different from other diseases, cancer has more frequent recurrence, shorter disease-free survival, and higher mortality rates (1), placing a substantial economic burden on cancer sufferers and their families. Poor households were most likely to face impoverishment and economic hardship, entering a vicious circle of "poverty from illness and disease from poverty" (13, 36). Health care allocation and use are disproportionately favored by the better-off with higher education levels and, therefore, may widen inequalities further.

It is well-known that health insurance schemes are associated with health care use. Previous studies have shown that insured individuals were more likely to use health care than uninsured ones (37, 38). An incidence-based study that examined socioeconomic inequalities in Australia found that, apart from providing free medical services in public hospitals, Medicare had policies to protect patients from catastrophic health expenditures (31), defined as health-related out-of-pocket costs of ≥40% of total non-food household consumption expenditures (39). In our study, we observed UEBMI's pro-rich contributions to inpatient service use as well as the limited effects of URBMI and NRCMS, indicating that these health insurance schemes failed to protect low-income cancer patients, especially in terms of inpatient services (40). This result can be explained by certain reasons. First, although >96% of patients with cancer were covered by health insurance, UEBMI, URBMI, and NRCMS did not reimburse all medical services and items, especially expensive targeted therapies. Second, about 55.36% of participants with cancer in our study were unemployed, bearing the heavy burden of cancer therapy. In addition, these findings may be attributed to differences in the benefit packages between the different health insurance plans (41). UEBMI had a greater reimbursement rate than other health insurance schemes. The UEBMI beneficiaries were more willing to use expensive drugs and medical compared to the URBMI and NRCMS cancer patients (42). Evidence from an community-based study in China has confirmed that, in order to lessen the compensation gap between different insurances, the expansion of benefits packages should be tailored to differences between cancer patients in terms of income, health needs, and other factors (32).

UEBMI had different implications in outpatient and inpatient services on inequality. It could be explained that the cancer treatment choices varied in the different socioeconomic statuses. Due to the high cost of inpatient services, cancer patients with lower socioeconomic status were more willing to use outpatient services to alleviate, while surgical treatment was often chosen among the rich cancer patients (34). Therefore, for outpatient utilization, the disparities were relatively small. In addition, from the patients' socioeconomic status perspective, cancer patients who were covered by UEBMI were all urban workers or retired workers, they usually had higher income and better education compared to those with URBMI and NRCMS (43). Hence, they had a stronger incentive to utilize health care, which led to the significant effect on inequalities of UEBMI. UEBMI played a role in protecting the lower-income cancer patients from catastrophic health expenditure and had reduced financial burden in outpatient utilization, while cancer patients with higher socioeconomic status used more inpatient services, increasing the inequalities in inpatient utilization.

We did not find an apparent influence in health care use inequalities by age, although greater use by elderly individuals was observed. A possible reason for this result could be found in the sample characteristics, as only 13.52% of participants were aged ≥75 years. However, poverty, limited insurance coverage, education and awareness were factors that contributed to inequalities in cancer patients' health care use, in line with previous reports (32, 36). Wealth, the health insurance benefits package, and high school education increased the use of health care among cancer patients. Higher-income individuals had greater access to education, healthy dietary habits, and cancer care. This was also a good explanation for the pro-rich contribution of socioeconomic status to health care use among patients with cancer. Hence, a sustained reduction in socioeconomic inequalities concerning poverty would promote universal equality in health. In addition, more equitable and effective benefits packages committed to provide financial protection against catastrophic illness, such as expanding the public health insurance coverage of inpatient care to cancer patients, should also be designed.

Our study has some limitations. First, the diagnosis of cancer was self-reported, which might have led to under- or overestimation of the cancer prevalence. The information about health care use was also self-reported, so recall biases could not be avoided. In further research, more data sources and methods should be adopted to control these biases. Second, this study performed a cross-sectional analysis, which prevented us from discussing results based on causal inference. Third, the study sample might be not representative. Our sample size was relatively small and only included individuals aged ≥45 years. Fourth, since URBMI and NCMS have been merged, a comparison between UEBMI and URRBMI could be a better choice in future research (43). Finally, quality or efficiency measures should be included in inequality research; unfortunately, our survey did not provide relevant indicators (44).

Conclusion

Significant differences were seen in the distribution of cancer care use across socioeconomic status groups in China, and a socioeconomic gradient was evident. Socioeconomic status and

health insurance were found to be associated with inequalities. Interventions aimed at reducing inequalities in health care use should focus on improving financial protections for people from socioeconomically disadvantaged households.

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/s.

Author contributions

HZ led the study including the interpretation of the results and manuscript drafting. LS and MC conceived and supervised the study. YF contributed to data analysis and drafting of the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of interest

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

Publisher's note

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Economic evaluation of sintilimab plus chemotherapy vs. pembrolizumab plus chemotherapy for the treatment of first-line advanced or metastatic squamous NSCLC

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Background and objective: Sintilimab has superior efficacy and safety in patients with advanced or metastatic squamous non-small cell lung cancer (NSCLC), but its cost-effectiveness in China is unclear. This study is to evaluate the cost-effectiveness of sintilimab plus chemotherapy vs. pembrolizumab plus chemotherapy for locally advanced or metastatic squamous NSCLC in China.

Methods: From the perspective of the Chinese health system, the partitioned survival model with three health states was established in a 3-week cycle and a lifetime time horizon. The two-stage method was used to estimate the overall survival hazard ratios to avoid the bias by crossover design in ORIENT-12 and KEYNOTE-407 studies. The anchored matching adjusted indirect comparison method (MAIC) was used for indirect comparison based on the individual patient data from ORIENT-12 and the publicly published KEYNOTE-407 study due to the lack of head-to-head clinical trials. Only direct medical costs were included, and utilities were derived from the published literature in the base case analysis. Sensitivity analysis was also performed to verify the robustness of the model results. In addition, the scenario analysis where the utilities were derived from the Quality of Life Questionnaire-Core 30 (QLQ-C30) scale in the ORIENT-12 by mapping to the EuroQol-5-dimension 5-level (EQ-5D-5L) was carried out to explore the uncertainty of the results.

Results: Compared with pembrolizumab + chemotherapy, sintilimab + chemotherapy incurred a lower lifetime cost ($12,321 vs. 36,371) and yielded fewer quality-adjusted life-years (QALYs) (0.9902 vs. 1.0085), which resulted in an incremental cost-effectiveness ratio (ICER) of $1,314,208/QALY. A sintilimab strategy is a cost-effectiveness option under the WTP of 1–3 times the GDP per capita in China ($11,250/QALY~$33,749/QALY). The utility value of the post-progression, the unit cost of albumin paclitaxel, and the utility value of the progression-free state were the main drivers in the deterministic sensitivity

analysis (DSA). According to the probabilistic sensitivity analysis (PSA), sintilimab + chemotherapy was 100% cost-effective when the WTP was 1–3 times China's per capita GDP. The results of the scenario analysis showed that sintilimab + chemotherapy obtained more QALYs (1.2319 vs. 1.1815) and lower costs ($12,321 vs. 36,371), which implied that sintilimab + chemotherapy may dominate the pembrolizumab + chemotherapy.

Conclusion: Compared with pembrolizumab + chemotherapy, sintilimab + chemotherapy is more cost-effective for first-line treatment in Chinese patients with locally advanced or metastatic squamous NSCLC.

KEYWORDS

economic evaluation, NSCLC, PD-1 inhibitors, pembrolizumab, sintilimab

Introduction

Lung cancer has become one of the cancers with the highest morbidity and mortality in the world (1). According to the survey statistics of the International Agency for Research on Cancer in 2018, there were 2,093,876 new lung cancer patients and 1,761,007 new lung cancer deaths worldwide 2018, accounting for 11.6% of new cancer cases and 18.4% of new cancer deaths, respectively. According to the report of the China National Cancer Center, in China, there were 787,000 new cases of lung cancer and 631,000 new lung cancer deaths in 2015, with an incidence rate of 35.96/100,000 (2). Squamous (SQ) non-small cell lung cancer (NSCLC) cases account for about 17% of the total NSCLC cases where the proportion of patients with negative driver gene mutations is about 80% (3). PD-1 drugs provide a choice for the treatment of these patients with negative driver genes. PD-1/L1 is a surface co-inhibitory protein that belongs to the immunoglobulin superfamily (4). By binding with ligands, it can downregulate the immune system response to treat patients. According to the *Guidelines of Chinese Society of Clinical Oncology (CSCO) for Immune Checkpoint Inhibitor Clinical Practice 2021* and the *Guidelines of Chinese Society of Clinical Oncology (CSCO) for Non-Small Cell Lung Cancer*, pembrolizumab combined with chemotherapy was recommended as Class 1A first-level treatments, and sintilimab combined with platinum-based chemotherapy as a Class 1A second-level recommended therapy (5, 6).

Sintilimab is a programmed cell death protein 1 (PD-1) inhibitor that produces a tumor immune response by binding to PD-1, blocking the binding of PD-1 to programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2), relieving the immunologic suppression and activating the function of T cells. In June 2021, sintilimab combined with chemotherapy (gemcitabine plus platinum) was approved for the treatment of first-line locally advanced or metastatic squamous NSCLC in China based on the ORIENT-12 study, which was a randomized, double-blind phase III clinical trial conducted in China (7). The study was a head-to-head clinical trial of sintilimab combined with chemotherapy in Chinese patients with advanced or metastatic squamous NSCLC. The main outcomes were published in January 2021, and until the data cutoff date (25 March 2020), the progression-free survival (PFS) of sintilimab combined with the chemotherapy group was significantly better than placebo combined with the chemotherapy group (5.5 vs. 4.9 months).

Although sintilimab combined chemotherapy is recommended in the CSCO guideline 2021, there is no study proving its cost-effectiveness. According to the *China Guidelines for Pharmacoeconomic Evaluations 2020* (8), it is recommended that the selection of a comparator should prioritize standard treatment for the same indication. Pembrolizumab combined with chemotherapy is the standard treatment for patients with advanced or metastatic squamous NSCLC. Although the price of sintilimab is much lower than pembrolizumab, the difference in clinical efficacy and health outcome between the two strategies is unclear due to the lack of head-to-head clinical trials. Therefore, this study aimed to evaluate the cost-effectiveness of sintilimab combined with chemotherapy vs. pembrolizumab combined with chemotherapy for the treatment of first-line advanced or metastatic squamous NSCLC in China.

Methods

Model structure

A three-state partitioned survival model (PSM) (9) was developed in Microsoft Excel (Figure 1) to estimate long-term health outcomes and costs for different interventions. One published study proved that the Markov model and PSM would get similar results under the same model structure and assumptions, but it is relatively easier to construct the PSM and more appropriate when individual data are available (10). Additionally, the PSM was also preferred for the economic evaluation of interventions with limited health status according to *NICE DSU Technical Support*

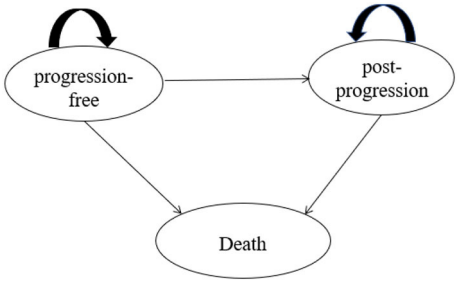

FIGURE 1
Partitioned survival model structure.

TABLE 1 HRs for PFS and OS after adjustment of two-stage method.

Adjustment results	HR-OS
Sintilimab + chemotherapy vs. Placebo + chemotherapy	
Before two-stage correction	0.843
After two-stage correction	0.561
Pembrolizumab + chemotherapy vs. Placebo + chemotherapy	
Before two-stage correction	0.710
After two-stage correction	0.590

HR, hazard ratio; PFS, progression-free survival; OS, overall survival; MAIC, matching-adjusted indirect comparison.

Document 19 and *China Guidelines for Pharmacoeconomic Evaluations 2020*.

The PSM included three states, namely, progression-free (PF), post-progression (PP), and death. The PF state was defined as the initial state of patients, and patients were assumed to receive treatments until disease progression or death occurred. During the PF state, patients were in a stable state or remission. Patients who experienced disease progression would transfer to the PP state, and the definition of progression was consistent with the Response Evaluation Criteria in Solid Tumors (RECIST) in ORIENT-12. Within the PP state, patients would move on to receive subsequent therapies that were aligned with the trial data of ORIENT-12, and they would experience a lower utility weighting than in the PF state. Patients in PF and PP states both have a certain probability of death.

Each health state in the model is associated with corresponding costs and quality-of-life levels. Quality-adjusted life years (QALYs), life years gained (LYGs), and total costs were measured throughout the lifetime. The cycle length of the model was 3 weeks, which was aligned with the administration cycle of the drugs in the ORIENT-12. Only direct medical costs were taken into consideration since the Chinese healthcare system perspective was adopted. All costs and health outcomes were calculated based on the 2020–2021 prices and discounted at 5% according to the *China Guidelines for Pharmacoeconomic Evaluations 2020*. In addition, 1–3 times GDP per capita in China ($11,250–$33,750 per QALY gained in 2020, US$1 = 6.44 CNY) was considered as a willingness-to-pay threshold for the cost-effective analysis (8).

Patient population

The target population of the economic evaluation was Chinese patients aged older than 18 with histologically or cytologically confirmed diagnosis of stage III or IV squamous NSCLC who had not previously received systemic treatments. For the sintilimab plus chemotherapy group (intervention group), patients received sintilimab 200 mg every 3 weeks in combination with gemcitabine and either cisplatin or carboplatin for four cycles. Patients without progression after combination therapy would continue to receive sintilimab 200 mg monotherapy as a maintenance treatment for up to 24 months. For pembrolizumab combined with chemotherapy (comparator group), patients received pembrolizumab 200 mg plus carboplatin and paclitaxel/nab-paclitaxel every 3 weeks. After four cycles, patients continued to receive only pembrolizumab every 3 weeks until 24 months. The treatments were consistent with corresponding clinical trials ORIENT-12 and KEYNOTE-407. The detailed information associated with the trial design, efficiency, and safety presented in the ORIENT-12 and KEYNOTE-407 trials can be obtained in the published literature (7, 11).

Model inputs

Efficacy data

Efficacy data for the intervention group was obtained from the ORIENT-12 trial. The individual patient-level data (IPD) of ORIENT-12 was obtained through the company Innovent Biologics (Suzhou) Co., Ltd., Suzhou, Jiangsu, People's Republic of China's official authorization. The efficacy data for the control group was derived from published literature of KEYNOTE-407. Due to the lack of head-to-head clinical trials between the two groups, indirect comparisons are required in this study.

Given the existence of crossover will cause the HR value of OS to be underestimated, the two-stage method (12, 13), which is aimed at reducing the bias, was used for both sintilimab and pembrolizumab groups before indirect comparison. The adjustment results are shown in Table 1.

Since the efficiency of placebo plus chemotherapy was evaluated in both ORIENT-12 and KEYNOTE-407, the anchored matching adjusted indirect comparison (MAIC) method (14) was adopted in this model. The PFS and OS data of the sintilimab group were chosen as the reference treatment to fit

TABLE 2 The result of baseline adjustment.

Adjustment factor	Sintilimab group (before adjustment)	Pembrolizumab group	Sintilimab group (after adjustment)
Proportion of male	91.60%	81.40%	81.40%
Average age (years)	61.48	65.00	65.00
Proportion of brain metastasis	3.92%	7.69%	7.69%
Proportion of stage IV cancer	65.83%	63.15%	63.15%
Proportion of smoking history	84.59%	92.67%	92.67%
Proportion of ECOG score = 1	85.43%	73.70%	73.70%

TABLE 3 HRs for PFS and OS after MAIC.

Adjustment results	HR-PFS	HR-OS
Sintilimab + chemotherapy vs. Placebo + chemotherapy		
Before MAIC	0.529	0.561
After MAIC	0.647	0.555
Pembrolizumab + chemotherapy vs. Placebo + chemotherapy	0.570	0.590
Sintilimab + chemotherapy vs. Pembrolizumab + chemotherapy	0.88	1.06

HR, hazard ratio; PFS, progression-free survival; OS, overall survival; MAIC, matching-adjusted indirect comparison.

the pembrolizumab group using MAIC-adjusted HR (sintilimab group vs. pembrolizumab group). In the adjustment process, six key baseline demographic and disease characteristics factors, namely average age, gender, brain metastasis, stage of cancer, smoking history, and Eastern Cooperative Oncology Group (ECOG) score, which were reported in KEYOTE-407, were included. The results of baseline characteristics and adjusted HR are shown in Tables 2, 3.

Besides, due to the limited follow-up time in clinical trials, in order to obtain lifetime clinical data of patients, 6 types of parametric distribution models were used to extrapolate the lifetime survival outcomes of the sintilimab group based on the IPD of ORIENT-12. Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics along with visual inspection were used to evaluate optimal parametric distributions. As a result, the best-fitting distribution for PFS and OS data of sintilimab plus chemotherapy was log-normal and Weibull distribution, respectively. However, the visual inspection result was not good and there were logic errors in the Cholseky decomposition under the Weibull distribution, so the suboptimal distribution and log-normal distribution were chosen for OS data. Testing results were shown in the Supplementary material. The pembrolizumab group chose the same parametric distribution as the sintilimab group.

Utility weights

The utility values of health states were derived from the published literature (15) (PF = 0.804, PP = 0.321) (16), which used the time trade-off method to obtain metastatic NSCLC utilities in several countries, including China. In addition, the disutilities associated with the incidence of AEs with incidence ≥ 5% and grade ≥ 3 in the ORIENT-12 and KEYNOTE-407 studies were obtained from published literature (17, 18).

Resource use and costs

Patients in the state of PF were assumed to have drug costs, follow-up costs, administration costs, and management costs of AEs; patients in the state of PP, medical management costs and subsequent treatment costs were included. Drug costs included the cost of sintilimab, pembrolizumab, chemotherapy drugs, and subsequent treatments. The patient assistance plans (PAP) of sintilimab (19) and pembrolizumab (15) were taken into consideration. Subsequent treatments were aligned with the data of ORIENT-12, and the weighted costs were calculated by the proportion of different treatment options (shown in the Supplementary material). We assumed that the subsequent treatments of the pembrolizumab group were the same as that of the sintilimab group.

The cost of follow-up and medical service costs were calculated in two stages, namely, PF state and PP state. The unit price of each item of follow-up and medical service costs was obtained from the medical service price document of 11 provinces in China. Details of the calculation are shown in the Supplementary material.

Costs of AE management were estimated according to the duration of AEs and the incidence of AEs. AEs with an incidence ≥5% and grade ≥3 in the ORIENT-12 and KEYNOTE-407 studies were included in our study. The unit price of AEs treatment drugs was calculated based on the online price database (MEENET). The end-of-life care costs were derived from the published literature. In addition, we assumed that the mean weight of patients was 65 kg and the mean body surface area was 1.6 m^2 to estimate the dosages of drugs, according to the recommendation from the National Healthcare Security Administration (NMPA) in China. All costs are expressed in 2021 US dollars (US$1 = 6.44 CNY). Details of all cost parameters are shown in Table 4.

Sensitivity analyses

To verify the stability of model results, the one-way deterministic sensitivity analysis (DSA) and probabilistic

TABLE 4 Key parameters and their variations.

Parameters	Deterministic	Distribution	Low	High	Source
Unit drug costs ($)					
Sintilimab	441.69	Constant	353.36	441.69	MENET*
Pembrolizumab	2783.78	Constant	2227.02	2783.78	MENET*
Paclitaxel (High dose)	26.26	Gamma	21.00	31.40	MENET*
Paclitaxel (Low dose)	11.02	Gamma	10.56	11.47	MENET*
Carboplatin (High dose)	8.04	Gamma	4.72	8.37	MENET*
Carboplatin (Low dose)	4.72	Gamma	3.77	5.66	MENET*
Gemcitabine	9.32	Gamma	1.24	9.94	MENET*
Cisplatin (Low dose)	1.86	Gamma	1.13	2.96	MENET*
Cisplatin (High dose)	2.66	Gamma	1.18	6.80	MENET*
Subsequent treatment	4351.23	Constant	3480.98	5221.47	MENET*
End-of-life care	2,298.86	Gamma	892.71	6,140.16	(20)
Unit follow-up costs ($)					
Imaging examination	57.48	Gamma	45.99	68.98	Health care document**
Blood chemistry	46.50	Gamma	37.20	55.80	Health care document**
Blood routine	3.11	Gamma	2.49	3.73	Health care document**
Urine routine	0.62	Gamma	0.50	0.75	Health care document**
Unit medical service costs ($)					
Diagnosis	3.11	Gamma	1.55	4.66	Health care document**
Intravenous injection	1.71	Gamma	1.55	2.14	Health care document**
Nursing	3.73	Gamma	2.98	4.47	Health care document**
Hospitalization	6.53	Gamma	5.22	7.83	Health care document**
Unit AE management costs ($)					
Neutrophil count decreased	115.01	Gamma	51.11	357.80	Expert opinion
White blood cell count decreased	115.01	Gamma	51.11	357.80	Expert opinion
Platelet count decreased	1,505.92	Gamma	1,240.17	1,771.67	Expert opinion
Anemia	138.75	Gamma	106.73	160.10	Expert opinion
Incidence of AEs					
Sintilimab Arm					
Neutrophil count decreased	15.1%	Beta	12%	18%	ORIENT-12 IPD
White blood cell count decreased	11.7%	Beta	9%	14%	ORIENT-12 IPD
Anemia	12.8%	Beta	10%	15%	ORIENT-12 IPD
Platelet count decreased	13.4%	Beta	11%	16%	ORIENT-12 IPD
Pembrolizumab Arm					
Neutrophil count decreased	23%	Beta	18%	28%	KEYNOTE-407
Platelet count decreased	8.3%	Beta	7%	10%	KEYNOTE-407
Anemia	15.8%	Beta	13%	19%	KEYNOTE-407
Duration of AEs (Days)					
Neutrophil count decreased	4.19	Normal	3.35	5.03	Expert opinion
Anemia	6.83	Normal	5.46	8.20	Expert opinion
White blood cell count decreased	4.5	Normal	3.60	5.40	Expert opinion
Platelet count decreased	47.29	Normal	37.83	56.75	Expert opinion
Utilities					
PF state	0.804	Beta	0.643	0.965	(16)
PP state	0.321	Beta	0.257	0.385	(16)
Disutilities					
Neutrophil count decreased	0.20	Beta	0.16	0.24	(16)

(Continued)

TABLE 4 Continued

Parameters	Deterministic	Distribution	Low	High	Source
White blood cell count decreased	0.20	Beta	0.16	0.24	(16)
Platelet count decreased	0.11	Beta	0.09	0.13	(17)
Anemia	0.07	Beta	0.06	0.09	(18)

PF, progression-free; PP, post-progressive; IPD, individual patient data. *The price of the drug was obtained from MENET, the online price database in China. (https://menet.com.cn). **The price of follow-up and drug administration were obtained from the healthcare document of 11 provinces in China. ***The inclusion criteria of AEs were that the incidence of AEs ≥ 5% and grade ≥ 3.

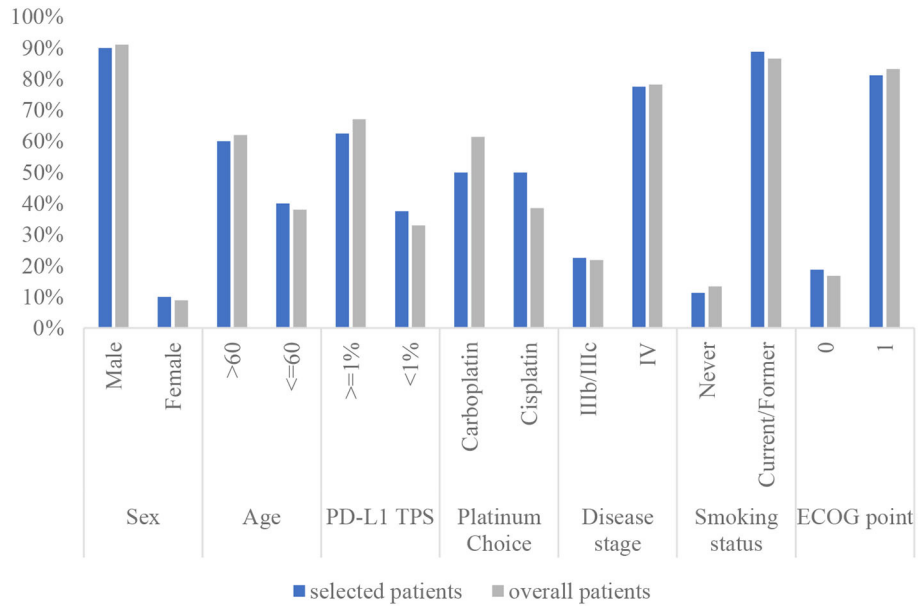

FIGURE 2
The characteristics of the selected patients compared with that of the overall patients in the clinical trial. PD-L1 TPS, programmed cell death-1 tumor proportion score; ECOG PS, Eastern Cooperative Oncology Group performance status.

sensitivity analysis (PSA) were performed. In the DSA, key parameters were varied by the standard error, 95% confidence interval, or ±20% of the deterministic value, except for the price of sintilimab and pembrolizumab (varied from 50 to 100%). PSA was performed using a second-order Monte Carlo simulation with 10,000 iterations. The parametric distribution assumptions were based on the recommended guidelines in *Decision Modeling for Health Economic Evaluation*. In addition, the survival parameters in the PSA were assessed through Cholesky decomposition.

Scenario analysis

Since the literature utility values used in the base-case analysis were not fully applicable to Chinese patients with squamous NSCLC, the utility calculated based on the Research and Treatment Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) score collected from ORIENT-12 was used in the scenario analysis. According to the *NICE DSU Technical Support Document 10*, the mapping should be considered a second-best solution to collect EQ-5D values. We converted QLQ-C30 scores into EuroQol-5-dimension (EQ-5D) 5-level scores by adopting a mapping algorithm derived from published research (16).

To calculate the health state utilities, 80 patients were included after removing the logically incorrect data (health utilities of PF lower than those of PP). The baseline characteristics of the selected patients and all populations in the clinical trial are shown in Figure 2. For the sintilimab group, the utility value of PF and PP states was 0.730 and 0.615, respectively. Considering the utilities derived from patient-level data have included the impact of AEs, the health state utilities of the pembrolizumab group were adjusted according to the differential incidence of AEs between the two groups.

TABLE 5 Summary of the cost and health outcomes results.

	Sintilimab plus chemotherapy	Pembrolizumab plus chemotherapy
QALYs	0.99	1.00
PF health state	0.65	0.73
PP health state	0.33	0.27
LYs	1.84	1.74
Total costs	$12,321	$36,371
Drug costs	$2,523	$26,768
Administration costs	$1,932	$1,866
Disease management and monitoring costs	$1,224	$1,162
AE costs	$250	$173
Subsequent therapy costs	$4,351	$4,351
End-of-life care costs	$2,039	$2,051
Incremental costs	-$24,050	
Incremental QALYs	−0.0183	
Incremental LYs	0.1005	
ICUR	$1,314,280/QALY	
ICER	Dominated	

QALY, quality-adjusted life year; PF, progression-free; PP, post-progressive; LY, life year; AE, adverse event; ICUR, incremental cost-utility ratio; ICER, incremental cost-effectiveness ratio.

Results

Base case

The result of the base-case analysis is presented in Table 5. For Chinese advanced or metastatic squamous NSCLC patients, compared with pembrolizumab, the sintilimab strategy yielded lower QALYs of 0.0183 (0.9902 vs. 1.0085) and lower costs of $24,050 ($12,321 vs. 36,371). The ICER was $1,341,208/QALY, which indicated that a sintilimab strategy is a cost-effectiveness option under the WTP of 1–3 times the GDP per capita in China ($11,250/QALY∼33,749/QALY).

Sensitivity analyses

Deterministic sensitivity analyses

The tornado diagram illustrated the top ten most influential key parameters in the one-way DSA (Figure 3). The utility of the PP state, the unit cost of albumin paclitaxel, and the utility of the PF state were the main driving parameters in the model, while other parameters had weak influences on the model results. As shown in Figure 3, the ICER value was most sensitive to the utility of the PP state, which implied that the changes in PP utility value may lead to a change in optimal strategy choice.

Probabilistic sensitivity analyses

The PSA showed an average QALY gain of −0.0168 and incremental costs of –$21,827, resulting in a probabilistic ICER of $1,299,226/QALY, which was consistent with the base-case results. A scatter plot of the incremental cost-effectiveness plane showed that most of the iteration results from the PSA fall in the third quadrant, while a small number fall in the fourth quadrant (Figure 4). According to the CEAC curve, at a WTP threshold of $11,250/QALY∼$33,749/QALY (1–3 GDP per capita in China), the probability that sintilimab plus chemotherapy was cost-effective compared with pembrolizumab plus chemotherapy was almost 100% (Figure 5).

Scenario analysis

The scenario analysis results are shown in Table 6. Over a lifetime, the sintilimab plus chemotherapy group gained 1.23 QALYs with a cost of $12,321, while the pembrolizumab plus chemotherapy group gained 1.18 QALYs with a cost of $36,371. Compared with pembrolizumab plus chemotherapy, the incremental QALYs and cost for the sintilimab plus chemotherapy group were 0.0504 QALYs and –$24,050, which implied that sintilimab plus chemotherapy dominated pembrolizumab plus chemotherapy for the treatment of first-line advanced or metastatic squamous NSCLC in China. This was mainly because sintilimab plus chemotherapy obtained more QALYs during the PP state and the difference between PF and PP used in the scenario analysis was much smaller than that in the base-case analysis.

Discussion

The research evaluated the cost-effectiveness of sintilimab plus chemotherapy vs. pembrolizumab plus chemotherapy in patients with locally advanced and metastatic squamous NSCLC from a Chinese healthcare system perspective based on ORIENT-12 and KEYNOTE-407 studies.

Under the recommended thresholds of China's GDP per capita in 2020, the base-case results implied that sintilimab plus chemotherapy was more cost-effective vs. pembrolizumab plus chemotherapy. The result of PSA was in line with the base-case result, which shows that the sintilimab strategy has a high probability to be cost-effective. However, since the health outcome gap between the two strategies is very small, a small change in parameter value can cause a change in the study result. As shown in the scenario analysis and DSA, the result was sensitive to changes in utility value, which implied that the cost-effectiveness between these two strategies was not robust. Based on the breakdown results of QALYs, the benefits of the health outcome of sintilimab were mainly obtained in the PP stage. The difference in the incidence of AEs between the two strategies is the main reason for this phenomenon. Since the

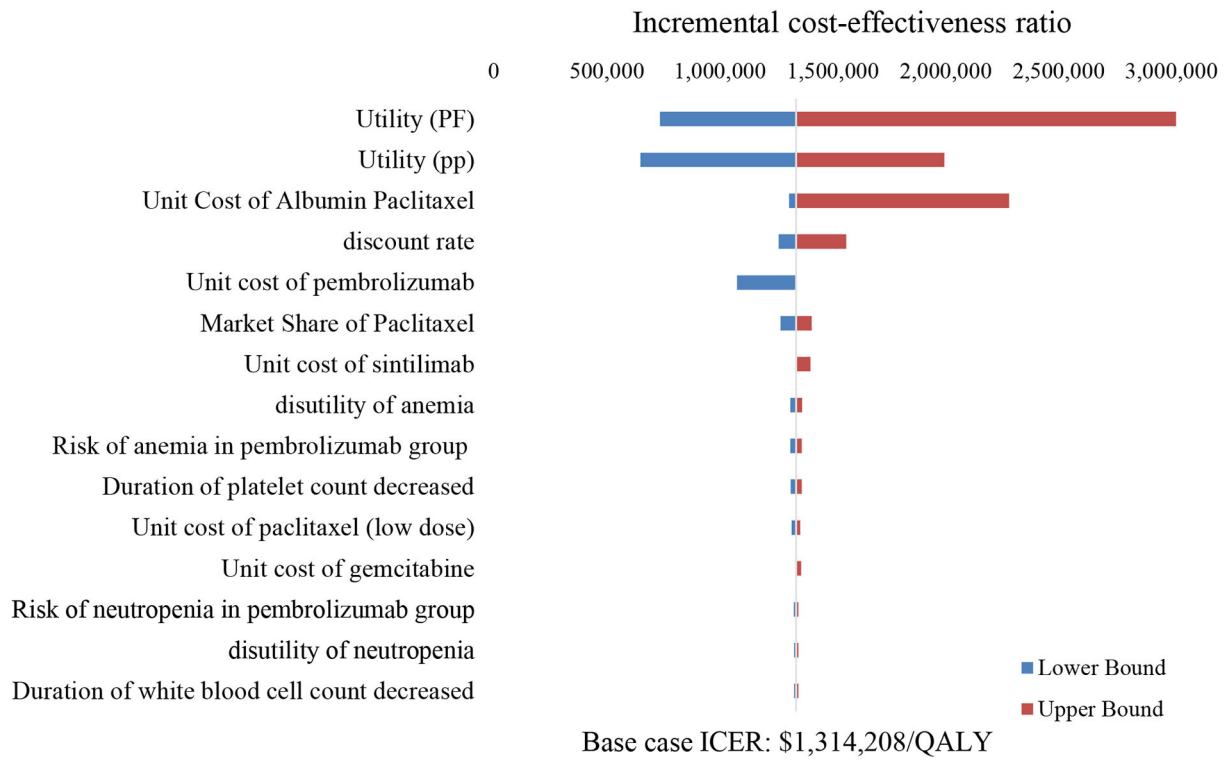

FIGURE 3
Tornado diagram. PF, progression-free; PP, post-progression.

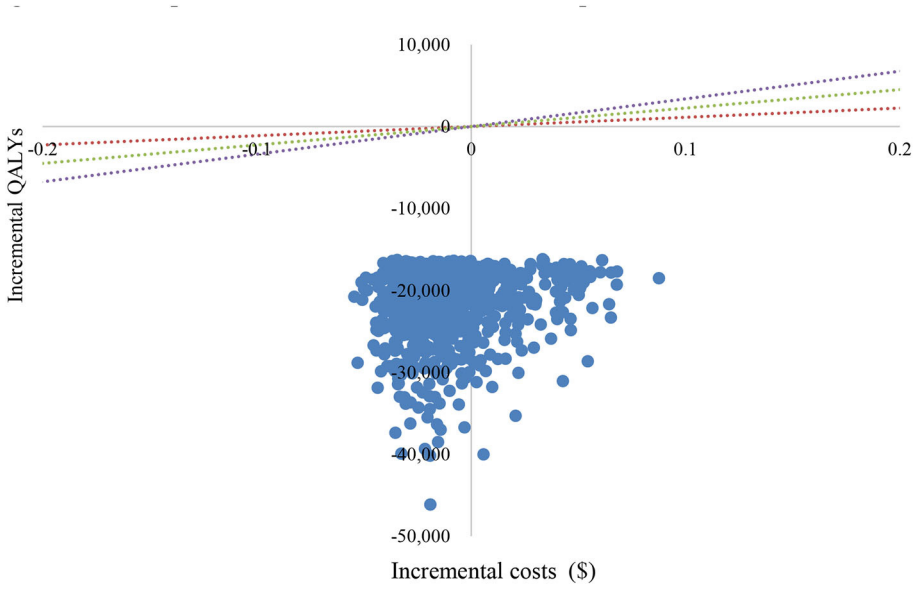

FIGURE 4
Scatter plot of incremental cost-effectiveness plane. QALY, quality-adjusted life year.

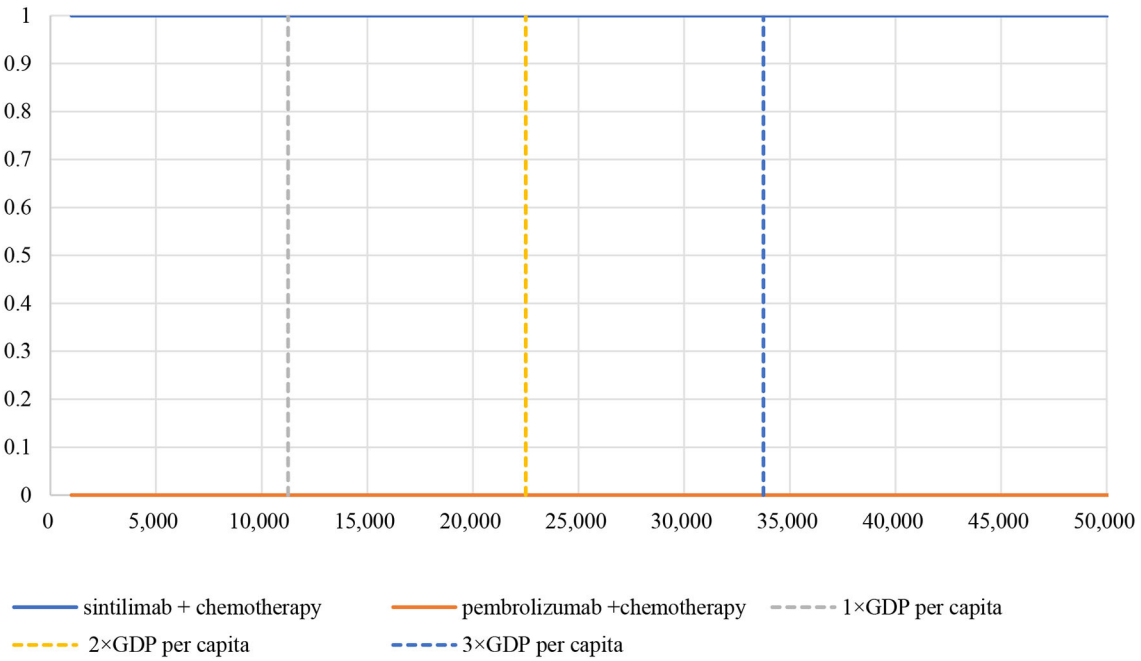

FIGURE 5
Cost-effectiveness acceptability curve. WTP, willingness-to-pay; GDP, gross domestic product.

incidence of AEs in sintilimab is higher than pembrolizumab, the loss of health outcomes due to AEs in the PFS stage is higher. In addition, this also shows that patients treated with sintilimab will have a certain degree of improvement in quality of life even if their disease progresses.

The published economic evaluations of advanced NSCLC in China mainly compared pembrolizumab with chemotherapy (21, 22). However, although pembrolizumab shows good efficacy and safety for advanced NSCLC patients, it is usually not a cost-effective option in the Chinese context due to its expensive price. Recently, the listing of domestic PD-1 inhibitors, which have good cost performance, has provided more medication options for Chinese NSCLC patients. But there is a lack of economic evidence focused on domestic PD-1 inhibitors. To the best of our knowledge, this is the first study to compare the cost-effectiveness of sintilimab plus chemotherapy vs. pembrolizumab plus chemotherapy for NSCLC.

In addition, our study is important and instructive because it draws attention to some issues that should be heeded in the cost-effectiveness analyses of anti-oncology drugs when using indirect comparison methods, especially the crossover problems that can be solved by the two-stage method. Clinical trials for advanced cancers often adopted a crossover design. It means that patients are allowed to receive alternative therapy following disease progression on assigned treatment, which leads to a bias in the clinical efficacy of anti-oncology drugs. Cost-effectiveness analyses of oncology drugs usually obtain outcomes from crossover trials (23). Due to the crossover design, the treatment effect compared with the comparator on survival (such as HR) may be confounded (24). In this study, the two-stage method was used to adjust for the effect of subsequent-line therapies on survival outcomes for both the sintilimab and pembrolizumab groups to reduce the bias.

It should also be addressed that there were several limitations. First, the utility value used in both base-case and scenario analysis has limitations. For the utility value of base-case analysis, the target population for calculating this utility value includes not only squamous patients but also non-squamous patients, which did not exactly match the target population of this study. For the utility value of scenario analysis, only 80 patients were included in the utility value calculation, and the mapping formula is based on the UK population rather than the Chinese population, which might cause a bias in health outcomes. Second, the study relaxed the PH assumption of PFS and OS curves in the sintilimab group. PH hypothesis testing is supposed to be done in order to ensure curves used in the study meet the PH assumption when anchored indirect comparisons are applied. In the -ln(-ln(survival)) chart of sintilimab OS and PFS, the two curves remain parallel for most of the time with only a small overlap at the beginning of the curves. Therefore, the PH assumption was still assumed to be met in this study. Besides, although the best-fitting distribution for OS data of sintilimab plus chemotherapy was the Weibull distribution according to the results of AIC and

TABLE 6 The results of scenario analysis.

	Sintilimab plus chemotherapy	Pembrolizumab plus chemotherapy
QALYs	1.23	1.18
PF health state	0.59	0.67
PP health state	0.64	0.51
LYs	1.84	1.74
Total costs	$12,321	$36,371
Drug costs	$2,523	$26,768
Administration costs	$1,932	$1,866
Disease management and monitoring costs	$1,224	$1,162
AE costs	$250	$173
Subsequent therapy costs	$4,351	$4,351
End-of-life care costs	$2,039	$2,051
Incremental costs	-$24,050	
Incremental QALYs	0.0504	
Incremental LYs	0.1005	
ICUR	Dominated	
ICER	Dominated	

QALY, quality-adjusted life year; PF, progression-free; PP, post-progressive; LY, life year; AE, adverse event; ICUR, incremental cost utility ratio; ICER, incremental cost-effectiveness ratio.

BIC, the log-normal distribution was chosen because the visual inspection result was not good and there are many logic errors in the Cholesky decomposition under the Weibull distribution.

Conclusion

According to the results of the base-case analysis and the sensitivity analyses, the QALYs gained between the sintilimab and pembrolizumab groups were similar, while the cost of the sintilimab group was much lower. Consequently, sintilimab plus chemotherapy is more cost-effective compared with pembrolizumab plus chemotherapy in China as the first-line treatment for locally advanced or metastatic squamous NSCLC patients in China.

Data availability statement

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

Author contributions

PC, XW, SZ, MR, and YW developed the economic model and performed the analyses. XW and SZ interpreted the results and wrote the draft manuscript. XW, SZ, MR, and YW reviewed, analyzed, and interpreted the data. PC, HL, and AM contributed to the design of the primary model and the interpretation of the results. All authors reviewed and approved the final version.

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Conflict of interest

HS was employed by Innovent Biologics (Suzhou) Co., Ltd.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.956792/full#supplementary-material

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Breast and cervical cancer screening adherence in Jiangsu, China: An ecological perspective

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Background: High screening coverage can effectively reduce the mortality in breast and cervical cancer. Further research on extending the coverage of breast and cervical cancer screening in China is required. This study explored factors influencing women's "two-cancer" screening service utilization using an ecological approach.

Methods: Data were obtained from the National Health Services Survey (NHSS) conducted in 2018 in Jiangsu, China. A total of 3,500 women aged 18–64 years were included in the analysis. Chi-squared test, hierarchical multiple logistic regression analysis, and binary logistic regression analysis were performed.

Results: In total, 44.1% of the women had been screened for breast cancer (BC) and 40.9% for cervical cancer (CC). Breast cancer screening (BCS) and cervical cancer screening (CCS) differed significantly in the following common categories: age, gestational experiences, chronic disease status, body mass index (BMI), exercise, health checkup, marital status, number of children, employment, education, family doctors, and health records. In the results of hierarchical multiple logistic regression analysis, the explanatory power of the final model was 37.5% and the area under the receiver operating characteristic curve was 0.812. The results showed that being in the age group of 35–64 years, having gestational experiences, having chronic diseases, exercising, having a health checkup, being married, having children, and being employed were statistically significant positive predictors of "two-cancer" screening adherence. The household size was a barrier. For BCS, obesity was also a negative factor, and a higher overall self-related health status was a positive factor. Being married and living in households of three or more families were not predictors. For CCS, having health records was also positively significant, while having chronic disease did not influence adherence.

Conclusion: The findings provide an ecological explanation for women's BCS and CCS service utilization. Both proximal and distal factors should be considered to achieve a high coverage rate.

KEYWORDS

breast cancer screening (BCS), cervical cancer screening (CCS), ecological perspective, cancer prevention, hierarchical multiple logistic regression

Introduction

Breast and cervical cancer are common malignancies worldwide. Breast cancer (BC) ranks first in incidence among female malignancies in 2020 (1). According to GLOBOCAN 2018 estimates produced by the International Agency for Research on Cancer (IARC), cervical cancer (CC) ranked 4th for both incidence and mortality among all malignancies (2). The latest data from the National Cancer Center (NCC) of China showed that the crude and age-standardized incidence rates (ASIR) and age-standardized mortality rates (ASMR) of female breast and cervical cancer were both increased significantly from 2000 to 2016 (3). An upward trend in annual percentage change in screening for the "two cancers" was reported for both BC and CC. The ASIR of BC was 3% and ASMR was 1%. The ASIR of CC was 8.5% and ASMR was 5.4% (3). According to the report of IARC in 2020, the ASIR of BC, which ranked 1st among the top 10 cancers with highest ASIR in China, reached 39.1 per 100,000 worldwide, and the ASIR of CC, which was 6th on the same ranking, reached 10.7 (4).

Cancer screening, which is a secondary prevention, aims for early detection, diagnosis, and treatment. For breast and cervical cancer, early diagnosis and proper treatment can be life-saving. Mortality can be effectively reduced because of high coverage of cancer screening, according to the experiences of developed countries (5, 6) such as the United Kingdom and the United States (5, 7, 8). Breast cancer screening (BCS) in the United Kingdom has been nationwide as early as the 1990's. The coverage rates of cervical cancer screening (CCS) were 90% in Finland and 80% in Iceland (5). In China, a free screening program for the "two cancers" for rural women was launched in 2009 (9). In recent years, rural women's upper age limitation for participating in the program has changed from 59 to 64 years (10). The Healthy China Initiative of 2019–2030 showed that the rates of CCS and BCS are projected to reach 80% in 2022 and 90% in 2030 (11). Unfortunately, even with free screening services and encouragement from community healthcare institutions, the participation rate is relatively low, particularly in rural areas. Past research revealed that the "two-cancer" screening rate was 42.7% in Wenling, Zhejiang (12). The findings of a multistage stratified sample method in the eastern, central, and western areas of China indicated that the BSC rate in rural and urban populations was 65.6% (13). Even though the rate is gradually increasing, there could be further efforts to achieve high coverage. Therefore, to improve the status of screening service utilization, a study on what influences women's screening willingness is desired.

A previous study indicated that there are two reasons for differences in medical service utilization behavior. One reason is differences in health conditions, and the other is differences in medical services accessibility in different areas, groups, and systems (14). A previous study also showed that screening service utilization behavior is affected by multiple factors related to physical and social environments such as age, income, education, screening service delivery, perception of disease risk, and physician's recommendation (15). In this study, we will explore factors influencing women's "two-cancer" screening service utilization in China using an ecological approach that includes proximal and distal factors. The results may explain determinants of demand-side factors and supply-side factors based on women's perspectives.

Materials and methods

Data and sampling

Data were drawn from the 6th National Health Services Survey (NHSS) collected by the National Health and Family Planning Commission (NHFPC) of China in 2018. The data used were from the province of Jiangsu. Using a multistage stratified random sampling technique, first, six districts or counties in six cities were sampled: Gusu in Suzhou, Jinhu in Huaian, Pizhou in Xuzhou, Wujin in Changzhou, Xishan in Wuxi, and Yangzhong in Zhenjiang. Then, 61 villages or resident committees were drawn from the six districts or counties. Finally, 3,660 households were selected from the village or resident committees. A total of 11,550 people were included. Given the purpose of this study, 3,500 women who were between 18 and 64 years of age and whose answers for screening, family numbers, etc., were complete were enrolled.

Dependent and independent variables

The ecological perspective serves to direct attention to both behavior and its individual and environmental determinants, i.e., views of Urie Bronfenbrenner (16, 17). According to Bronfenbrenner, environmental influences on behavior are divided into the micro-, meso-, exo-, and macrosystem levels of influence. Health ecology, proposed by Collins (18), is derived from ecological theory. This is the application of ecology in the field of health. It emphasizes that an individual's health is the result of the interaction and interdependence of individual factors, health services, and both material and social environmental factors. These factors also restrict each other and affect the health of individuals and groups through multilevel interactions. According to the application of the Health Ecology Model (HEM) (Figure 1) in the health service use field (14), the determinants of health service utilization include personal traits, behavior characteristics, interpersonal network, work and life, and social policies enabling resources: (1) personal traits, the core level, refer to innate factors and predisposing characteristics of a disease, such as age, and sex; (2) behavior characteristics,

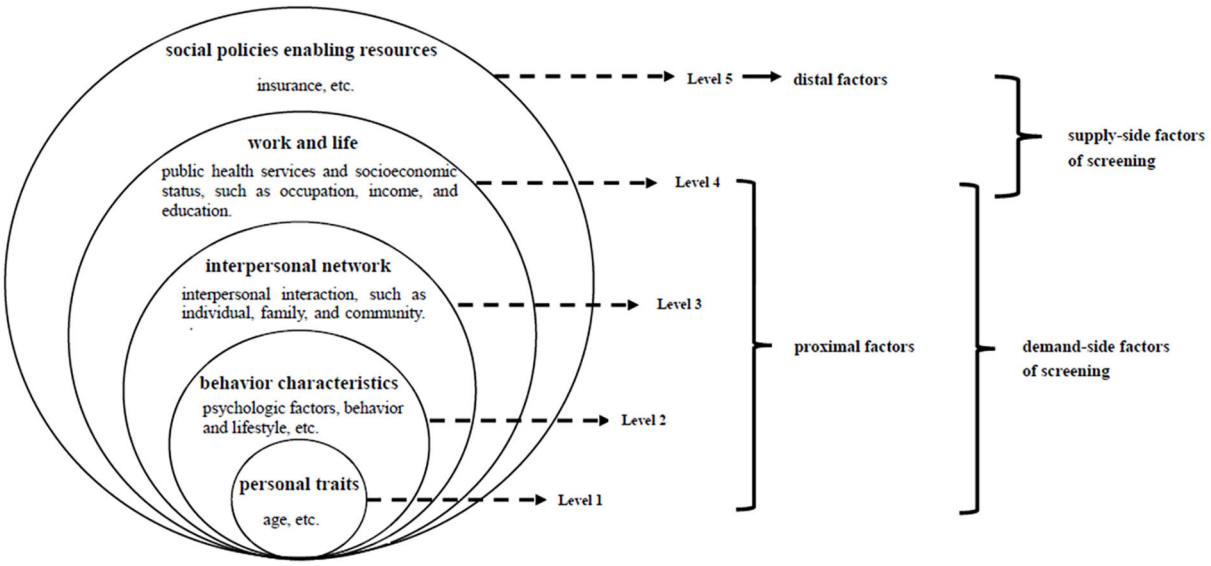

FIGURE 1
Ecological perspective on "two-cancer" screening.

TABLE 1 Hierarchical model of predictor variables in the study.

Independent variables					Dependent variables
Level 1: Personal traits	**Level 2: Behavior characteristics**	**Level 3: Interpersonal network**	**Level 4: Work and life**	**Level 5: Social policies enabling resources**	
Age	Health behaviors	Marital status	Income	Family doctors	To be screened or not
Gestational experiences	HRQoL	Number of children	Employment	Health records	
Chronic disease status		Household size	Education	Health insurance	
BMI			Distance from the nearest hospital		

BMI, body mass index; HRQoL, health-related quality of life.

the 2nd level, refer to psychological factors, behavior, and lifestyle, etc.; (3) interpersonal network, the 3rd level, refers to interpersonal interaction such as individual, family, and community; (4) work and life, the 4th level, refer to public health services and socioeconomic status such as occupation, income, and education; (5) social policies enabling resources, the 5th level, refers to insurance, etc. The first four levels are proximal factors, and the fifth level is considered a distal factor. For women's "two-cancer" screening, these levels are comprehensive and could explain the determinants of demand-side and supply-side factors based on women's perspectives (Figure 1). Combined with the measurement of the NHSS and HEM, the following dimensions (Table 1) were considered based on the existing literature.

Predictor variables

The predictor variables were hierarchized into five levels. They were analyzed categorically.

Level 1: Personal traits

The personal trait indices in this study included age, gestational experiences, chronic disease status, and body mass

index (BMI). We calculated the prevalence of screening among two age categories according to free screening age (10) and women's average age of marriage reported in the marriage data in Jiangsu in 2017: (1) 18–34 and (2) 35–64 years. Gestational experiences were reported in three standard categories: 0, 1, or above. We assessed the presence of any chronic disease, which was defined as "with" or "without." BMI consisted of the following four categories according to the Guidelines for Prevention and Control of Overweight and Obesity in Chinese Adults developed by the National Health Commission of the People's Republic of China in 2006 (19): (1) underweight: $<$ 18.5 kg/m^2, (2) normal weight: 18.5–23.9 kg/m^2, (3) overweight: 24.0–27.9 kg/m^2, and (4) obese: $\geq$ 28 kg/m^2.

Level 2: Behavior characteristics

Behavior characteristics were based on indicators that reflect actual health. Therefore, women's health behaviors and health-related quality of life (HRQoL) were adopted. History of smoking and alcohol consumption (in the last 12 months), health checkups (in the last 12 months), and exercise status were used to estimate health behaviors. They were all defined as "yes" or "no." The European Quality of Life-5 Dimensions (EQ-5D) was used to estimate HRQoL including the health profile presented by the descriptive system and the overall self-rated health status presented by the EQ-5D visual analog scale (EQ VAS). Response scores on the health profile on the scale ranged from 1 (no problem) to 3 (extreme problems). Index value was calculated according to the time trade-off value set developed in China in 2018 (20). It was assessed as below or above the average. Scores on overall self-rated health status were categorized into three groups according to the level of application in the previous study of BCS and CCS (21): low (0–79), medium (80–91), or high (92–100).

Level 3: Interpersonal network

Marital status, number of children, and household size were all included in the interpersonal network. Marital status was reported in two standard categories: single or married. Number of children was grouped as 1 or 0. Household size was grouped as 1, 2, 3 or above.

Level 4: Work and life

Income, employment, education, and distance from the nearest hospital were used as indicators of work and life. Income was categorized according to median annual per capita household income. Employment status was reported in four standard categories: (1) unemployed or out of work, (2) retired, (3) employed, and (4) in-school student. Education was categorized into four groups: (1) primary school or below, (2) junior or senior high school, (3) technical school, and (4) college or above. Distance from the nearest hospital was grouped as either "$<$ 1 km" or "1 $\geq$ km."

Level 5: Social policies enabling resources

Family doctors, health records, and insurance status were used to estimate social policies enabling resources. Family doctors and health record statuses were reported in three standard categories: "I don't know this service," "yes," or "no." Insurance status was defined as "insured" or "uninsured."

Outcome variables

First, the screening utilization of "two cancers" in the last 12 months was the outcome variable that was dichotomized into non-attendance in both BCS and CCS, and attendance in either one or both of them. Second, BCS attendance or not and CCS attendance or not were separately considered in order to deeply explore more specific and clearer information regarding BCS and CCS.

Statistical analysis

A data analysis was performed using IBM SPSS Statistics version 24.0. Descriptive statistics were used on each independent variable, which was expressed in absolute value or percentage, to determine the distribution. Chi-squared tests were conducted on the following two groups: those who had attended BCS and those who had attended CCS in the last 12 months. A hierarchical multiple logistic regression analysis was conducted to evaluate determinants affecting non-attendance in both BCS and CCS, and attendance in either one or both of them in the last 12 months. Five hierarchical levels were used in this study. The independent variables were entered with the simultaneous forced entry method in the regression model by Block 1 (personal traits), Block 2 (behavior characteristics), Block 3 (interpersonal network), Block 4 (work and life), and Block 5 (social policies enabling resources). A binary logistic regression analysis was conducted to explore the potential association of the five characteristics as predictor variables and BCS attendance and CCS attendance or not as outcome variables. The standardized regression coefficient β, adjusted coefficient of determination (adjusted R^2), and area under the receiver operating characteristic curve were observed. The results were expressed as odds ratio (OR) and respective 95% confidence intervals (CI). Differences were considered statistically significant at a two-sided $p < 0.05$. All variables integrated into the regression analysis had no missing data, so a complete case analysis was conducted.

Results

Characteristics of respondents

Of the 3,500 respondents, 175 (5%) were screened for BC only, 63 (1.8%) for CC only, and 1,369 (39.1%) for both BC and CC. The remaining 1,893 (54.1%) women underwent neither BCS nor CCS. The descriptive statistics for all the independent variables of the 3,500 respondents are presented in Table 2. The women's mean age was 44.66 years [standard deviation (SD) = 12.317], and 74.2% were 35–64 years of age. Of all the participants, only 8.2% had no gestation. The proportion of respondents without chronic diseases was 72.4%. Majority of the participants (59.9%) were of normal weight.

For behavior characteristics, most had no smoking (99.3%) or alcohol intake (94.2%) history. In total, 49.2% of the women never exercised or exercised less than once weekly, and 46.9% of them did not present for a routine health checkup in the last 12 months. In terms of HRQoL, the mean of EQ-5D index score was 0.9865, and 80.2% of the women scored above the average. The overall self-rated health status of more than half (59.7%) of the respondents was medium.

The majority of women (89.8%) were married. In addition, 97.7% of the respondents had one or more children. Only 3.1% of them lived alone. The proportion of women living in households with three families or more accounted for 83.5%.

The median annual per capita household income was 20,000 yuan, and 44.6% of the women had more than that. Of the 3,500 respondents, 2,409 were classified as employed and accounted for the largest proportion (68.8%), followed by being unemployed or out of work (17.1%), retired (12.2%), and students (1.9%). The number of women (45.1%) who had an educational level of junior high school or senior high school was the largest. The proportion of women whose residence was <1 km from the nearest hospital was 48.7%.

About 62.9% and 53% of the respondents reported that they did not know of family doctors and health records, respectively. Only 15.5% of the women had family doctors and 36.5% had health records. Almost all the respondents (98.8%) were insured.

Group differences in the different attendance groups

Table 2 also presents differences between the different attendance groups according to the five variables. The BCS and CCS statuses of the women in each category are shown in Table 2. The chi-squared test results showed that going for a BCS significantly differed in all dimensions of level 1; history of alcohol ($p < 0.05$), exercise ($p < 0.001$), and health checkup ($p < 0.001$) of level 2; marital status ($p < 0.001$) and number of children ($p < 0.001$) of level 3; income ($p < 0.05$), employment ($p < 0.001$), and education ($p < 0.001$) of level 4; family doctors ($p < 0.001$), health records ($p < 0.001$), and insurance status ($p < 0.05$) of level 5. For attendance in CCS, there were significant differences in the same dimensions as BCS except for history of alcohol ($p > 0.05$), income ($p > 0.05$), and insurance status ($p > 0.05$).

Determinants affecting attendance in "two-cancer" screening

To identify which factors influenced the screening of women's "two cancers", a hierarchical multiple logistic regression analysis was performed (Table 3). The variable for personal traits was entered into Model 1. Even though age 35–64 years and gestational experiences were found to have significant associations with attendance in screening of the "two cancers" and this model could significantly predict women's attendance ($p < 0.001$), the explanatory power of 8.8% was not satisfactory. Variables for personal traits and behavior characteristics were entered into Model 2. In Model 2, besides age 35–64 years and gestational experiences, women who exercised every week, went for a health checkup in the last 12 months, and with a high level of overall self-rated health status were more likely to undergo screening for the "two cancers." The explanatory power of this model increased to 36% ($p < 0.001$) compared to Model 1. Based on the significant variables in Model 2, the newly entered variables in Model 3, including marital status (married vs. single), number of children (1 or above vs. 0), and household size (2 vs. 0), were all significantly related to women's screening attendance, and had an explanatory power of 36.6% ($p < 0.001$). In Model 4, having chronic diseases and living in households of three or more families changed from not being significantly associated with screening to being predictive factors. Additionally, being employed, the newly entered variable, was also significantly associated with the outcomes. However, high overall self-rated health status was not significant. The explanatory power of this model increased to 37.4% ($p < 0.001$). In addition to the above dimensions with significant differences in Model 4, no variables were newly significant in Model 5; however, the R^2 (37.5%) value of the final model still increased slightly ($p < 0.001$).The Hosmer-Lemeshow (H-L) test showed a good model degree of fit ($p = 0.203$). The area under the receiver operating characteristic curve was 0.812. In other words, with the entry of proximal factors and the addition of distal factors, the explanatory power increased and the model was gradually stabilized.

Factors associated with BCS and CCS

To explore more specific and clearer information regarding BCS and CCS, a binary logistic regression analysis was conducted. The factors associated with BCS and CCS are shown

TABLE 2 Distribution of variables of participants and group differences in the different attendance groups.

Variables			N (%)	BCS			CCS		
				No (*n*/%)	Yes (*n*/%)	χ2	No (*n*/%)	Yes (*n*/%)	χ2
Personal traits									
Age		18–34	903 (25.8)	676 (74.9)	227 (25.1)	177.749***	712 (78.8)	191 (21.2)	196.613***
		35–64	2,597 (74.2)	1,280 (49.3)	1,317 (50.7)		1,356 (52.2)	1,241 (47.8)	
Gestational experiences		0	287 (8.2)	255 (88.9)	32 (11.1)	137.842***	266 (92.7)	21 (7.3)	146.606***
		1	991 (28.3)	522 (52.7)	469 (47.3)		566 (57.1)	425 (42.9)	
		2 or above	2,222 (63.5)	1,179 (53.1)	1,043 (46.9)		1,236 (55.6)	986 (44.4)	
Chronic disease status		Without	2,535 (72.4)	1,480 (58.4)	1,055 (41.6)	23.251**	1,552 (61.2)	983 (38.8)	17.371***
		With	965 (27.6)	476 (49.3)	489 (50.7)		516 (53.3)	449 (46.5)	
BMI		Normal weight	2,096 (59.9)	1,188 (56.7)	908(43.3)	15.830**	1,269 (60.5)	827 (39.5)	12.263**
		Underweight	220 (6.3)	142 (64.5)	78 (35.5)		143 (65.0)	77 (35.0)	
		Overweight	964 (27.5)	496 (51.5)	468 (48.5)		529 (54.9)	435 (45.1)	
		Obese	220 (6.3)	130 (59.1)	90 (40.9)		127 (57.7)	93 (42.3)	
behavior characteristics									
Health behaviors	History of smoking	Yes	24 (0.7)	15 (62.5)	9 (37.5)	0.429	15 (62.5)	9 (37.5)	0.117
		No	3,476 (99.3)	1,941 (55.8)	1,535 (44.2)		2,053 (59.1)	1,423 (40.9)	
	History of alcohol	Yes	202 (5.8)	99 (49.0)	103 (56.3)	4.111*	110 (54.5)	92 (45.5)	1.901
		No	3,298 (94.2)	1,857 (56.3)	1,441 (43.7)		1,958 (59.4)	1,340 (40.6)	
	The status of exercise	No	1,721 (49.2)	1,085 (63.0)	636 (37.0)	70.388***	1,126 (65.4)	595 (34.6)	56.322***
		Yes	1,779 (50.8)	871 (49.0)	908 (51.0)		942 (53.0)	837 (47.0)	
	Health checkup	No	1,643 (46.9)	1,334 (81.2)	309 (18.8)	804.457***	1,353 (82.3)	290 (17.7)	693.253***
		Yes	1,857 (53.1)	622 (33.5)	1,235 (66.5)		715 (38.5)	1,142 (61.5)	
HRQoL	Health profile	Low	692 (19.8)	380 (54.9)	312 (45.1)	0.331	391 (56.5)	301 (43.5)	2.380
		High	2,808 (80.2)	1,576 (56.1)	1,232 (43.9)		1,677 (59.7)	1,131 (40.3)	
	Overall self-rated health status	Low	800 (22.9)	463 (57.9)	337 (42.1)	2.158	476 (59.5)	324 (40.5)	2.643
		Medium	2,088 (59.7)	1,147 (54.9)	941 (45.1)		1,214 (58.1)	874 (41.9)	
		High	612 (17.5)	346 (56.5)	266 (43.5)		378 (61.8)	234 (38.2)	
Interpersonal network									
Marital status		Single	358 (10.2)	278 (77.7)	80 (22.3)	76.648***	294 (82.4)	64 (17.9)	87.548***

(Continued)

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TABLE 2 Continued

Variables		N (%)	BCS			CCS		
			No (*n*/%)	Yes (*n*/%)	χ2	No (*n*/%)	Yes (*n*/%)	χ2
	Married	3,142 (89.8)	1,678 (53.4)	1,464 (46.6)		1,774 (56.5)	1,368 (43.5)	
Number of children	0	80 (2.3)	71 (88.8)	9 (11.3)	35.867***	75 (93.8)	5 (6.3)	40.695***
	1 or above	3,420 (97.7)	1,885 (55.1)	1,535 (44.9)		1,993 (58.3)	1,427 (41.7)	
Household size	1	110 (3.1)	54 (49.1)	56 (50.9)	2.946	58 (52.7)	52 (47.3)	2.388
	2	467 (13.3)	253 (54.2)	214 (45.8)		270 (57.8)	197 (42.2)	
	3 or above	2,923 (83.5)	1,649 (56.4)	1,274 (43.6)		1,740 (59.5)	1,183 (40.5)	
Work and life								
Income	Low	1,938 (55.4)	1,118 (57.7)	820 (42.3)	5.724*	1,169 (60.3)	769 (39.7)	2.736
	High	1,562 (44.6)	838 (53.6)	724 (46.4)		899 (57.6)	663 (42.4)	
Employment	Unemployed or out of work	598 (17.1)	391 (65.4)	207 (34.6)	84.484***	404 (67.6)	194 (32.4)	78.140***
	Retired	427 (12.2)	195 (45.7)	232 (54.3)		212 (49.6)	215 (50.4)	
	Employed	2,409 (68.8)	1,307 (54.3)	1,102 (45.7)		1,387 (57.6)	1,022 (42.4)	
	In-school student	66 (1.9)	63 (95.5)	3 (4.5)		65 (98.5)	1 (1.5)	
Education	Primary school or below	992 (28.3)	568 (57.3)	424 (42.7)	18.699***	579 (58.4)	413 (41.6)	26.685***
	Junior high school/ senior high school	1,580 (45.1)	824 (52.2)	756 (47.8)		877 (55.5)	703 (44.5)	
	Technical school	200 (5.7)	122 (61.0)	78 (39.0)		131 (65.5)	69 (34.5)	
	College or above	728 (20.8)	442 (60.7)	286 (39.3)		481 (66.1)	247 (33.9)	
Distance from the nearest hospital	<1 km	1,704 (48.7)	956 (56.1)	748 (43.9)	0.064	1,009 (59.2)	695 (40.8)	0.022
	≥1 km	1,796 (51.3)	1,000 (55.7)	796 (44.3)		1,059 (59.0)	737 (41.0)	
social policies enabling resources								
Family doctors	Don't know	2,202 (62.9)	1,300 (59.0)	902 (41.0)	27.386***	1,362 (61.9)	840 (38.1)	26.521***
	Yes	541 (15.5)	257 (47.5)	284 (52.5)		270 (49.9)	271 (50.1)	
	No	757 (21.6)	399 (52.7)	358 (47.3)		436 (57.6)	321 (42.4)	
Health records	Don't know	1,854 (53.0)	1,131 (61.0)	723 (39.0)	49.069***	1,197 (64.6)	657 (35.4)	65.804***
	Yes	1,276 (36.5)	617 (48.4)	659 (51.6)		641 (50.2)	635 (49.8)	
	No	370 (10.6)	208 (56.2)	162 (43.8)		230 (62.2)	140 (37.8)	
Insurance status	Uninsured	41 (1.2)	30 (73.2)	11 (26.8)	5.028*	30 (73.2)	11 (26.8)	3.405
	Insured	3,459 (98.8)	1,926 (55.7)	1,533 (44.3)		2,038 (58.9)	1,421 (41.1)	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. BMI, body mass index; HRQoL, health-related quality of life.

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TABLE 3 Hierarchical multiple logistics regression analysis of factors that were related to "two-cancer" screening.

Variables			Model 1		Model 2		Model 3		Model 4		Model 5	
			β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)
Personal traits												
Age		35–64	0.76	2.13 (1.76–2.57)***	0.79	2.20 (1.77–2.74)***	0.76	2.13 (1.71–2.66)***	0.82	2.26 (1.76–2.91)***	0.81	2.24 (1.74–2.88)***
Gestational experiences		1	1.46	4.30 (2.92–6.34) ***	1.73	5.66 (3.73–8.60)***	1.36	2.90 (2.42–6.31)***	1.28	3.61 (2.21–5.90)***	1.28	3.60 (2.20–5.89)***
		2 or above	1.34	3.82 (2.60–5.61)***	1.70	5.49 (3.62–8.31)***	1.31	3.71 (2.30–5.99)***	1.26	3.52 (2.15-5.75)***	1.25	3.50 (2.14–5.73)***
Chronic disease status		With	0.11	1.11 (0.95–1.30)	0.12	1.13 (0.93–1.38)	0.12	1.23 (0.92–1.38)	0.21	1.23 (1.003–1.50)*	0.21	1.23 (1.01–1.51)*
BMI		Underweight	0.17	1.18 (0.87–1.61)	0.20	1.22 (0.86–1.73)	0.20	1.22 (0.86–1.73)	0.23	1.26 (0.89–1.79)	0.23	1.26 (0.89–1.79)
		Overweight	0.07	1.07 (0.91–1.25)	0.01	1.01 (0.84–1.21)	−0.002	0.998 (0.83–1.20)	0.02	1.02 (0.85–1.22)	0.02	1.02 (0.85–1.23)
		Obese	−0.24	0.78 (0.60–1.04)	−0.30	0.74 (0.53–1.03)	−0.30	0.74 (0.53–1.03)	−0.28	0.76 (0.54–1.06)	−0.29	0.75 (0.54–1.05)
Behavior characteristics												
Health behaviors	History of smoking	No			0.54	1.71 (0.66–4.43)	0.49	1.63 (0.63–4.23)	0.47	1.60 (0.60–4.25)	0.50	1.64 (0.62–4.35)
	History of alcohol	No			−0.25	0.78 (0.55–1.09)	−0.25	0.78 (0.56–1.10)	−0.23	0.79 (0.56–1.11)	−0.24	0.79 (0.56–1.11)
	The status of exercise	Yes			0.45	1.57 (1.34–1.84)***	0.46	1.58 (1.34–1.85)***	0.48	1.61 (1.37–1.91)***	0.47	1.60 (1.36–1.89)***
	Health checkup	Yes			2.11	8.27 (7.03–9.72)***	2.13	8.37 (7.12–9.85)***	2.12	8.34 (7.07–9.83)***	2.12	8.33 (7.04–9.85)***
HRQoL	Health profile	High			−0.04	0.96 (0.77–1.19)	−0.06	0.94 (0.75–1.17)	−0.12	0.89 (0.71–1.11)	−0.12	0.89 (0.71–1.11)
	Overall self-rated health status	Medium			0.17	1.19 (0.96–1.47)	0.16	1.17 (0.95–1.45)	0.11	1.12 (0.91–1.39)	0.11	1.11 (0.90–1.38)

(Continued)

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TABLE 3 Continued

Variables		Model 1		Model 2		Model 3		Model 4		Model 5	
		β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)
	High			0.32	1.38 (1.04–1.82) *	0.29	1.33 (1.01–1.77)*	0.27	1.31 (0.99–1.74)	0.27	1.31 (0.99–1.74)
Interpersonal network											
Marital status	Married					0.48	1.62 (1.13–2.34)**	0.42	1.52 (1.05–2.20)*	0.41	1.51 (1.04–2.18)*
Number of children	1 or above					1.15	3.14 (1.50–6.60)**	1.17	3.22 (1.52–6.80)**	1.17	3.23 (1.53–6.84)**
Household size	2					−0.57	0.57 (0.34–0.94)*	−0.56	0.57 (0.35–0.95)*	−0.55	0.58 (0.34–0.96)*
	3 or above					−0.46	0.63 (0.40–1.01)	−0.49	0.62 (0.38–0.99)*	−0.48	0.62 (0.38–0.999)*
Work and life											
Income	High							0.004	1.00 (0.84–1.20)	0.01	1.01 (0.85–1.21)
Employment	Retired							0.10	1.11 (0.81–1.51)	0.09	1.10 (0.81–1.50)
	Employed							0.48	1.62 (1.29–2.03)***	0.49	1.64 (1.30–2.05)***
	In-school student							−0.90	0.41 (0.11–1.51)	−0.93	0.40(0.11–1.47)
Education	Junior high school/ senior high school							0.12	1.13 (0.92–1.39)	0.11	1.12 (0.91–1.37)
	Technical school							−0.11	0.90 (0.61–1.33)	−0.12	0.88 (0.60–1.31)
	College or above							0.18	1.19 (0.87–1.63)	0.15	1.16 (0.85–1.59)
Distance from the nearest hospital	≥1 km							−0.02	0.98 (0.83–1.14)	−0.02	0.98 (0.84–1.15)

(Continued)

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TABLE 3 Continued

Variables		Model 1		Model 2		Model 3		Model 4		Model 5	
		β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)	β	OR(95%CI)
Social policies enabling resources											
Family doctors	Yes									−0.06	0.94 (0.73–1.21)
	No									0.04	1.04 (0.82–1.32)
Health records	Yes									0.12	1.13 (0.92–1.39)
	No									0.15	1.16 (0.85–1.60)
Insurance status	Insured									−0.39	0.68 (0.31–1.47)
-2 Log likelihood		4,589.267		3,731.028		3,709.682		3,679.150		3,675.080	
χ2		239.367		1,097.606		1,118.952		1,149.484		1,153.554	
Sig		0.000		0.000		0.000		0.000		0.000	
Nagelkerke R^2		0.088		0.360		0.366		0.374		0.375	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. BMI, body mass index; HRQoL, health-related quality of life.

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in Table 4. Age 35–64, having gestational experiences, exercising, going for a health checkup, having children, and being employed were the common positive factors for both women's BCS and CCS. In addition, women who had a chronic disease and those who had a high level of overall self-rated health status were more likely to undergo BCS. Women who were married and had health records had a higher likelihood of undergoing CCS. However, household size was a barrier not only for women's BCS utilization but also for CCS. Obese women were also less likely to be screened for BCS. The Hosmer-Lemeshow (H-L) test showed a good degree of fit for BCS ($p = 0.427$) and CCS ($p = 0.147$). The area under the receiver operating characteristic curve was 0.816 and 0.807 for BCS and CCS, respectively.

Discussion

Recently, an increasing number of young women have been discovered to have developed BC and CC. Cancer screening is an effective secondary prevention strategy that plays an important role in women's health. Since the implementation of the policy on free screening in 2009, screening rates have increased. However, there is still a gap according to the Healthy China Initiative of 2019–2030. This is the first study based on an ecological perspective to explore the determination of women's "two cancers" screening utilization using hierarchical multiple logistic regression analysis.

The results of this study indicated that the rates of BCS (44.1%) and CCS (40.9%) in all ages were both relatively low. Only 50.7% and 47.8% of women who were eligible for free screening attended BCS and CCS, respectively. These are far from the 2022–2030 targets (11). Thus, increasing women's enthusiasm for screening is desired. The findings of hierarchical multiple logistic regression analysis showed that the latter model was interpreted more strongly than the former model, from Model 1 to 5, for the screening attendance of "two cancers". The binary logistic regression analysis showed the enabling factors and risk factors for BCS and CCS utilization. The view that screening is determined by multiple factors related to the physical and social environments (15) was verified once again. Thus, it is necessary to consider both proximal and distal factors. Social resources should match with women's screening needs.

There were differences between the age groups. Age 35–64 years was positively associated with screening attendance compared with age 18–34 years. In recent years, the rural women's upper age limitation of participating in the screening program for the "two cancers" was increased from 59 to 64 years (10). The boost may have been given by the policy. In China, the women with 45–55 years of age are at high risk for BC (22). This may make women more alert for screening. Because the incidence age of women's "two cancers" is gradually getting younger, it may be useful to continue to expand the program for a free screening. Women's gestational experiences were also significantly related to BCS and CCS, which is consistent with a previous study in the Midwestern United States (23). Women who have not been pregnant more easily miss the screening because of the erroneous view that they are at a lower risk of cervical cancer. It was not shocking that the BCS and CCS non-attendance rates of the women who did not have a gestational experience were up to 88.9% and 92.7%. Therefore, advocacy and education regarding reasons for the diseases should be strengthened, especially for these women. A previous study showed that women with at least one chronic health condition were more likely to be screened (24). Our study also showed that women with chronic diseases such as hypertension, diabetes, and any other chronic diseases diagnosed by a doctor were significantly screened, especially by BCS. This may be explained by more communication with the doctor for health prevention when they visit the doctor. Some studies have shown that the number of visits to a doctor is positively related to attendance in mammography screening (25, 26). Doctors and other health staff members should strengthen their guidance of screening. Obesity is a recognized risk factor for the development of breast cancer, and obese women are at increased risk of cervical cancer. There are inconsistent results regarding the relationship between BMI and screening in women. A previous study has shown that underweight, overweight, and obese women were more likely to delay breast examination and Pap smear testing compared to women with normal weight (27). Charkhchi et al., however, did not find a significant relationship between obesity and BCS or CCS rates (28). Our findings showed that obesity was a barrier to BCS, which is consistent with a study in China (29), but was not significantly related to CCS. These results indicate that obese women may lack risk awareness regarding the relationship between obesity and BCS or CCS. Thus, it is necessary to provide risk education to women with obesity.

A previous study reported that physical exercise increased clinical breast examination and mammography by 0.21 times and 0.13 times, respectively (30). Our results also showed that weekly exercise was positively associated with screening attendance. Health attitudes may be the reason for participating in screening (31). Jin et al. (32) indicated that women who underwent regular medical checkups were more likely to be screened. Our findings also showed these results. In addition to health attitudes (31) and communication with healthcare staff (32), a possible reason is that the project for "two-cancer" screening may be included in some health checkups. Thus, it is important to promote women's attitudes. It is key to mobilizing women to participate in health checkups. At the same time, a communication mechanism between medical workers and women needs to be established. Surprisingly, history of smoking and alcohol consumption were not significantly related to screening attendance in this study. The data on the effect of smoking and alcohol consumption on screening were also contradictory in a previous study. Some studies reported a positive association between absence of alcohol and smoking

TABLE 4 Binary logistic regression analysis of factors associated with BCS and CCS.

Variables			BCS		CCS	
			β	OR(95%CI)	β	OR(95%CI)
Personal traits						
Age		35–64	0.92	2.50 (1.93–3.23)***	0.94	2.55 (1.97–3.29)***
Gestational experiences		1	1.36	3.89 (2.34–6.49)***	1.41	4.08 (2.33–7.15)***
		2 or above	1.31	3.70 (2.22–6.18)***	1.41	4.09 (2.34–7.17)***
Chronic disease status		With	0.23	1.26 (1.03–1.55)*	0.02	1.02 (0.83–1.25)
BMI		Underweight	0.10	1.10 (0.77–1.58)	0.33	1.39 (0.97–1.98)
		Overweight	0.01	1.01 (0.84–1.22)	0.04	1.04 (0.87–1.25)
		Obese	−0.37	0.69 (0.49–0.97)*	−0.09	0.92 (0.66–1.28)
Behavior characteristics						
Health behaviors	History of smoking	No	0.35	1.42 (0.54–3.78)	0.22	1.25 (0.48–3.28)
	History of alcohol	No	−0.25	0.78 (0.55–1.10)	−0.12	0.89 (0.63–1.25)
	The status of exercise	Yes	0.46	1.58 (1.34–1.87)***	0.44	1.55 (1.31–1.83)***
	Health checkup	Yes	2.16	8.65 (7.29–10.25)***	2.01	7.42 (6.30–8.86)***
HRQoL	Health profile	High	−0.06	0.95(0.76–1.18)	−0.14	0.87 (0.70–1.09)
	Overall self-rated health status	Medium	0.19	1.21 (0.97–1.50)	0.12	1.13 (0.91–1.39)
		High	0.32	1.38 (1.04–1.83)*	0.12	1.13 (0.85–1.50)
Interpersonal network						
Marital status		Married	0.33	1.39 (0.95–2.02)	0.59	1.64 (1.12–2.40)*
Number of children		1 or above	1.17	3.21 (1.48–6.97)**	1.60	4.95 (1.87–13.13)**
Household size		2	−0.52	0.59 (0.36–0.99)*	−0.64	0.53 (0.32–0.88)*
		3 or above	−0.46	0.63 (0.39–1.02)	−0.57	0.57 (0.35–0.92)*
Work and life						
Income		High	−0.05	0.96 (0.80–1.15)	−0.02	0.98 (0.82–1.17)
Employment		Retired	0.24	1.28 (0.93–1.74)	0.23	1.25 (0.92–1.71)
		Employed	0.56	1.75 (1.39–2.20)***	0.54	1.71 (1.36–2.15)***
		In-school student	−0.70	0.50 (0.13–1.86)	−1.46	0.23 (0.03–1.95)

(Continued)

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TABLE 4 Continued

Variables		BCS		CCS	
		β	OR(95%CI)	β	OR(95%CI)
Education	Junior high school/ senior high school	0.13	1.14 (0.93–1.40)	0.05	1.05 (0.85–1.28)
	Technical school	−0.11	0.90 (0.60–1.34)	−0.25	0.78 (0.53–1.16)
	College or above	0.21	1.23 (0.89–1.69)	0.02	1.02 (0.75–1.40)
Distance from the nearest hospital	≥1 km	−0.02	0.98 (0.84–1.15)	−0.03	0.97 (0.83–1.14)
Social policies enabling resources					
Family doctors	Yes	−0.02	0.99 (0.76–1.27)	−0.07	0.93 (0.72–1.20)
	No	0.05	1.05 (0.83–1.34)	−0.08	0.92 (0.73–1.17)
Health records	Yes	0.09	1.10 (0.89–1.35)	0.26	1.30 (1.06–1.59)*
	No	0.09	1.09 (0.80–1.50)	0.06	1.06 (0.77–1.45)
Insurance status	Insured	−0.39	0.68 (0.31–1.50)	−0.47	0.63 (0.28–1.40)
-2 Log likelihood		3,621.523		3,647.894	
$\chi 2$		1,181.897		1,087.922	
Sig		0.000		0.000	
Nagelkerke R^2		0.384		0.360	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. BCS, breast cancer screening; CCS, cervical cancer screening; BMI, body mass index; HRQoL, health-related quality of life.

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and screening (31, 33), while others revealed that individuals who did not drink or smoke were less likely to be screened (34). In addition, some authors have not found any associations (35, 36). The results of this study also revealed that having a high level of health profile was not significantly related to screening attendance, which is not consistent with a study in Korea (37). We deduced the possible explanation that women with a higher health profile were more likely to ignore their health problems than others. Therefore, it is necessary to improve healthcare awareness. However, women with a high overall self-rated health status were more likely to be screened for BC. This means that women may pay more attention to BC than CC. The data also reported that the proportion of participants in BCS was 5.3% higher than that in CCS for women who had higher scores.

Marital status and family are important components of the interpersonal network. The results showed that being married was significantly associated with screening, especially for CCS. In addition, having children was significantly associated with screening attendance. Leinonen's study also showed that being unmarried and having no children predicted non-adherence to CCS (38). Sex life is an important factor affecting the development of CC. In addition, Ogunwale (39) reported that perceptions of support from male partners played an important role in women's CCS. This may explain why married women are more likely to be screened for CC. A previous study revealed that higher levels of social support networks led to a more positive attitude toward preventive healthcare (40). Kristiansen (41) showed that women living in households of two to four persons were less likely to not undergo mammography screening. However, in this study, larger household size was a barrier to women's BCS and CCS. The screening rates of all the women did not reach 50%, which indicated that support from family was weak and that the role of the family was not fully functional. Therefore, knowledge, risk education, and screening-related advocacy may not only be enhanced for women but may also be emphasized for family members. If possible, connectedness to the neighborhood or society should be established.

The findings showed that women who were employed had a higher likelihood of participation in screening than those who were unemployed or out of work. Charkhchi's study also revealed that being employed significantly increased breast screening adherence (28). The reasons for this result may be that women with work have more access to information and knowledge of screening through communication with colleagues (42), and have more opportunities for physical examinations organized by the unit (43) than women who were unemployed or out of work. Those who were retired faced a situation similar to that of unemployed women. Students may have more access to information, but there is no significant association between in-school students and screening attendance. Thus, on one hand, more publicity channels should be expanded. However, the screening awareness among school students should be improved through health education. This study revealed that there were group differences in women's educational level, but that this was not related to the uptake of screening, which is consistent with Charkhchi's (28) study. Higher income was not significantly related to screening attendance, which is similar to the study of Yan (44). For both high-income and low-income women, there was a higher rate of participants choosing non-attendance in this study. There were no significant differences in distance from the nearest hospital. Additionally, it was not significantly associated with screening attendance. A similar result was reported in You's study (45).

Having family doctors and health records was not significantly associated with screening for the "two cancers." Fortunately, women with health records are more likely to be screened for CC. However, these women's BCS and CCS non-attendance rates both nearly reached 50%. These results indicate that family doctors and health staff do not currently play a role in increasing adherence to screening recommendations. A previous study also showed that lack of physicians' recommendations was one of the barriers identified and was caused by lack of knowledge and awareness of screening benefits (46). Therefore, to improve the attitude of family doctors and health staff, their knowledge popularization and education about screening should be strengthened. Being insured was not significantly related to screening attendance. Over 50% of the insured women did not undergo BCS or CCS. We speculate that this may be related to income. In total, 55.4 % of the women had lower income. The cost of screening cannot be reimbursed through insurance. Low-income women may not be willing to pay extra for screening even if they are insured. Thus, insurance was not a screening predictor. Previous studies have reported similar results (43).

Limitation

The results are meaningful for promoting the screening of the two cancers. However, this study has some limitations. First, the samples were all from Jiangsu province, so there may be limitations to the nationwide generalization of the conclusions. Second, marital status, children, and families were included in the interpersonal network, which was not sufficient to some extent. Interpersonal interactions in the society or the community are also important. Thus, support from the society or the community may be added in the future. Third, the three Level 5 variables in the hierarchical multiple logistic regression analysis, which were drawn from the NHSS, were not significantly associated. It is possible that more variables regarding social policies should be measured in further studies.

Conclusion

This study provides an ecological explanation for why women undergo or choose to abstain from BCS and CCS. As the five variables are entered into the regression model with the simultaneous forced entry method, the explanatory power of the model is increased. Both proximal and distal factors should be considered. The findings are of great significance in improving women's "two-cancer" screening service utilization.

Data availability statement

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding authors. Requests to access the publicly available datasets used in this study should be directed to heyuan@njmu.edu.cn.

Author contributions

YH and YS: methodology, software, and writing-review and editing. YS, YH, MCh, and WL: data curation. YS and YM: visualization. YH: conceptualization, resources, supervision, project administration, and funding acquisition. MCh and WL: resources, supervision, and project administration. All authors: writing original draft preparation, 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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The impact of national centralized drug procurement on health expenditures for lung cancer inpatients: A difference-in-differences analysis in a large tertiary hospital in China

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The availability and affordability of medicines remain major health challenges around the world. In March 2019, the Chinese government introduced a pilot National Centralized Drug Procurement (NCDP) program in order to reduce drug prices and improve the affordability of effective and safe medicines. This study aimed to assess the impact of NCDP policy on health expenditures of cancer patients. Using inpatient discharge records from a large hospital in the pilot city, we performed a difference-in-differences design to estimate the change in health expenditures before and after the policy. We found that the implementation of NCDP was associated with a significant decrease in total expenditures (14.13%) and drug expenditures (20.75%) per inpatient admission. There were also significant reductions in non-drug-related expenditures, including a 7.65% decrease in health service expenditures, a 38.28% decrease in diagnosis expenditures, and a 25.31% decrease in consumable material expenditures per inpatient admission. However, the NCDP implementation was associated with a 107.97% increase in the traditional Chinese medicine expenditures. Overall, the study provided evidence that the NCDP policy has achieved its goals of high-quality and affordable healthcare. The drug expenditures of lung cancer patients revealed a continuous decline, and the policy may have spillover effects on other healthcare expenditures. Further studies are needed to evaluate the long-term effects of NCDP on policy-related expenditures and health outcomes.

KEYWORDS

cancer, drug policy, evidence-based policy, health economics, policy evaluation

Introduction

The affordability and availability of medicines remain the major issues for healthcare systems globally, especially for patients in developing countries (1–5). Despite a series of drug policies being implemented since the major healthcare reform in China from 2009, such as the National Essential Medicine Policy and the Zero Mark-up Drug Policy, drug expenditures are still increasing every year and the rising drug expenditures have been serious burdens for both family and society in China (6, 7).

To reduce drug expenditures of patients, in March 2019, China launched the National Centralized Drug Procurement (NCDP) program. There were 11 cities selected as the first round of NCDP pilot cities, including four municipalities (Beijing, Tianjin, Shanghai, and Chongqing) and seven major cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu, and Xi'an); thus, the policy was also known as the "4+7" policy. As a major reform of the current drug procurement system, the NCDP requested all public hospitals in the pilot cities to purchase 60 to 70% of their total annual demand for selected drugs, which aimed to achieve a lower price in exchange for a larger volume of purchase (8).

Anticancer drugs account for the highest proportion of pharmaceutical spending among all therapeutic classes in China, and the heavy economic burden on cancer patients attracted the attention of policymakers (9–13). In the first round of NCDP, Pemetrexed and Gefitinib, two anticancer drugs for the first-line lung cancer treatment were included, which were the two most expensive drugs in the procurement list and had prices cut by 71 and 76%, respectively (5). Unlike drugs for chronic disease in the NCDP program, anticancer drugs are often used in combination with other treatments (14). Previous studies found that, despite the fact that drug price decreased after the policy (e.g., the Drug Zero Mark-up policy), there were no measurable changes in total expenditures, as the expenditures for diagnostic tests and medical consumables were increased (15). Therefore, whether the decline in drug prices can reduce the economic burden on patients after the NCDP remains to be further verified.

Although previous studies have reported the potential impact of the NCDP policy on drug expenditures, none of them focused on anticancer drugs. Most studies found that the volume of policy-related drugs increased, while the purchase spending declined after the implementation of NCDP (4, 16, 17). The policy effects on antihypertensive drugs, antibiotic drugs, and nucleoside analogs were consistent with the overall policy effects (18–20).

Additionally, the data of most previous studies were pharmaceutical procurement records and they evaluated the drug purchase spending at health facility level. Although there is strong consistency between drug purchase data and drug use data (such as prescriptions and claims), it is possible that the policy effects on patients could not be evaluated through procurement records (21, 22). Only one study used the hospital information system data, but this study applied an interrupted time series design and estimated the average monthly drug expenditures of patients treated in outpatient and emergency departments (23).

In this study, we used inpatient discharge records from a large oncology specialized hospital in Chengdu, one of the pilot cities, and adopted a difference-in-differences (DID) approach to evaluate the impact of NCDP policy on the health expenditures of lung cancer inpatients. Using individual-level data and a quasi-experimental design, our study added strong patient-level evidence to comprehensively reflect the policy effects on expenditures of patients during hospitalization.

Materials and methods

Study design

We performed a DID design to estimate the NCDP policy effects, which is a popular study design to compare outcomes before and after a policy change for one group affected by the policy (treatment group) and another group not affected by the policy (control group) (24, 25). As a strong quasi-experimental design to mimic the experimental design, DID analysis is much better than traditional observational studies of controlling only for observed confounding *via* regression modeling (26).

The two bid-winning products, Pemetrexed and Gefitinib, were recommended for the first-line chemotherapy and targeted therapy for the treatment of non-small cell lung cancer (NSCLC). Thus, the treatment group of DID design included the patients with lung cancer who mainly received chemotherapy and targeted therapy during the hospitalization. And the control group included the patients with other types of cancer who received chemotherapy and targeted therapy, for whose expenditures were not affected by the NCDP policy.

Setting and data source

Chengdu was one of the pilot cities in the first round of NCDP policy, and the policy was implemented on 25 March 2019. We used the data from a large tertiary-grade level-A oncology specialized hospital in southwest China, which had more than 400,000 outpatients and 60,000 inpatients annually and could be representative enough for the pilot city. The data were extracted from 1 January 2019 to 31 December 2019 from inpatient discharge records of the hospital, which contained the information of patients during hospitalization, including

Abbreviations: NCDP, National Centralized Drug Procurement; DID, Difference-in-differences; NSCLC, Non-Small Cell Lung Cancer; TCM, traditional Chinese medicine; CNY, Chinese Yuan; CI, confidence interval.

diagnosis, treatment, operation, expenditures, and payment way. Ethical approval for the study was not required because no potentially identifiable human data were used and presented in this study.

Sample selection

Based on the International Classification of Diseases 10 (ICD-10) codes, we identified therapy type and cancer type of patients by primary diagnosis and secondary diagnosis, respectively. We included patients with the following criteria: (1) inpatient; (2) the patient was discharged from the hospital between 1 January 2019 and 31 December 2019; and (3) the main therapy (primary diagnosis) was chemotherapy or targeted therapy. Considering the representativeness of cancer patients, we excluded the patients with rare cancer (< 500 observations). Overall, a total of 23,443 cases were selected in our study, including patients with lung cancer, breast cancer, cervical cancer, ovarian cancer, colon cancer, rectal cancer, gastric cancer, non-follicular lymphoma, liver cancer, nasopharyngeal cancer, corpus uteri cancer, and esophageal cancer. The ICD codes for inclusion and exclusion criteria are summarized in Table 1.

Outcome measurements

The outcomes were expenditures of cancer patients per hospitalization which contain the expenditures could be reimbursed or not, including total expenditures, drug expenditures (Western medicine), health service expenditures, diagnosis expenditures, treatment expenditures, consumable material expenditures, and traditional Chinese medicine (TCM) expenditures. Health service expenditures included general medical service fees, medical operation fees, nursing fees, and other health service fees. Treatment expenditures included surgical treatment fees and non-surgical treatment fees. Diagnosis expenditures included pathological diagnosis fees, laboratory diagnosis fees, imaging diagnosis fees, and clinical diagnosis fees.

TABLE 1 ICD-10 code for inclusion and exclusion criteria.

Variable name	ICD-10 Code	Diagnosis
Primary diagnosis	Z51.1	Chemotherapy session for neoplasm
	Z51.8	Other specified medical care (Target therapy)
Secondary diagnosis	C50	Malignant neoplasm of breast
	C53	Malignant neoplasm of cervix uteri
	C34	Malignant neoplasm of bronchus and lung
	C56	Malignant neoplasm of ovary
	C18	Malignant neoplasm of colon
	C20	Malignant neoplasm of rectum
	C16	Malignant neoplasm of stomach
	C83	Non-follicular lymphoma
	C22	Malignant neoplasm of liver and intrahepatic bile ducts
	C11	Malignant neoplasm of nasopharynx
	C54	Malignant neoplasm of corpus uteri
	C15	Malignant neoplasm of esophagus

Statistical analysis

We described patient characteristics and outcomes stratified by groups and time. Patient characteristics included age, gender, metastasis, treatment type, payment way, and length of stay. To test the difference between the two groups, we used t-test for continuous variables and chi-square test for categorical variables.

Following the DID design, the impact of NCDP policy was estimated by comparing the differences between (1) changes between the pre- and post-intervention periods within the treatment group (patients with lung cancer) and (2) changes between the pre- and post-intervention periods within the control group (patients with other types of cancer). We applied the DID method using the following equation:

$$\log(Y_{it}) = \beta_0 + \beta_1\, Treat_i + \beta_2 Time_t + \beta_3\, Treat_i * Time_t + \beta\, \Sigma Z_{it} + \delta_t + \varepsilon_{it} \quad (1)$$

where Y_{it} refers to the expenditures of a patient i who was hospitalized in time t. $Treat_i$ is a dummy variable that coded 1 for the lung cancer patient and 0 otherwise. $Time_t$ is also a dummy variable that coded 0 before the NCDP policy and 1 after the policy. The vector Z_{it} is a vector of covariates to adjust for characteristics of patients. δ_t is a series of variables used to control monthly linear and quadratic time trends. We used ordinary least square with robust standard errors in DID regression. The DID estimation β_3 is an interaction variable between $Treat_i$ and $Time_t$, which represents the effects of NCDP. Since the expenditures were not always normal distribution, all the expenditure data used in DID regression were expressed in the logarithmic form. Thus, the interpretation of β_3 is the rate of change in log(Y) as X varies. The percentage change in Y as X varies could be calculated as $100(e^{\beta_3}$ -1)%, which directly reflected the effects of NCDP on expenditures (27). There were no missing data in the dataset.

An important assumption of DID analysis is that there would be parallel trends in the outcomes between the treatment group and the control group in the absence of the NCDP policy. We tested the parallel trends assumption in two ways. First, we plotted the monthly trends of medical expenditures by the treatment group and the control group, respectively. Then,

we implemented an event study approach that would more specifically trace out the timing of effects (28). The regression model was defined in the following equation:

$$Y_{it} = \beta_0 + \sum_{j=-3,\ -2,\ 1,\ 2,\ 3\ldots} \beta_j\ Treat_i * Month_j + \beta \Sigma Z_{it} + \varepsilon_{it} \quad (2)$$

where $Month_j$ is a dummy variable that coded 1 if the patient was discharged from the hospital in the month j. And j means the month prior or post to the policy. We identified that April was the first month after the implementation of the NCDP (j = 1). Then, we constructed a series of dummies: 3 months before policy (j = −3), 2 months before policy (j = −2), 1 month after policy (j = 1), and 2 and more months after policy (j = 2, 3, . . .). The month just prior to policy (j = −1) was excluded as the reference. Other variables are the same as the equation (1). β_j represents the difference between the treatment group and the control group in the month j. The common trends assumption is appropriate if the coefficients before the policy are not statistically significant.

To explore the robustness of our main results, we carefully reviewed the clinical guidelines and policies related to cancer to see whether there are some significant changes in the study period. Then, we performed a series of sensitivity analyses to eliminate the potential influence of selection bias and confounding. First, we implemented a placebo test based on a series of randomized treatment groups. Second, we excluded breast cancer, cervical cancer, ovarian cancer, and corpus uteri cancer patients in the control group to avoid confounding by gender differences. Third, we plotted the raw data of our whole sample and found that the expenditures rapidly fell in November and rose in December. Considering that there might be some events at the end of the year (such as medical insurance settlement and hospital performance assessment), we excluded the patients in November 2019 for inconsistent trends of outcomes in the month (29). Finally, considering the potential seasonality in one-year time, we added Fourier terms to capture it. All statistical analyses were performed using Stata 15.1.

Results

There were 27,412 inpatients with chemotherapy or targeted therapy in the dataset. We excluded patients with rare cancer (< 500 cases) and finally included 23,443 patients. Patients in the treatment group were lung cancer patients (N = 3,636), and patients in the control group were patients with other types of cancers (N = 19,807), including breast cancer (N = 6,511), cervical cancer (N = 3,980), ovarian cancer (N = 1,770), colon cancer (N = 1,452), rectal cancer (N = 1,372), gastric cancer (N = 1,304), non-follicular lymphoma cancer (N = 858), liver cancer (N = 699), nasopharyngeal cancer (N = 640), corpus uteri cancer (N = 612), and esophageal cancer (N = 609).

The descriptive statistics are summarized in Table 2. Baseline absolute differences in age, gender, metastasis, treatment type, payment way, and length of stay were statistically significant. These characteristics were controlled in the DID regression model.

Trends for health expenditures of cancer patients

Table 3 reports the descriptive analysis of all outcomes and Figure 1 visualizes the trends in monthly health expenditures by the treatment group and the control group. The trends were similar for the two groups before the NCDP policy, indicating that the two groups were comparable. After the policy, trends in all types of expenditures declined in both the groups, but the changes were more notable in the treatment group. For example, the change of total expenditures for patients in the treatment group was −21.37% [the average total expenditures per hospitalization was 14,536.21 Chinese Yuan (CNY) before the policy and 11,429.45 CNY after the policy], and the change of total expenditures for patients in the control group was −19.17% (the average total expenditures per hospitalization was 13,166.93 CNY before the policy and 10,642.66 CNY after the policy).

Impact of the NCDP policy on health expenditures for lung cancer patients

The last three columns of Table 3 show the DID estimations and the policy effects. The DID estimation coefficients of total expenditures and drug expenditures were significantly negative, indicating that the NCDP policy could significantly reduce the overall spending of lung cancer patients. After the implementation of NCDP policy, the total expenditures and drug expenditures decreased by 0.1523 and 0.2326 log points, respectively, that is, a −14.13% change in total expenditures and a −20.75% change in drug expenditures.

Meanwhile, the results also identified significant decreases in health service expenditures (−7.65%), diagnosis expenditures (−38.28%), and consumable material expenditures (−25.31%) after the NCDP policy. The decrease in health service expenditures was mainly attributable to the decline in general medical service fees and nursing fees (Supplementary Table S1). The decrease in diagnosis expenditures was mainly attributable to the decline in laboratory diagnosis fees and imaging diagnosis fees (Supplementary Table S2). In addition, despite the declining trends in TCM expenditures, we found that the DID estimation coefficient was significantly positive, indicating that the NCDP implementation was associated with a 107.97% increase in TCM expenditures.

TABLE 2 Baseline characteristics for cancer patients in treatment group and control group.

Variables	Treatment group			Control group			Difference (*p*-value)
	Overall (*N* = 3,636)	Before NCDP (*N* = 839)	After NCDP (*N* = 2,797)	Overall (*N* = 19,807)	Before NCDP (*N* = 4,020)	After NCDP (*N* = 15,787)	
Age [Mean (SD)]	58.63 (8.81)	57.33 (9.49)	59.02 (8.56)	52.64 (10.30)	52.70 (10.43)	52.63 (10.27)	<0.001
Length of stay [Mean (SD)]	6.24 (4.29)	6.91 (4.52)	6.03 (4.20)	5.12 (3.75)	5.62 (4.14)	4.99 (3.63)	<0.001
Gender [*N* (%)]							
Male	2,594 (71.3%)	578 (68.9%)	2,016 (72.1%)	4,868 (24.6%)	1,069 (26.6%)	3,799 (24.1%)	<0.001
Female	1,042 (28.7%)	261 (31.1%)	781 (27.9%)	14,939 (75.4%)	2,951 (73.4%)	11,988 (75.9%)	
Metastasis [*N* (%)]							<0.001
No	1,144 (31.5%)	317 (37.8%)	827 (29.6%)	15,264 (77.1%)	3,069 (76.3%)	12,195 (77.2%)	
Yes	2,492 (68.5%)	522 (62.2%)	1,970 (70.4%)	4,543 (22.9%)	951 (23.7%)	3,592 (22.8%)	
Treatment type [*N* (%)]							<0.001
Maintenance chemotherapy for malignant tumors	2,445 (67.2%)	520 (62.0%)	1,925 (68.8%)	8,542 (43.1%)	1,595 (39.7%)	6,947 (44.0%)	
Chemotherapy of malignant tumors after surgery	984 (27.1%)	285 (34.0%)	699 (25.0%)	10,049 (50.7%)	2,254 (56.1%)	7,795 (49.4%)	
Targeted therapy for malignancies	109 (3.0%)	19 (2.3%)	90 (3.2%)	104 (0.5%)	22 (0.5%)	82 (0.5%)	
Chemotherapy of malignant tumors before surgery	12 (0.3%)	3 (0.4%)	9 (0.3%)	848 (4.3%)	140 (3.5%)	708 (4.5%)	
Other treatment types	86 (2.4%)	12 (1.4%)	74 (2.6%)	264 (1.3%)	9 (0.2%)	255 (1.6%)	
Payment type [*N* (%)]							<0.001
Urban Employee Basic Medical Insurance	3,200 (88.0%)	751 (89.5%)	2,449 (87.6%)	17,551 (88.6%)	3,583 (89.1%)	13,968 (88.5%)	
Urban Resident Basic Medical Insurance	362 (10.0%)	82 (9.8%)	280 (10.0%)	1,562 (7.9%)	383 (9.5%)	1,179 (7.5%)	
New Cooperative Medical Scheme	5 (0.1%)	0 (0.0%)	5 (0.2%)	32 (0.2%)	8 (0.2%)	24 (0.2%)	
Other payment types	69 (1.9%)	6 (0.7%)	63 (2.3%)	662 (3.3%)	46 (1.1%)	616 (3.9%)	

(1) The overall difference between the treatment group and the control group.

Common trends test for DID

We tested for parallel trends by evaluating the differences in temporal trends between the intervention group and comparison group. Figure 2 shows the point estimates and 95% confidence interval (95% CI) of coefficients for the interaction variable between the month dummy variable and the intervention dummy variable. The coefficients of interaction before the policy were not significant (the 95% CI of coefficients contained zero), indicating that in the absence of the policy, the unobserved differences between the treatment group and the control group were the same over time. These results support that our identification strategy is appropriate.

Sensitivity analyses

We conducted four sensitivity analyses to prove that the main results are robust. First, we performed a placebo test to indirectly see whether the non-direct observable characteristics will affect the benchmark regression results (30). We kept the policy launched time and created a series of virtual treatment groups that were not affected by the policy. More specifically, the research sample in our main analysis contains 23,443 patients, of whom 3,636 patients were in treatment group. Therefore, we randomly selected 3,636 patients as a virtual treatment group, and the remaining 19,807 patients were used for a control group. Then, we conducted the DID regression as equation (1). This process was repeated 500 times and the distribution diagrams of the coefficients of DID are shown in Figure 3. The result found that the mean value of β was close to zero and significantly different from the actual regression coefficients (the red vertical dashed line), indicating that the main results were driven by the NCDP policy rather than other factors (e.g., the change of treatment patterns).

Second, we restricted our sample to avoid confounding by gender differences. Third, because all outcomes rapidly fell in November and rose in December, we excluded the patients in November and repeated the DID regression. Fourth, we used Fourier terms to control for the seasonality

TABLE 3 Expenditures of cancer patients and effects of the NCDP policy on medical expenditures (CNY).

	Descriptive statistics (Mean)						DID estimation [β (95% CI)]		Effects of the NCDP $100(e^{\beta}-1)$ %
	Treatment group			Control group			(1)	(2)	
	Before NCDP	After NCDP	Change	Before NCDP	After NCDP	Change	Unadjusted model	Adjusted model	
Total expenditures	14,536.21	11,429.45	−21.37%	13,166.93	10,642.66	−19.17%	−0.1789*** (−0.2365, −0.1214)	−0.1523*** (−0.2006, −0.1040)	−14.13%
Drug expenditures	7,715.74	5,704.04	−26.07%	7,147.97	5,485.11	−23.26%	−0.2633*** (−0.3589, −0.1676)	−0.2326*** (−0.3219, −0.1432)	−20.75%
Health service expenditures	1,946.45	1,607.89	−17.39%	1,310.30	1,135.49	−13.34%	−0.1186*** (−0.1777, −0.0595)	−0.0796*** (−0.1177, −0.0414)	−7.65%
Diagnosis expenditures	2,488.98	2,261.07	−9.16%	2,499.16	2,351.08	−5.93%	−0.5338*** (−0.6361, −0.4315)	−0.4826*** (−0.5749, −0.3903)	−38.28%
Treatment expenditures	511.79	502.54	−1.81%	526.08	419.56	−20.25%	−0.1220* (−0.2252, −0.0188)	−0.0476 (−0.1410, 0.0459)	−4.65%
Consumable material expenditures	706.86	505.52	−28.48%	795.68	668.91	−15.93%	−0.2987*** (−0.3823, −0.2150)	−0.2918*** (−0.3606, −0.2230)	−25.31%
TCM expenditures	990.97	714.60	−27.89%	720.25	454.56	−36.89%	0.7620*** (0.5399, 0.9841)	0.7322*** (0.5169, 0.9476)	107.97%

(1) We used Ordinary Least Square with robust standard errors in DID regression. (2) The unadjusted regression model only included the indicators of time and policy, and the interaction of time and policy. The regression model adjusted for participant characteristics and time trend variables, including age, gender, metastasis, treatment type, payment type, and length of stay. (3) The outcomes of expenditures in DID regression were transformed to logarithm, so the policy effects could be calculated by $100(e^{\beta}-1)$ %. (4) *p < 0.05, ***p < 0.001.

in study period. Other settings were the same as equation (1) in sensitivity analyses 2, 3 and 4, and the results are shown in Supplementary Tables S3–S5, which are similar to the main analysis.

Discussion

Interpretation of findings

To the best of our knowledge, this was the first study that investigated the effects of NCDP policy on hospitalization expenditures of cancer patients. We focused on cancer patients who were most likely affected by high medical costs. Our study showed that after the implementation of NCDP, the total expenditures and drug expenditures of hospitalization for lung cancer patients decreased by 14.13 and 20.75%, respectively. This result was consistent with previous studies and it was reasonable because the NCDP policy was expected to reduce pharmaceutical spending and improve the accessibility of medical services (21–23). The prices of the 25 winning drugs in the first round of NCDP dropped by an average of 52% with the highest drop of 96% (5). Such significant drug price reduction also affected the prices of non-selected original drugs (31). Eli Lilly, for example, the original development company of Pemetrexed, offered to reduce the price of Pemetrexed by 30% in some provinces.

The NCDP policy might have spillover effects on non-drug-related expenditures. Our study found significant decreases in health service expenditures, diagnosis expenditures, and consumable material expenditures, indicating that the patients' demand for medical services decreased during hospitalization. We figured out two possible explanations. First, gefitinib, one of the selected drugs, is an oral targeted anticancer drug used to treat NSCLC. Patients normally take oral anticancer drugs just at home thus reducing the length of hospital stays. As a result, demand of patients for treatment and healthcare in hospitals decreased after the NCDP. Second, the Chinese government launched the national performance appraisal of tertiary public hospitals since 2019 (29). A key indicator of income structure is the percentage of healthcare service income of total healthcare income, which is calculated by (healthcare service income/total income) *100%. The healthcare service income is the total healthcare income except for drugs, consumables, and diagnostic income. This indicator is expected to be increased according to the document from the government (32). As the drug expenditures and total expenditures declined, physicians might decrease the use of diagnostic tests and consumable materials to make sure that the indicator was increased or stable. We calculated this percentage and showed the monthly trends in Supplementary Figure S1. The percentage of healthcare service income of total income for cancer patients

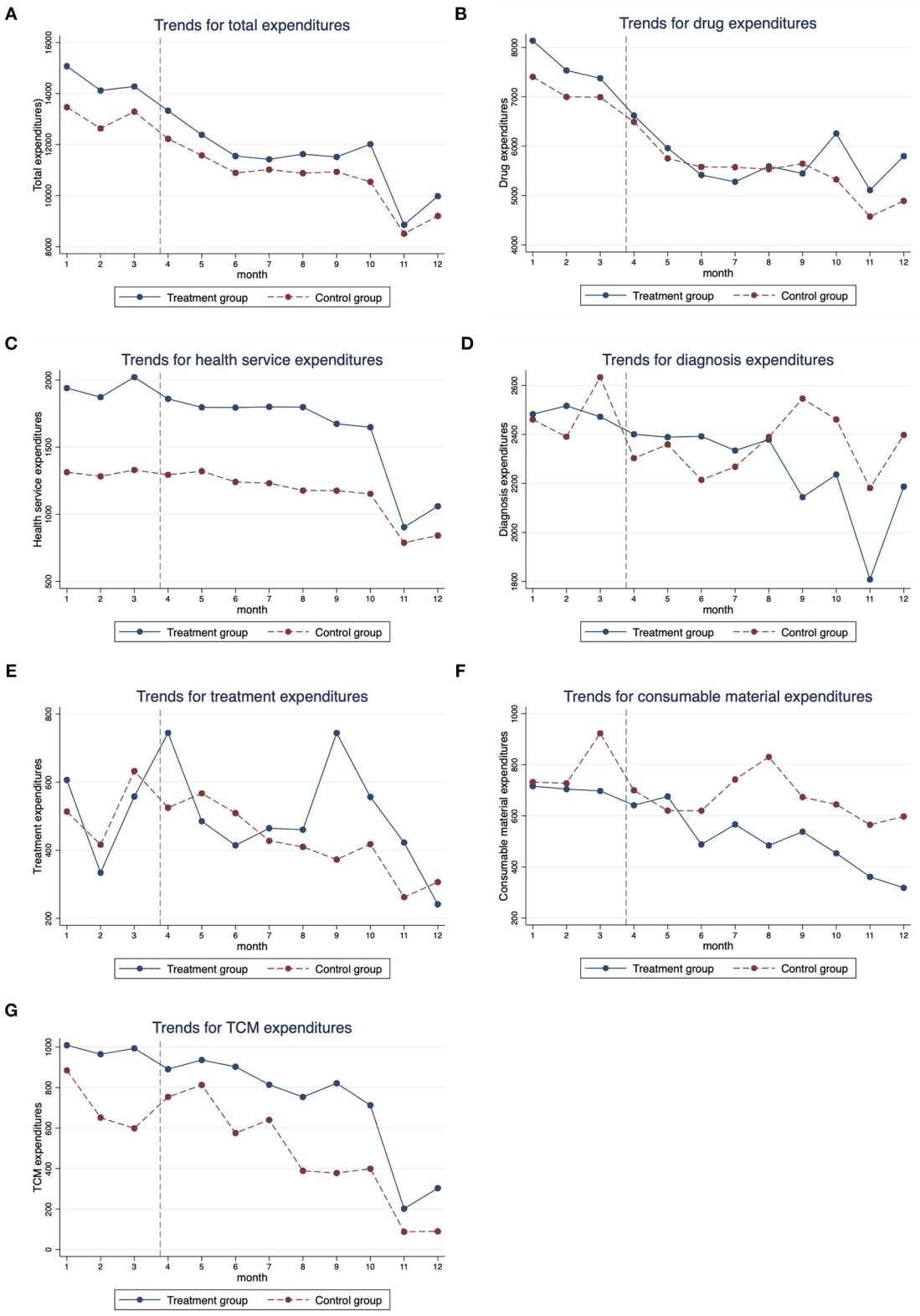

FIGURE 1
Monthly trends for medical expenditures of cancer patients from January 2019 to December 2019. **(A)** Total expenditures, **(B)** drug expenditures, **(C)** health service expenditures, **(D)** diagnosis expenditures, **(E)** treatment expenditures, **(F)** consumable material expenditures, and **(G)** TCM expenditures.

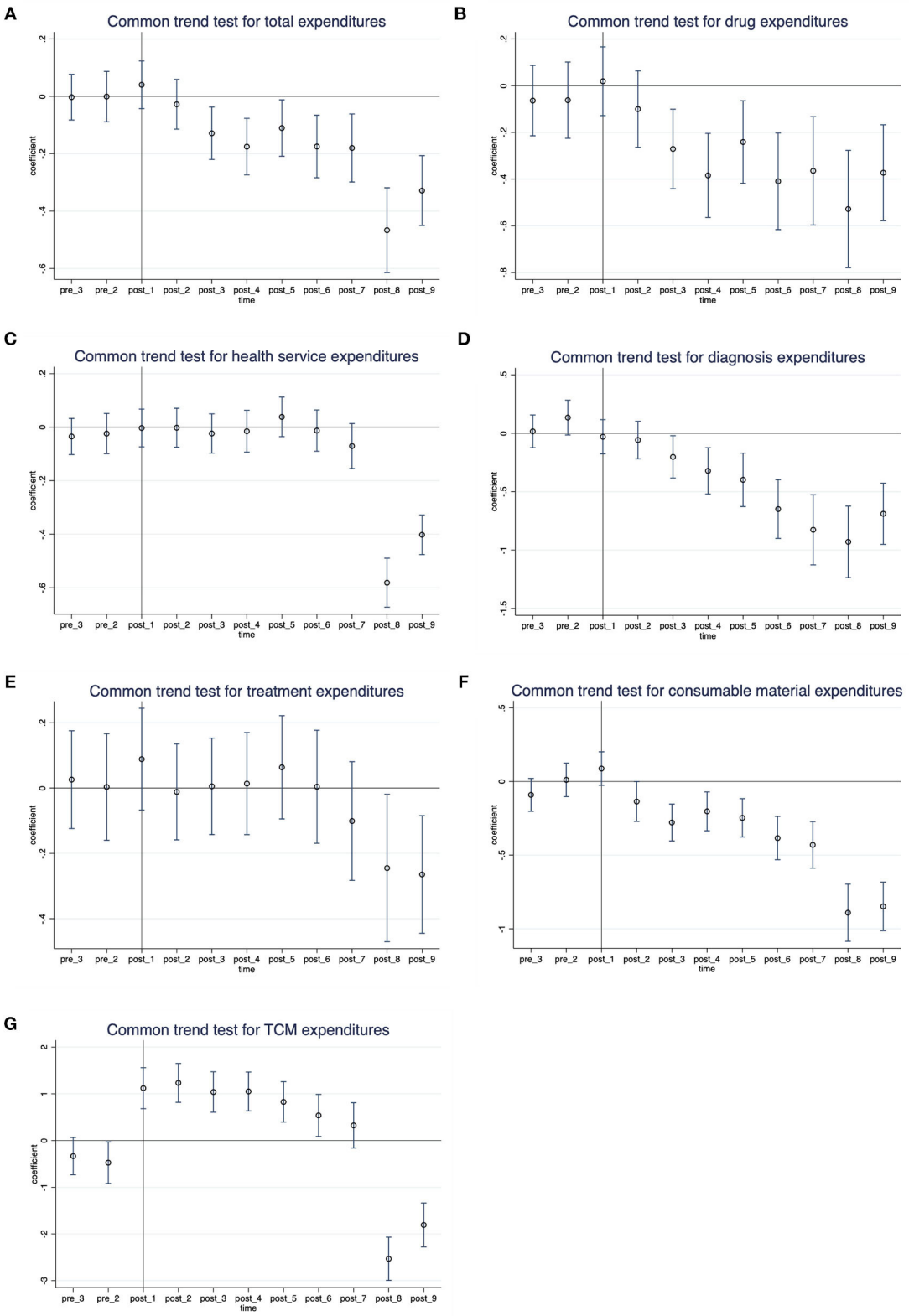

FIGURE 2
Common trends test for DID: Monthly differences between the treatment group and control group. **(A)** Total expenditures, **(B)** drug expenditures, **(C)** health service expenditures, **(D)** diagnosis expenditures, **(E)** treatment expenditures, **(F)** consumable material expenditures, and **(G)** TCM expenditures.

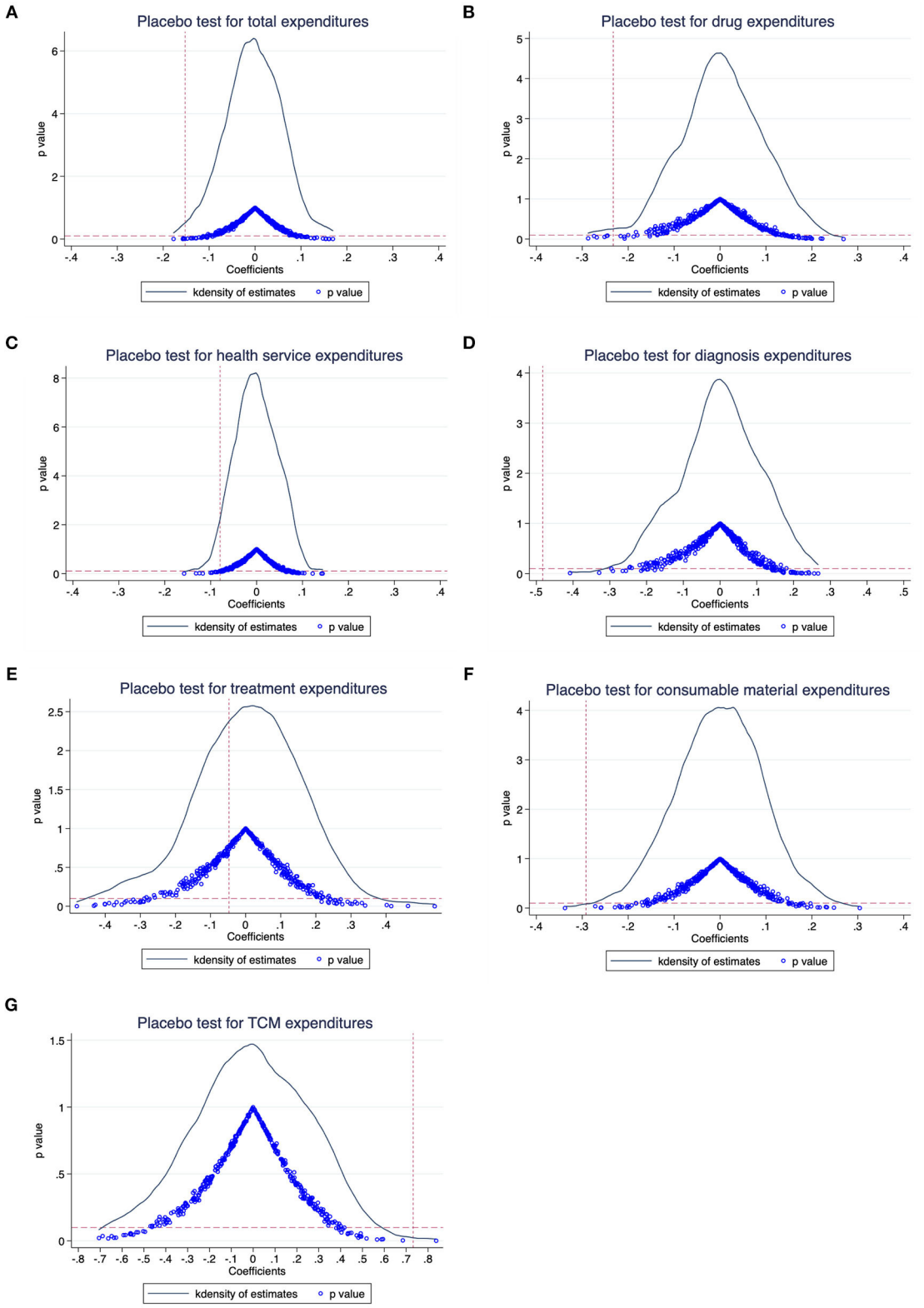

FIGURE 3
Placebo test results: The distribution diagrams of the coefficients. **(A)** Total expenditures, **(B)** drug expenditures, **(C)** health service expenditures, **(D)** diagnosis expenditures, **(E)** treatment expenditures, **(F)** consumable material expenditures, and **(G)** TCM expenditures.

was among 20%, and there was an increasing trend in the treatment group and a stable trend in the control group. Similar effects have been reported in previous studies. An earlier study about the Beijing Comprehensive Healthcare Reform found that after separating drug sales from hospital revenue, not only the drug costs but also the consumable costs were reduced (33). The spillover effects of NCDP could be considered to promote medical system reform in China in other aspects apart from drug bidding. We look forward to more studies to evaluate this effect.

However, this study found that the NCDP implementation was associated with a 107.97% increase in TCM expenditures. Similar results have been identified in other health policies in China. After the implementation of the National Essential Medicine System, many doctors reported that their fee-for-service activities increased, such as the prescribing of raw herbs and unprocessed traditional medicines (34). And the number of Western medicines per outpatient prescription decreased, while that of TCMs increased after the Drug Zero Mark-up policy (35). These studies suggested that physicians may increase prescriptions of TCM after such drug policies. A potential explanation is that the policy has an "income effect." As the prices of drugs drop significantly, patients are more willing and affordable for these complementary and alternative treatments to relieve pain and improve the quality of life (36). In addition, some articles found that the purchase volume and expenditures of alternative drugs (which have an alternative relationship with the bid-winning products in clinical use) increased significantly after the implementation of NCDP policy (19, 20). Therefore, as the increase of TCM used could be related to several aspects, we could not give a specific reason for this effect, which should be considered in future studies.

Policy implications

The study has several policy implications. First, this study provided evidence that the NCDP policy can indeed improve the affordability of selected drugs and reduce the financial burden on lung cancer patients. Until December 2021, six rounds of NCDP have been introduced, and the centralized procurement of high-value devices such as coronary stent, joint prosthesis, and intraocular lens has also been gradually carried out. More and more clinical necessary drugs and medical devices were included in the category of NCDP; thus, more patients could benefit from the policy. Second, after the implementation of NCDP, the health service expenditures, diagnosis expenditures, and consumable material expenditures of cancer inpatients have also been reduced, which indicated that the reform can promote the rational use of medical services and consumables in public hospitals. Third, we found that there was a significant increase in the use of alternative drugs after the policy. The policymakers should consider the related effects of health policy and monitor the utilization of both selected drugs and policy-related drugs to avoid the irrational use of such drugs (37, 38). Meanwhile, it is also necessary to promote the reform of the salary system in public hospitals and deal with the reliance on drug and consumable sales by increasing the income from health services.

Strengths and limitations

Our study has a few strengths. First, our study used patient-level data to assess the effects of NCDP pilot program on lung cancer patients. To the best of our knowledge, this was the first study using patient discharge records to evaluate the impact of NCDP on various types of expenditures of patients, not only the drug expenditures but also other expenditures such as diagnosis expenditures and consumable material expenditures. The findings can comprehensively reflect the effects of NCDP on expenditures of patients during hospitalization. Second, we applied a DID study design to minimize the potential confounding in observational studies and improve the strength of findings. DID can remove bias in treatment effect estimation due to confounding by unobserved time-varying factors that have changed the outcome in treatment group and control group in the same way (25). We tested the assumption of parallel trends for DID analysis, and a series of sensitivity analyses were conducted to approve the robustness of main results.

There are some potential limitations in our study. First, the data was collected from a single healthcare institution, which may limit the generalizability of findings. However, it is the largest oncology specialized hospital in southwest China. Therefore, our sample is representative to evaluate the NCDP policy effects on cancer inpatients in pilot cities. Second, we included patients for only 1-year interval and focused on the first round of NCDP implemented in 2019. There were a series of policies focused on anticancer drugs in recent years, for example, the National Reimbursement Drug List was changed in January 2020 and the second round of NCDP was implemented in April 2020. In order to eliminate any possible confounding, we finally extracted the data from January 2019 to December 2019. Meanwhile, there were also some reforms during the study period, such as hospital vertical consolidation and prospective global budget, which may also explain the reduction in drug and non-drug costs among patients with cancer. Therefore, we used the DID method to minimize the impact of these reforms on our estimation. Third, information regarding oncological characteristics (stage and subtypes) were unavailable, for which we were unable to include more potential confounding. Finally, there were some potential reasons that might lead to the underestimation of policy effects. Our outcomes were the expenditures per hospitalization. But a patient might receive medication several times and seek services out of the hospital. Gefitinib is a common oral targeted therapy drug for NSCLC, and patients

can buy and take it out of the hospital. The policy impact on actual spending of cancer patients might be larger than our estimation. Future studies should consider the whole economic burden for cancer patients using regional electronic medical record data.

Conclusion

Using a DID design, we evaluated the impact of the pilot NCDP program on health expenditures of lung cancer inpatients. Our finding showed that the policy was associated with significant decreases in all types of expenditures, except for the TCM expenditures. Overall, the reform achieved its goals of high-quality and affordable healthcare. Further studies should assess the impact of NCDP on health outcomes, and consider the long-term effects of the drug procurement scheme.

Data availability statement

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

Author contributions

Conception or design of the work: S-yZ and XS. Data collection: S-yZ. Data analysis and interpretation: Y-jZ, YR, QZ, Y-xH, XZ, and KZ. Drafting the article: Y-jZ. Critical revision of the article: YR, JT, S-yZ, and XS. All authors have 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/fpubh.2022.956823/full#supplementary-material

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Economic evaluation of first-line nivolumab plus cabozantinib for advanced renal cell carcinoma in China

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Background: In the Checkmate9ER trial, first-line treatment with nivolumab combined with cabozantinib (NI + CA) has shown efficacy for advanced renal cell carcinoma. This study aims to evaluate the impact of the health and economic outcomes of NI + CA in China.

Methods: Clinical efficacy data were derived from pivotal phase III CheckMate 9ER trial. A three-state partitioned survival model was established based on disease progression. Progression-free survival and overall survival of NI + CA vs. sunitinib were fitted with log-logistic and log-normal distributions, respectively. Mixture cure, non-mixture cure, and Royston/Parmar spline models were used to evaluate model robustness. The results derived the computational cost from the Chinese healthcare system perspective. The primary outcomes were quality-adjusted life-years (QALYs), total cost in US dollars, as well as incremental cost-effectiveness ratios (ICERs) at the willingness-to-pay threshold in China. One-way and probabilistic sensitivity analysis were also used to assess the robustness of the model.

Results: In the base-case analysis result, 0.86 additional QALYs could be obtained in the NI+CA (3.84 QALYs) versus the sunitinib strategy (2.97 QALYs). The ICER of NI+CA compared with the sunitinib strategy was US$292,945 per QALY. The ICER value in the NI+CA strategy was higher than the Chinese willingness-to-pay threshold of US$38,024 per QALY. Although NI+CA can improve long-term patient survival significantly over sunitinib in the treatment of advanced renal cell carcinoma, it is unlikely to be cost-effective due to high cost. The results of the one-way sensitivity analysis showed that drug cost, health utility value at the stage of disease progression, and subsequent treatment proportion had a greater impact on the stability of ICER values.

Conclusions: Nivolumab combined with cabozantinib can prolong the life of patients with advanced renal cell carcinoma and improve their quality of life, but there is a corresponding increase in medical cost. The NI + CA strategy is unlikely to be considered cost-effective in the treatment of advanced RCC from the perspective of Chinese healthcare system.

KEYWORDS

cost-effectiveness, nivolumab, cabozantinib, partitioned survival, renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) is a common form of cancer, accounting for 2%−3% of all cancers globally, and has shown an increasing trend over the past decade (1–3). According to global cancer statistics, the annual incidence and mortality rates of kidney cancer during 2020 in China were ∼66,800 and 23,400, respectively (4). The number of disability-adjusted life years caused by renal cancer in China is as high as 643,000 years, accounting for 0.17% of the total disability-adjusted life years (5). This disease poses a severe economic burden and public health problem, especially for countries with limited health resources (6).

Anti-angiogenic therapy with sunitinib, a small molecule tyrosine kinase inhibitor, has historically been an effective tool for the first-line treatment of patients with RCC characterized by the inactivation or deletion of the von Hippel-Lindau (VHL) gene (7, 8). Sunitinib has been approved by the Food and Drug Administration as a first-line treatment for advanced and/or metastatic RCC (mRCC). The Guidelines of the Chinese Society of Clinical Oncology (CSCO) for Kidney Cancer includes the first-line sunitinib treatment as a category 1A recommended regimen for patients with mRCC across all risk groups (9). In evaluating the cost-effectiveness of mRCC treatment, sunitinib has always been a strong standard in line with the principles in the China Guidelines for Pharmacoeconomic Evaluations 2020 (10). However, it has now been replaced by treatment with different combinations of immune checkpoint inhibitors (ICIs), kinase inhibitors, and signal transduction blockers based on multiple randomized controlled trials (RCTs) (11–15). Nivolumab is a monoclonal antibody developed against PD-1 that has considerable clinical benefits and an acceptable safety profile for a variety of tumor types (16). Cabozantinib is a tyrosine kinase that has shown efficacy in the CABOSUN RCT and is used as monotherapy for advanced RCC (17). Recently, in a phase-III clinical trial, CheckMate 9ER, nivolumab combined with cabozantinib (NI + CA) showed clear safety and clinical activity in the first-line treatment of advanced RCC with clear histological features. The trial included 651 patients in 18 countries over 20 months. NI+CA significantly improved overall survival (OS), progression-free survival (PFS), and health-related quality of life (QOL) compared with the sunitinib strategy. The PFS was 16.6 months for the NI+CA strategy and 8.3 months for the sunitinib one (median, 16.6 vs. 8.3 months; HR, 0.51; 95% CI, 0.41–0.64). The OS probability at 12 months was 85.7% for the NI+CA strategy and 75.6% for the sunitinib one (HR, 0.60; 98.89% CI, 0.40 to 0.89; $P = 0.001$).

Based on this study, in 2021, the American Society of Clinical Oncology and the Chinese Society of Clinical Oncology recommended NI+CA as a substitute for first-line treatment of advanced RCC. The dual combination of ICIs and kinase inhibitors improves health outcomes in patients with advanced RCC. However, the two-drug combination generates higher medical costs than the ICI regimen, placing a higher economic burden on health insurance finances (18, 19). At present, there is no pharmacoeconomic evaluation of NI + CA strategy in patients with advanced RCC from the perspective of Chinese healthcare system. We thus compare the cost-effectiveness of the NI + CA strategy over sunitinib strategy to treat advanced RCC by using model data from CheckMate9ER. The findings provide evidence for use by patients with advanced first-line RCC and the physicians treating them, as well as health policymakers.

Model overview

A Treeage ProSuit 2020 was used to construct a three-state partitioned survival (PS) model to assess the economic benefits of NI + CA vs. sunitinib for first-line treatment of RCC from the perspective of the China health system. The model was constructed using a partitioned survival model, an approach widely used in health technology assessment to simulate disease progression and death in advanced RCC and other tumor indications (20, 21). A standard three-state partitioned survival model was employed (see Figure 1), with state membership determined by survival curves. The model cycle was 6 weeks and the study duration 20 years. The model mainly calculates direct medical costs and the adverse event rate was taken from the CheckMate9ER RCT study. Utility values were derived from previous studies (22). According to the China Guidelines for Pharmacoeconomic Evaluation issued by the Chinese Pharmaceutical Association, we discounted the cost and utility values by 5% per year. Three-times national GDP per capita in 2021 was used as the willingness-to-pay threshold (US$38,024 per QALY) (23). The results of the model were expressed as total cost, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER), being calculated using the January 2022 bank foreign exchange rate (US$1 vs. RMB6.3746). Because the economic evaluation was based on a literature review and experimental models, approval from an institutional review board or ethics committee was not required.

Clinical data

The inclusion criteria and treatment regimen for the study target population were obtained from the CheakMate9ER clinical trial (8). This study included 638 patients with a median follow-up time of 18.1 months. The included patients all had pathologically diagnosed RCC. They received one of the following two treatments at the start of the model: oral cabozantinib 40 mg/day in combination with intravenous nivolumab 240 mg/2 weeks, or oral sunitinib 50 mg/day for 4 weeks, followed by 2 weeks off. Both

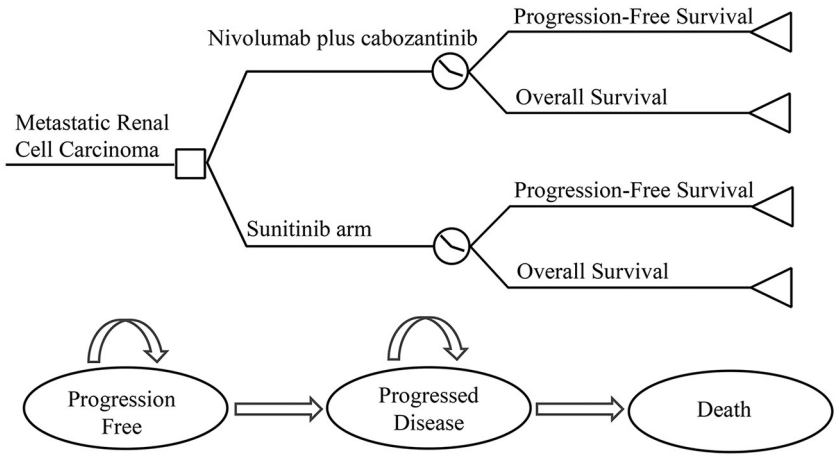

FIGURE 1
Model structure.

treatments were administered over a 42-day cycle. According to the CheckMate9ER trial, 86.1% of patients received VEGF receptor inhibitors, including axitinib, sunitinib, and pazopanib, after failure of first-line NI+CA therapy, and 73.6% of the patients in the sunitinib group received PD-L1 inhibitors for subsequent treatment, including nivolumab and pembrolizumab. ICIs were used for a maximum of 2 years during treatment. Patients who had not yet received subsequent treatment received only supportive care for the simplicity of the model.

Curve fit and progression risk estimates

We used Engauge Digitizerversion (https://github.com/markummitchell/engauge-digitizer) and extracted data points from the survival curve in the CheckMate9ER trial. According to Liu et al. (24, 25), individual patients data were reconstructed using the survHE package in R language (v4.1.2) combining KM curve information with the number at risk of events. Exponential, Weibull, log-logistic, log-normal, Gompertz, gen-gamma, Royston/Parmar spline model, and parametric mixture and non-mixture cure models were used to fit distributions to the reconstructed individual patients data (Supplementary Table S1). We compared the reconstructed KM curves with the model extrapolated survival curves (Figure 2). Through visual inspection and comparison with the PFS and OS in the original report, the optimal fitting distribution was judged according to Akaike information criterion (AIC) and Bayesian information criterion (BIC). Finally, log-logistic and log-normal distribution models were chosen to fit the data extracted from the survival curves of PFS for sunitinib and NI + CA, respectively. The log-normal distribution model was selected to fit the OS survival curves of the two groups. There is a plateau at the end of the patient survival curve and there may be an underestimation of survival by traditional parametric models (26). The Royston/Parmar spline, mixture cure, and non-mixture cure models were used to evaluate the robustness of the model.

Medical costs

In this study, only direct medical costs were considered, including drug treatment, adverse event management, follow-up, and hospital service item costs. The bid prices of drug costs were obtained from the China Pharmaceutical Information Network (www.menet.com). Among the considered drugs, cabozantinib has not been launched in China. The unit prices of cabozantinib were derived from the Centers for Medicare and Medicaid Services (CMS) (27), which belongs to an official government organization in the United States. The follow-up and hospital service item costs mainly included diagnosis, nursing, hospitalization, and intravenous infusion fees, as well as management, electrocardiogram, routine blood, biochemistry, blood coagulation, tumor marker, and enhanced computed tomography costs. Patient follow-up fees and charging standards for hospital service items came from Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University, Jiangsu Province. This model assumes that the average patient weight is 65 kg with a body surface area of 1.72 m^2. Grade 3–5 adverse events with an incidence above 5% during ICI use should not be ignored. This study derived adverse events (AE) cost partly from the literature (28). We also captured the cost of AE by administering a questionnaire to clinical experts. Table 1 provides detailed information about the costs.

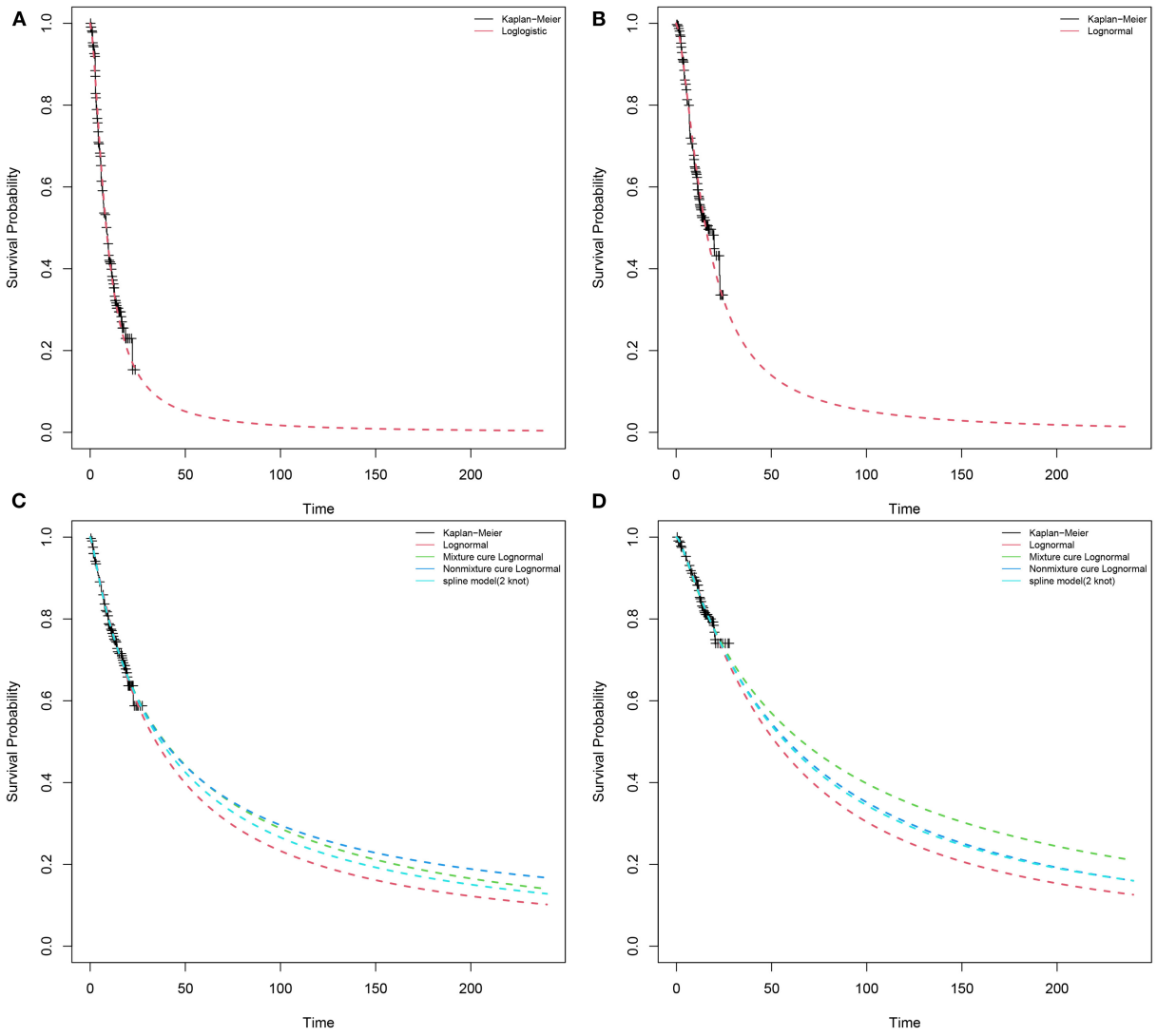

FIGURE 2
Results of the survival curve fit the NI + CA and sunitinib strategy of the base-case analysis in the partitioned survival model. **(A)** PFS of sunitinib strategy, **(B)** PFS of NI + CA strategy, **(C)** OS of sunitinib strategy, **(D)** OS of NI + CA strategy.

Utility values

Health utility values were obtained from the literature. We assumed a PFS status utility of 0.82 for nivolumab plus cabozantinib, a PFS utility of 0.73 for sunitinib, and a PD status utility of 0.66 (22). Our model included the ≥3-grade treatment related to AE with an incidence above 5%, as reported in the CheckMate9ER trial.

Sensitivity analysis

To test the robustness of the model, one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed on the parametric model. In the one-way sensitivity analysis, the independent effect of the changes in each parameter on the results was considered. The upper and lower limits of the input were derived from the literature. If the upper and lower 95% CI changes were not available, in which the parameter of cost is in the range of ±20%, the AE incidence and health utility value was designated as ±10%. A reasonable range of discount rate is 0–8%. In the probabilistic sensitivity analyses, a Monte Carlo simulation of 5,000 iterations was generated by simultaneously sampling the key model parameters from the prespecified distributions. A gamma distribution was set for cost parameters and a beta distribution for utility values parameters. The results were shown as a scatter diagram and a cost-effectiveness acceptable curve.

TABLE 1 Summary of main medical costs, utility values, and other parameters.

Parameter	Base case	Range		Distribution	Source
		Low	High		
Clinical inputs					
Survival model of sunitinib					
Log-logistic model of PFS	Shape, 1.6417 (SE, 0.0976); scale, 8.4452 (SE, 0.5531); AIC, 1,316				
Log-normal model of OS	Meanlog, 3.6682 (SE, 0.1574); SDlog, 1.6679 (SE, 0.1349); AIC, 1,316				
Survival model of NI + CA					
Log-normal model of PFS	Meanlog, 2.1406 (SE, 0.0686); SDlog, 1.0623 (SE, 0.0569); AIC, 709				
Log-normal model of OS	Meanlog, 4.1874 (SE, 0.2046); SDlog, 1.5868 (SE, 0.1603); AIC, 958				
Drug cost (US$)					
Nivolumab 100 mg	1,451.07	1,160.85	1,741.28	Gamma	MENET
Cabozantinib 60 mg	491.30	393.04	589.56	Gamma	(23)
Pembrolizumab 100 mg	2,810.84	2,248.67	3,373.01	Gamma	MENET
Sunitinib per table	15.37	12.29	18.44	Gamma	MENET
Axitinib per table	30.85	24.67	37.02	Gamma	MENET
Pazopanib per table	25.10	20.08	30.12	Gamma	MENET
Follow-up cost/cycle (US$)	72.48	57.98	86.97	Gamma	Local market
Management cost/cycle (US$)	46.43	37.15	55.72	Gamma	Local market
Supportive care per cycle (US$)	315.18	282	423	Gamma	(29)
Terminal care (US$)	1,893	946.5	2,839.5	Gamma	(29)
Cost of managing adverse events (US$)					
Diarrhea	43.30	34.64	51.96	Gamma	(29)
Hypertension	12.61	10.09	15.14	Gamma	(29)
ALT	25.09	20.07	30.12	Gamma	(29)
Proteinuria	121.65	97.32	145.98	Gamma	(29)
Palmar	102.21	81.77	122.65	Gamma	(29)
Subsequent treatment proportion					
Nivolumab + cabozantinib	0.86	0.77	0.94	Beta	(8)
Sunitinib	0.73	0.66	0.80	Beta	(8)
Risk of adverse events (grade III–IV)					
Sunitinib	0.75	0.602	0.903	Beta	(8)
Nivolumab + cabozantinib	0.71	0.564	0.847	Beta	(8)
Health utility					
Nivolumab + cabozantinib Stable disease	0.82	0.73	0.90	Beta	(20)
Sunitinib stable disease	0.73	0.657	0.803	Beta	(23)
Disease progression	0.66	0.726	0.594	Beta	(23)
Disutility due to AEs (grade ≥3)	0.157	0.127	0.188	Beta	(23)
Discount rate	0.05	0.00	0.08	Fixed in PSA	

Scenario analysis

We consider three possible scenario analysis. This study also used scenario analysis to consider the partitioned survival model time extrapolation. The price reduction magnitudes of first-line NI + CA were used to assess their impact on ICER. The approach to the simulated distribution of the Royston/Parmar spline or the non-mixture cure models differ from the standard parametric model. During extrapolation, different distributions of survival models often diverge, often resulting in variations in mean survival and cost-effectiveness estimates. The mixture cure, non-mixture cure, and Royston/Parmar spline models were used to evaluate model robustness.

Results

Base-case analysis

The model predicted that the expected result of the NI + CA strategy (3.84 QALYs) was superior to that of the sunitinib strategy (2.97 QALYs) to obtain 0.86 QALYs, but the corresponding cost was US$252,943 greater, resulting in an ICER of US$292,945 per QALY. The results of the base-case analysis are presented in Table 2.

Sensitivity analysis

One-way sensitivity analysis was represented by a tornado diagram (see Figure 3). The ICER constantly changes when we change the value of each individual by estimating it within a reasonable range. When comparing the NI + CA strategy, the most significant effect on the entire model was the utility value at the PFS stage, followed by the price of cabozantinib. The ICER value changed from US$243,662 to US$367,217 per QALY, being well above US$38,024 per QALY. The other model parameters had a moderate or negligible effect on the expected ICER. When the key model parameters were specifically distributed in the probabilistic sensitivity analysis of NI + CA vs. sunitinib, none of the NI + CA strategies were cost-effective in the Monte Carlo simulations with 5,000 iterations. The scatter diagram revealed the probability of an NI + CA strategy not being a cost-effective option when compared with the sunitinib strategy at a willingness-to-pay threshold of US$38,024/QALY (see Figure 4). The cost-effectiveness acceptability curve reveals the acceptability of NI + CA at different willingness-to-pay threshold (see Figure 5). Compared with sunitinib, NI + CA patients had 0, 60, and 95% probabilities of being cost-effective at patient thresholds above US$100,000, 300,000, and 500,000 per QALY, respectively.

Scenario analysis

The scenario analysis can be conducted to assess the variability resulting from differences in regions and settings (Table 2). When the model extrapolated with years changing to 5, 10, and 15 years, an interesting phenomenon occurred, with 80% of the medical costs of patients spent in the first 5 years, after which there was still a clinical benefit. In the second scenario analysis, when the purchase price of NI + CA was reduced to 25, 50, and 75%, the ICERs of NI+CA compared with sunitinib were US$75,981, 148,302, and 220,623 per QALY, respectively. The mixture cure model predicted 4.40 and 3.30 QALYs for NI+CA and sunitinib, respectively, with an ICER of US$235,788 per QALY. The non-mixture cure model predicted 4.11 and 3.38 QALYs for NI+CA and sunitinib, respectively, with an ICER of US$337,891 per QALY. The Royston/Parmar spline model predicted 4.08 and 3.18 QALYs for NI + CA and sunitinib, respectively, with an ICER of US$281,321 per QALY.

Discussion

The high cost of ICIs has always been a hindrance to the use of immunotherapy worldwide, especially where health resources are lacking or are unevenly distributed (29). In the CheckMate9ER study, the combination of immunotherapy and targeted therapy resulted in sustained clinical benefits of improving the QOL of patients with RCC (14). It also places a heavy medical expenditure burden on the financial expenditure of health insurance, especially compared with tyrosine kinase inhibitor monotherapy (18, 22). However, the cost-effectiveness analysis of NI+CA has not been conducted in China. Therefore, we used digital software to reproduce the safety and efficacy data in NI+CA and proposed a model design for the two medication strategies to assess their cost-effectiveness in first-line RCC strategy for long-term extrapolation more than for follow-up cycles. Our results provide important information that can assist in the development of clinical guidelines for the practice of medically treatable treatments based on resource availability.

The willingness-to-pay threshold adopted in this study was three times national GDP per capita (US$38,024 per QALY) in China in 2021, according to the China Guidelines from Pharmacoeconomic Evaluation and World Health Organization standards (23, 30). Based on the results of our model, the ICER of NI + CA with sunitinib was US$391,391.06 per QALY higher than our assumed willingness-to-pay threshold of US$38,024 per QALY. The disadvantage caused by such a huge gap in costs cannot be compensated for by its clinical production. From an economic viewpoint, sunitinib remains the primary option for advanced RCC patients in China with limited health resources. One-way sensitivity analysis indicated that the essential input parameters driving this model were the utility value at the PFS stage and the cost of cabozantinib. Therefore, the most realistic means of proportional cost to clinical value is to reduce the price of cabozantinib and nivolumab, while other nursing treatments can also be adopted in addition to drug therapy to improve the QALYs of patients with increased growth. Contrary to our expectations, cabozantinib had a higher impact on model ICER values than nivolumab. After the NI + CA group's utility value in the PFS stage, the drug-acquisition cost had the second greatest impact in our model. ICIs (pembrolizumab, nivolumab) are the drugs of choice over tyrosine kinase inhibitors in the subsequent treatment with the sunitinib strategy, which leads to a reduced impact of nivolumab on the overall cost of the model.

The cost-effectiveness acceptability curve showed the probability of NI + CA being a cost-effective strategy at different willingness-to-pay threshold per additional QALY gained (Figure 4). The NI + CA strategy is unlikely to

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TABLE 2 Results of base-case and scenario analysis.

Strategy	Total cost$	Incr cost$	LY	QALY	Incr Eff	ICER$/QALYs
Base-case analysis						
Sunitinib	105,820	NA	4.41	2.97	NA	NA
Nivolumab + cabozantinib	358,764	252,943	5.34	3.84	0.86	292,945
Scenario 1						
5 years						
Sunitinib	75,520	NA	2.80	1.90	NA	NA
Nivolumab + cabozantinib	316,594	241,073	3.26	2.41	0.51	473,856
10 years						
Sunitinib	92,640	NA	3.71	2.51	NA	NA
Nivolumab + cabozantinib	340,961	248,321	4.45	3.23	0.72	343,900
15 years						
Sunitinib	101,064	NA	4.16	2.81	NA	NA
Nivolumab + cabozantinib	352,484	251,421	5.02	3.62	0.82	307,894
Scenario 2						
Adjust nivolumab + cabozantinib 75% of its original price in the first-line setting						
Sunitinib	99,916	NA	4.41	2.97	NA	NA
Nivolumab + cabozantinib	290,413	190,498	5.34	3.84	0.86	220,623
Adjust nivolumab + cabozantinib 50% of its original price in the first-line setting						
Sunitinib	94,011	NA	4.41	2.97	NA	NA
Nivolumab + cabozantinib	222,063	128,052	5.34	3.84	0.86	148,302
Adjust nivolumab + cabozantinib 25% of its original price in the first-line setting.						
Sunitinib	88,106	NA	4.41	2.97	NA	NA
Nivolumab + cabozantinib	153,712	65,606	5.34	3.84	0.86	75,981
Scenario 3						
Distribution of OS using parametric survival model						
Sunitinib	105,820	NA	4.41	2.97	NA	NA
Nivolumab + cabozantinib	358,764	252,943	5.34	3.84	0.86	292,945
Distribution of OS using mixture cure model						
Sunitinib	115,260	NA	4.91	3.30	NA	NA
Nivolumab + cabozantinib	375,157	259,897	6.19	4.40	1.10	235,788
Distribution of OS using nonmixture cure model						
Sunitinib	117,410	NA	5.02	3.38	NA	NA
Nivolumab + cabozantinib	366,762	249,352	5.75	4.11	0.74	337,891
Distribution of OS using Royston/Parmar spline model						
Sunitinib	111,675	NA	4.72	3.18	NA	NA
Nivolumab + cabozantinib	365,818	254,143	5.71	4.08	0.90	281,321

LY, life year; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

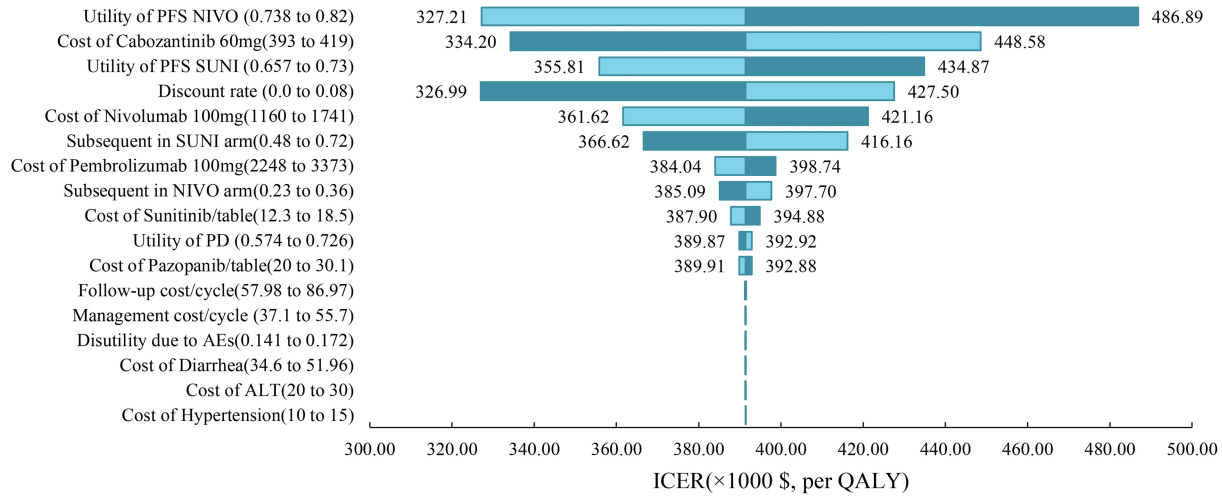

FIGURE 3
Tornado diagrams showing the effect of lower and upper values of each parameter on the ICERs of the NI + CA vs. sunitinib strategy.

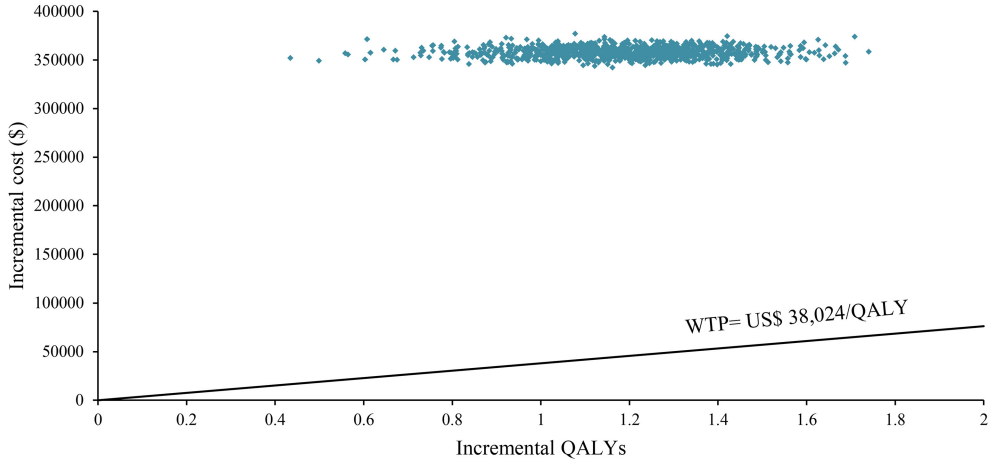

FIGURE 4
The scatter diagram in the partitioned survival model.

be considered cost-effective at a willingness-to-pay threshold of US$38,024 per QALY. However, the combination of the NI + CA strategy is valuable in clinical applications, with significant clinical efficacy and good safety. Healthcare systems can reasonably circumvent the economic burden, as patients with RCC who cannot afford the high price of immune drugs will certainly not suffer the burden. Therefore, if the price of the NI + CA strategy was reduced to 50 and 25% of the original price, the ICER would be reduced to US$148,302 and US$75,981 per QALY, respectively. This would yield an ICER well below the baseline outcome. In the scenario analysis, the model cycle was adjusted to explore the NI +CA strategy in clinical practice for different time horizon. The 5-year survival rate of RCC has been an important assessment reflecting the combined value of immunity. Interestingly, more than 80% of the medical costs of the NI+CA strategy are spent in the first 5 years and patients continue to benefit through subsequent survival. The extrapolation time of the model gradually became longer for 5, 10, and 15 years and the ICER value also decreased.

With the application of ICIs, the survival plot showed a significant plateau at the tail end. Compared with traditional standard parameters, it is necessary to apply the mixture cure, non-mixture cure, and Royston/Parmar spline models to reassess the uncertainty of patients' long-term survival (31). The mixed cure model has large heterogeneity and different distributions produce a large change in outcomes.

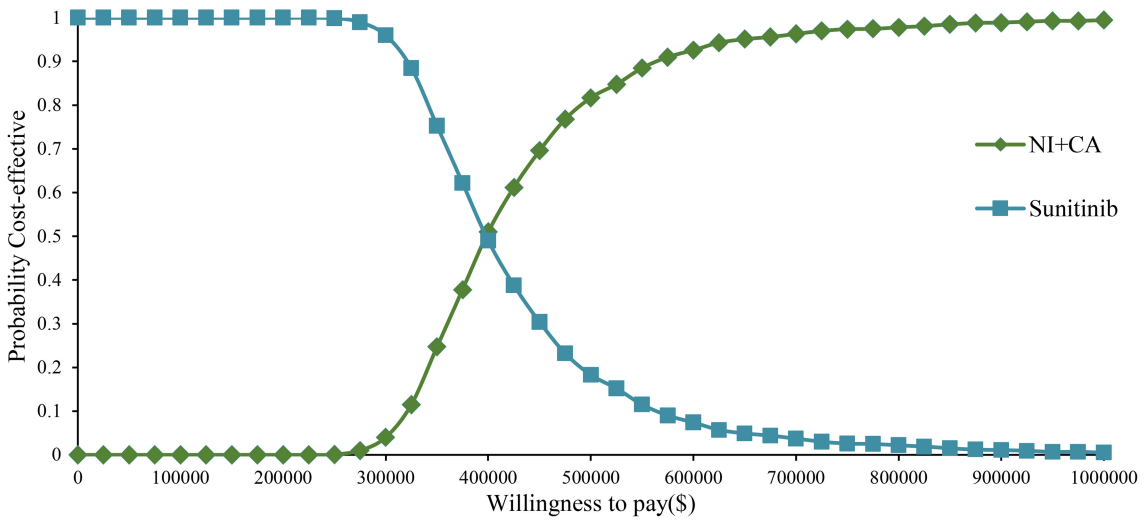

FIGURE 5
Cost-effectiveness acceptability curve in the partitioned survival model.

However, the use of the mixture cure and Royston/Parmar spline models brings more survival benefits to patients than the standard parametric model. In the scenario analysis, patients obtained more QALYs using other extrapolation methods. The ICER varied between models, with the lowest ICER of US$235,788 per QALY in the mixed cure model and the highest ICER of US$337,891 per QALY in the non-mixture cure model. However, this did not change the conclusion that NI + CA was not more cost-effective than sunitinib at a willingness-to-pay threshold of US$38,024 per QALY.

Similar to previous findings for ICIs, Li et al. (32) concluded that an ICER of US$508,987 per QALY for NI + CA vs. sunitinib is not economically feasible from the US health system perspective. From the perspective of the Chinese healthcare system, the ICER for the two groups of medication strategies in this study was US$292,945 per QALY. To further reduce the pharmaceutical burden on patients, the Chinese government has issued a series of policies, including establishing domestic generic drugs and the centralized procurement of drugs with quantity as the core. In the promotion of the procurement of drugs and high-value medical consumables with quantity, the average price reduction for the centralized procurement of the first six batches of drugs under this reform is 53%. Immunotherapy has been found to have a beneficial effect in renal cell cancers, suggesting the advantage of immunomodulating therapies over standard treatment. Nivolumab is an important therapeutic agent for Chinese patients with advanced RCC. As such, if nivolumab can successfully enter the catalog of medicines covered by national medical insurance system, the affordability and accessibility of renal cancer immunotherapy will be greatly improved. And for cabozantinib, although the drug has not yet been marketed in China, from the existing study conclusion, cabozantinib is unlikely to be cost-effective compared with other treatment regimens in China at its current price. We recommend that pharmaceutical companies set appropriate prices or charitable drug donation programs based on China's actual situation to give full play to the advantages of cabozantinib efficacy and safety in clinical treatment.

This study has several methodological strengths. First, the model was constructed using the PS model to perform a 20-year lifecycle analysis for RCC patients. The PS model avoids the calculation of transfer probabilities for cohort members by reconstructing individual patient data. This approach facilitates the validation of the model by other investigators (33, 34). Second, we did not simply specify pembrolizumab as a second-line treatment for all groups, explicitly following modeling based on the information published by the CheckMate9ER trial. This means that our calculated drug cost per subsequent cycle is quite in line with the use of a substantial clinical treatment pathway and significantly reduces the bias of the model in actual extrapolations.

This study has several limitations. First, cabozantinib has not been launched in China. The unit price of cabozantinib in our model was derived from CMS in the United States. Although we performed uncertainty analysis of the price parameters for cabozantinib, this study needs to be further validated after the cabozantinib price is available for a future Chinese launch. In the context of health insurance negotiations, the findings of this study have potential implications for pharmaceutical

companies to set prices, while providing a reference basis for health insurance decision-making departments to negotiate prices or decide whether to include them in the health insurance catalog. Second, we used efficacy and safety data from the CheckMate9ER trial for model extrapolation and log-logistic and log-normal parameter distributions to fit the long-term survival of patients. As such, the true efficacy of nivolumab in combination with cabozantinib still needs to be tested in a long-term follow-up study. It is necessary to assess the consistency of these simulation results with real-world efficacy. Third, we assumed that patients could not recover from a progressive disease state to a progression-free disease state, which might have overlooked the health recovery of some patients as well as deaths due to comorbidities. Fourth, we used the QOL scores of mRCC for the European population in the literature, which do not truly reflect the data for Chinese patients, among other population groups. This study showed no significant difference in the QOL between Asian and European populations. The robustness of the model would be significantly improved if future health utility analysis of RCC patients with relevant first-line NI + CA could be performed for the Chinese population. Finally, owing to a lack of some head-to-head trials for renal cell cancer, no strategy of the mutual combination of other PD-L1 drugs with tyrosine kinase inhibitors was included in this study.

Conclusions

According to the base-case and sensitivity analysis results, the NI+CA strategy is unlikely to be considered cost-effective over sunitinib in the treatment of advanced RCC from the perspective of Chinese healthcare system. ICIs and tyrosine kinase inhibitors benefit patients with advanced renal cancer but incur additional costs. Our findings support the efforts to reduce drug prices and enable this treatment to reduce the economic burden on the Chinese healthcare system.

Data availability statement

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

Author contributions

Conception and design: HW and YW. Administrative support: MA. Provision of study materials or patients: YW and ZH. Collection and assembly of data: HW, SL, and LL. (V) Data analysis and interpretation: HW, YW, and SY. Manuscript writing and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.954264/full#supplementary-material

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Trends in anti-HER2 drugs consumption and influencing factors

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Background: Human epidermal growth factor receptor 2 (HER2) inhibitors have been approved to treat various cancers with HER2 amplification. The Chinese government has made great efforts to improve the availability and affordability of these drugs. This study aimed to analyze the trends in anti-HER2 drug consumptions in Nanjing from 2012 to 2021, and explore influencing factors.

Methods: Data about use of anti-HER2 drugs in 2012–2021 were extracted from Jiangsu Medicine Information Institute. Six types of anti-HER2 drugs were included. Drug consumption was expressed as defined daily doses (DDDs) and expenditure. Time series analysis was adopted to find trends in consumption, while interrupted time series was used in analyzing the impact of policy on consumption. The correlation between DDDs and defined daily cost (DDC) was analyzed by Pearson's correlation test.

Results: The DDC, DDDs, and expenditure of anti-HER2 drugs changed little from 2012 to 2016. The DDC decreased intermittently, while the DDDs and expenditure of these drugs grew continuously from 2017 to 2021. The anti-HER2 monoclonal antibodies contributed to the majority of total consumption in 2012–2019. The DDDs of anti-HER2 tyrosine kinase inhibitors surpassed the DDDs of monoclonal antibodies in 2020–2021. Trastuzumab was the predominantly prescribed drug in 2012–2019, but the DDDs of pyrotinib surpassed the DDDs of trastuzumab in 2020–2021. The ln value of DDC or self-paid DDC of trastuzumab was negatively correlated with the ln value of its DDDs. The national health insurance coverage (NHIC) and national drug price negotiation policy about anti-HER2 drugs were initiated in 2017. Low-price generics and biosimilar of trastuzumab came into the market in 2020 and 2021, separately. Interrupted time series analysis showed that the DDDs increased significantly after the implementation of NHIC, price negotiation or generic drug replacement.

Conclusion: The consumption of anti-HER2 drugs has significantly increased and their DDC has decreased after the implementation of NHIC, price negotiation, or low-price generic drug replacement since 2017. Further efforts are needed to translate the high consumption into clinical benefits.

KEYWORDS

anti-HER2 drug, consumption, national health insurance coverage, national drug price negotiation, generic drug replacement

Background

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family. HER2 can form into heterodimers with other members, such as HER1, HER3 and HER4, and acts in the pathogenesis and progression of several human cancers (1, 2). Anti-HER2 drug, as a breakthrough invention, have increased the survival of cancer patients with HER2 amplification (3). Trastuzumab (Herceptin) is the first humanized monoclonal antibody targeting HER2, and has been approved for the treatment of HER2-positive breast cancer and gastric cancer (4). Subsequently, other anti-HER2 drugs, such as pertuzumab, lapatinib, and pyrotinib, have been commercialized to treat cancers with HER2 amplification.

However, the high cost of these drugs limits their access to eligible patients (5). In a survey conducted on breast cancer in Africa, trastuzumab could be provided by 10 out of 19 facilities, but afforded by only 5% of the patients (6). In Jiangsu, a developed province in China, only 33.39% of patients with early-stage breast cancer received trastuzumab in 2010–2013 (7).

The Chinese government has made great efforts to increase the availability and affordability of anti-HER2 drugs. In 2017, trastuzumab and lapatinib were covered by national health insurance with a reimbursement rate of 70–80% (8). Then, low-price generic and biosimilar drugs were introduced into the market, which have potentially increased the accessibility and affordability of anti-HER2 drugs (9). Meanwhile, several rounds of national price negotiations of anticancer drugs have been accomplished, after which the price of trastuzumab and lapatinib were significantly decreased (10). In this light, the consumption of anti-HER2 drugs may have demonstrated new trends in China. The aim of this study was to analyze the consumption trend of anti-HER2 drugs from 2012 to 2021 in Nanjing, the capital city of Jiangsu province and evaluate influencing factors.

Methods

Data sources

The data about anti-HER2 drugs consumption were provided by Jiangsu Medicine Information Institute (11, 12). In China, anti-HER2 drugs can only be prescribed by physicians and borrowed from hospital pharmacies by 2021. If these drugs were covered by medical insurance, only drugs sold by hospital pharmacies can be reimbursed before 2022. Hence, the sales in hospital pharmacies could present the consumption by patients. There are 106 hospitals (including secondary and tertiary hospitals) in Nanjing. Each hospital has a designated reporter, usually a pharmacist, who is responsible for registering the consumption of drugs. The designated reporter reports data to the Jiangsu Medicine Information Institute monthly. The reported information for each drug includes dosage form, package dose, manufacturer, price, monthly expenditure, and monthly consumption (in terms of grams). By analysis these data, we found 36 hospitals (33.96%) consumed anti-HER2 drugs in the past 10 years. Hence, these 31 tertiary hospitals and five secondary hospitals were included in our study.

Six kinds of anti-HER2 drugs were used in Nanjing by 2021, including trastuzumab, pertuzumab, inetetamab, trastuzumab-emtansine, lapatinib, and pyrotinib. Trastuzumab is sold as either original (Herceptin) or generic drugs (Zercepac). Inetetamab is a biosimilar drug of trastuzumab. The information of anti-HER2 drugs used in Nanjing is listed in Table 1.

Data analysis

The monthly sales data of anti-HER2 drugs were analyzed. Two analysts (Liu and Dou) were trained to screen and extract the data using a form, including price, dosage, selling time, specifications, pharmaceutical manufacturer. The quality of the data was checked by a supervisor (Fang).

Utilization analysis of anti-HER2 drugs

Consumption of anti-HER2 drugs was expressed as defined daily doses (DDDs) and expenditure (12, 13). The defined daily dose (DDD) is a statistical unit defined by the WHO Collaborating Centre for Drug Statistics Methodology (14). As there was no standard DDD for anti-cancer medicines, we obtained the data about DDD based on the daily doses and indications from the authoritative specification database. The greater the DDDs, the greater frequency of using the medicine.

TABLE 1 Information about the anti-HER2 drugs.

Drugs	Kinds	Manufacturer	Launch date	Reimbursement date	Price negotiation
Trastuzumab (original)	mAb	Roche (Switerland)	Sep-98	Jul-17	¥21999.42 to ¥7600.00 (Jul 17)
					¥7600.00 to ¥ 7270.20 (Aug 19)
					¥7270.20 to ¥ 5500.00
Trastuzumab (generic)	mAb	Henlius (China)	Aug-20	Dec-20	¥1688.00
Pertuzumab	mAb	Roche (Switerland)	Jun-12	Nov-19	¥4955.00
Inetetamab	mAb	Sunshine Guojian (China)	Jun-20	Dec-20	¥590.00
Trastuzumab-emtansine	ADC	AstraZeneca (UK)	May-19	_	¥19282.00
Lapatinib	TKI	GSK (UK)	Mar-07	Jul-17	¥121.43 to ¥ 70.00 (Jul 17)
					¥ 70.00 to ¥ 66.70 (Aug 19)
Pyrotinib	TKI		Aug-18	Nov-19	¥ 86.00

The expenditure was recorded in Yuan (¥). In our study, DDDs and expenditure were calculated with the following formula:

$$\begin{aligned} \text{DDDs} &= (\sum(\text{Total dose used in number of grams})/\text{DDD}) \\ \text{Expenditure} &= (\text{retail price per package}) \\ &* (\text{consumption amount in number of package}) \end{aligned}$$

Calculation of DDC

Price was expressed as the median defined daily cost (DDC) (15). DDC was the cost of per DDD drug. A higher DDC indicated that the drug was more expensive. The DDC was recorded in Yuan (¥). In our study, DDC were calculated with the following formula:

$$\text{DDC} = \text{expenditure}/(\text{the number of DDDs})$$

Analysis of DDDs changes

Interrupted time series (ITS) regression analysis was used to analyze the changes in the DDDs of anti-HER2 drugs in 2012–2021. When it was difficult or impossible to find a control group, the ITS model was designed in a quasi-experimental manner to analyze the longitudinal effects of the interventions. The ITS model could evaluate whether policy intervention had a transient or long-term impact (16). The national health insurance coverage (NHIC) policy, national price negotiation policy, and generic drug replacement were implemented intermittently. Hence, there were several months before the initiation, as well as after the end of policy intervention. To perform independent tests, the trends in DDD changes were expressed in three parts: (i) the slope before policy implementation, (ii) the level during policy intervention, and (iii) the slope after policy implementation. The following ITS model formula was used:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 D + \beta_3 P + \varepsilon$$

Y_t is the monthly consumption measured at each time point (T). T is the time point after the initiation of study (T = 1, 2, 3... 12). D is the dummy variable for the two time periods before and after policy implementation (D = 0 represents the period before policy implementation and D = 1 represents the period after policy implementation). P is the time point after policy intervention (P = 0 indicates before policy intervention and P = 1, 2, 3, 6 indicates after policy intervention). β_0 is the intercept (which refers to the consumption at the baseline), β_1 is the slope before the intervention, β_2 is the level of change during the intervention, β_3 is the change in the consumption caused by the policy intervention, $\beta_1 + \beta_3$ is the slope after the intervention, and ε is the error term (17). The ITS model is presented in Supplementary Figure 1.

The Durbin–Watson test was used to test the first-order autocorrelation of the data (15). It is extremely possible that the observations are independent. The feasible generalized least square method was used to modify the first-order autocorrelation errors if needed (18). Correlation between the lg value of DDDs and the lg value of DDC was analyzed by Pearson's correlation test and linear regression analysis. All analyses were performed using STATA v.14 software (STATA Corporation, College Station, TX, USA), and $p = 0.05$ was considered significant.

Results

Trends in anti-HER2 drug consumption

The DDDs of all anti-HER2 drugs changed slightly from 2012 to 2016, but kept increasing since 2017. The number of DDDs increased by 76.64% in 2017, 86.78% in 2018, 155.31% in

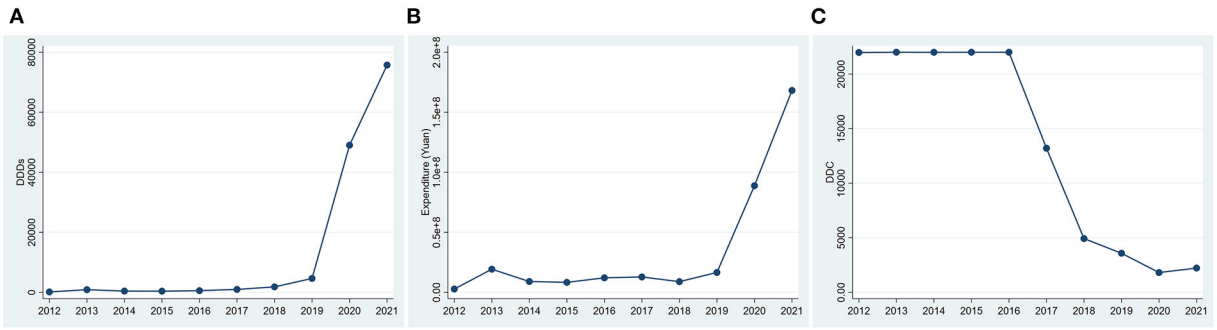

FIGURE 1
Consumption of anti-HER2 drugs in Nanjing from 2012 to 2021. **(A)** DDDs of anti-HER2 drugs; **(B)** Expenditure of anti-HER2 drugs. **(C)** DDC of anti-HER2 drugs. DDDs, defined daily doses; DDC, defined daily cost.

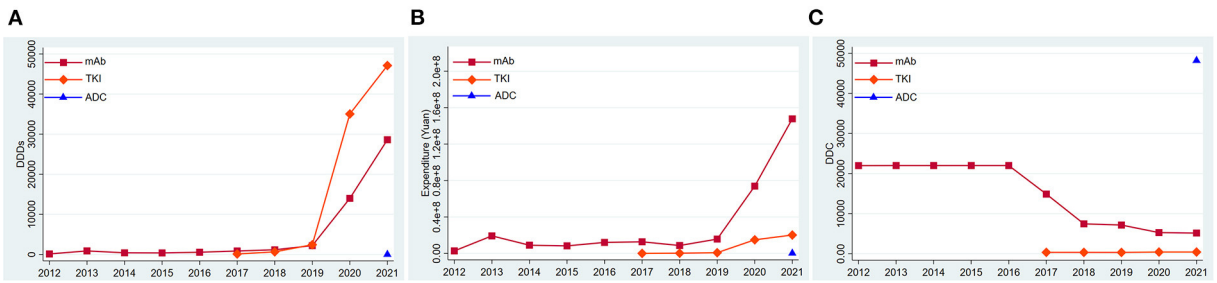

FIGURE 2
Consumption of three kinds of anti-HER2 drugs in Nanjing from 2012 to 2021. **(A)** DDDs of three kinds of anti-HER2 drugs; **(B)** Expenditure of three kinds of anti-HER2 drugs; **(C)** DDC of three kinds of anti-HER2 drugs. DDDs, defined daily doses; DDC, defined daily cost.

2019, 962.10% in 2020, and 54.46% in 2021, all compared to that in the previous year (Figure 1A). Accordingly, the expenditure also kept increasing significantly from 2017 to 2021 (Figure 1B). The average DDC of all anti-HER2 drugs changed slightly from 2012 to 2016, but decreased markedly from 2017 to 2020 (Figure 1C). The DDC decreased by 39.99% in 2017, 62.71% in 2018, 27.28% in 2019 and 49.41% in 2020, all compared to that in the previous year (Figure 1C). The average DDC changed little in 2021 (Figure 1C).

Consumption of three generations of anti-HER2 drugs

According to their molecular structures, the anti-Her2 drugs fall into three categories: monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs). From 2012 to 2016, only anti-HER2 mAbs were used in the market, and its DDDs (Figure 2A), expenditure (Figure 2) and DDC changed little. The DDC of mAbs decreased gradually (Figure 2C), while their number of DDDs increased year by year since 2017 (Figure 2A). Overall, the mAb made up the majority of the total consumption from 2012 to 2018. The TKIs entered the market in 2017. The DDDs of TKIs increased significantly and surpassed the DDDs of mAbs in 2019 (Figure 2A). The expenditure of TKIs had an upward trend (Figure 2B), while its DDC had a downward trend (Figure 2C). An ADC (Trastuzumab-emtansine) was launched in 2021, and its DDC was much higher than those of other anti-HER2 drugs (Figure 2C). The DDDs and expenditure of ADC were much lower than those of mAbs and TKIs (Figures 2A,B).

Consumption of each type of anti-HER2 drug

Trastuzumab was always on the market in the past 10 years. Its DDDs, expenditure, and DDC changed slightly from 2012 to 2016. The DDDs (Figure 3A) and expenditure (Figure 3B) of trastuzumab showed an ascending trend, while its DDC showed a descending trend since 2017 (Figure 3C). Lapatinib came into the market in March 2007, and has been used in Nanjing since 2017. Its DDDs (Figure 3A), expenditure (Figure 3B), and DDC (Figure 3C) changed little from 2017 to

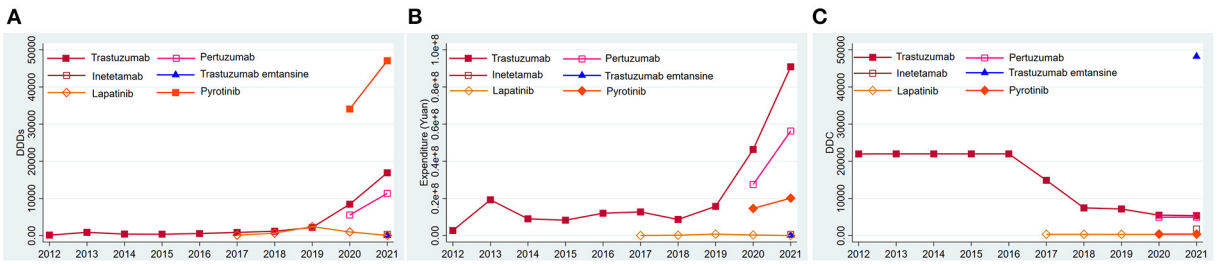

FIGURE 3
Consumption of six types of anti-HER2 drugs in Nanjing from 2012 to 2021. **(A)** DDDs of six types of anti-HER2 drugs; **(B)** Expenditure of six types of anti-HER2 drugs; **(C)** DDC of six types of anti-HER2 drugs. DDDs, defined daily doses; DDC, defined daily cost.

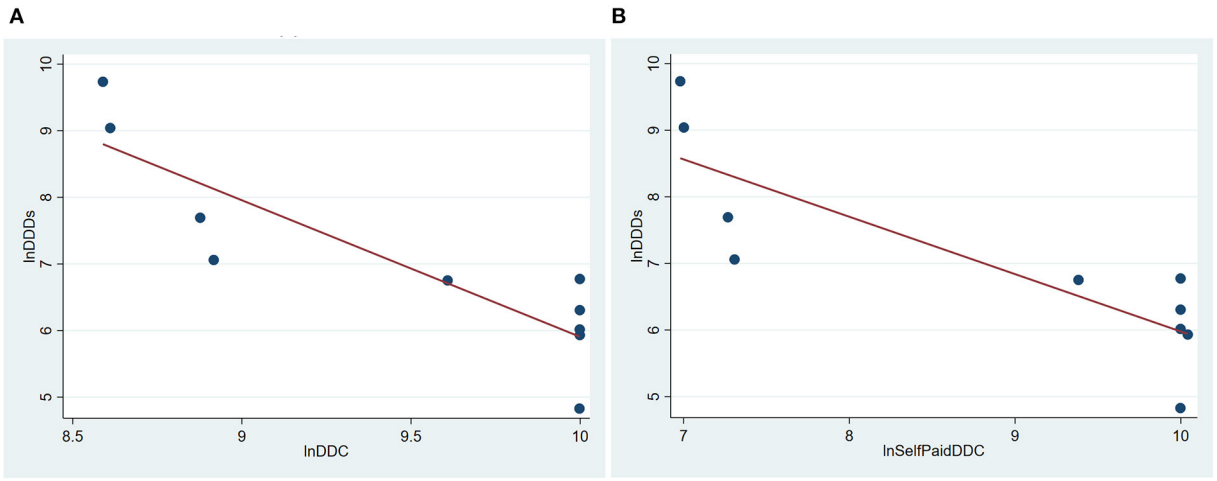

FIGURE 4
Correlation of DDC and DDDs of trastuzumab in Nanjing from 2012 to 2021. **(A)** Correlation between total DDC and DDDs of trastuzumab in Nanjing from 2012 to 2021; **(B)** Correlation between self-paid DDC and DDDs of trastuzumab in Nanjing from 2012 to 2021. DDDs, defined daily doses; DDC, defined daily cost.

2021 (Figures 3A–C). Pertuzumab and Pyrotinib came into the Nanjing market in 2020, and their DDDs increased by 104.77 and 38.17% separately in 2021 (Figure 3A). Trastuzumab was the predominantly prescribed drug in 2012 to 2019, but the DDDs of Pyrotinib surpassed the DDDs of trastuzumab in 2020 to 2021. Inetetamab and trastuzumab-emtansine came into the market in 2021, but their consumptions were relatively low (Figures 3A,C). The DDC of trastuzumab-emtansine was the highest in all the anti-HER2 drugs (Figure 3C).

Relationship between DDC and DDDs

From 2012 to 2021, the price of trastuzumab has been reduced for several times. Hence, we analyzed the relationship between their DDC and DDDs. Its DDC decreased gradually, while DDDs increased continuously since 2017. The ln value of its DDC had a negative correlation with its ln value of DDDs ($R^2 = 0.7720$, $P = 0.001$) (Figure 4A). As trastuzumab has been enrolled into the national insurance in 2017, self-paid cost (out of pocket cost) was the real expenditure patients paid. A negative correlation existed between the ln value of self-paid DDC and the ln value of DDDs of trastuzumab ($R^2 = 0.7119$, $P = 0.002$, Figure 4B).

Factors associated with DDD changes

Previous studies have reported that some policies, such as NHIC, price negotiation, and low-price generics replacement are impactors of drug consumption. As shown in Table 2, the mean DDDs of the anti-HER2 drugs improved after the implementation of NHIC, price negotiation, or low-price generics replacement. Hence, we analyzed their influence on the DDDs by ITS analysis.

TABLE 2 The influence of insurance and price on drug consumption.

Drug	Change	Time	Average DDDs of 6 months before change (DDDs per month)	Average DDDs of 6 months after change (DDDs per month)	DDDs change (%)
Trastuzumab (original drug)	Covered by medical insurance, DDC decreased from ¥21999.42 to ¥7600.00	Jul 2017	59.83	107.00	78.84
Trastuzumab (original drug)	DDC decreased from ¥7600.00 to ¥ 7270.20	Aug 2019	88.33	118.50	34.16
Trastuzumab (original drug)	DDC decreased from ¥7270.20 to ¥ 5500.00	Jan 2020	209.50	387.67	85.05
Trastuzumab (generic drug)	Covered by medical insurance	Dec 2020	-	182.95	-
Pertuzumab	Covered by medical insurance	Nov 2019	-	164.50	-
Inetetamab (biosimilar)	Covered by medical insurance	Dec 2020	-	36.00	-
Trastuzumab-emtansine	-	May 2019	-	-	-
Lapatinib	Covered by medical insurance, DDC decreased from ¥121.43 to ¥ 70.00	Jul 2017	-	49	-
Lapatinib	DDC decreased from ¥ 70.00 to ¥ 66.70	Aug 2019	72.33	303.33	319.37
Pyrotinib	Covered by medical insurance	Nov 2019	-	-	-

As show in Table 2, pertuzumab, inetetamab, lapatinib, and pyrotinib were unavailable before the initiation of NHIC; original trastuzumab was subjected to NHIC and price negotiation synchronously in July 2017; trastuzumab-emtansine remained out of covered NHIC by 2021. Hence, only the effect of NIHC on the DDDs of generic trastuzumab (Zercepac) was analyzed by ITS analysis. Zercepac came into the Nanjing market in October 2020 and included by the NHIC in December 2020, after which its DDDs increased significantly ($P < 0.001$, Figure 5A).

The prices of original trastuzumab (Herceptin) has been negotiated for rounds. In July 2017, Herceptin had a great price drop and was covered by health insurance, with a reimbursement rate of 70%. The time series was divided into two parts. As indicated by the results in Table 2, the DDDs of trastuzumab (Herceptin) increased after July 2017. After the initiation of NHIC and price negotiation policy, its DDDs significantly increased ($P = 0.021$, Figure 5B). This was the synergetic effect of NHIC and price negotiation. In August 2019, Herceptin underwent the second round of price negotiation, and its DDC had a slight decrease (from ¥7600.00 to ¥ 7270.20). Hereafer, its DDDs increased, but did not reach statistical difference ($P = 0.285$, Figure 5C). A similar trend was found in the DDDs of lapatinib ($P = 0.319$, Figure 5D) when its DDC decreased from ¥ 70.00 to ¥ 66.70 in Aug2019.

Low-price generic drug replacement showed a significant effect on the consumption of trastuzumab. Generic trastuzumab (Zercepac) came into the Nanjing market in October 2020. Thereafter, the number of monthly DDDs of generic trastuzumab increased significantly, and reached 516.5 in December 2021, which was about half of that of the original drug. Meanwhile, the DDDs of original trastuzumab (Herceptin) had a decreasing trend ($P < 0.001$, Figure 5E).

Discussion

Our study showed the obvious trends in the consumption of anti-HER2 drugs in Nanjing from 2012 to 2021. Reimbursement, price negotiation, and generic drug replacement all increased their consumption. Our findings provide valuable evidence for the government and health institutes to adopt measures to improve drug availability and affordability.

Trastuzumab (Herceptin) is the first approved drug targeting HER2, and the only used in Nanjing before 2017. Previous studies have proved that its high price limits the patients' access to trastuzumab in underdeveloped areas without reimbursement policy (5–7). Lammers et al. (5) identified potential barriers to the expansion of trastuzumab use in the United States, Mexico, Turkey, Russia and Brazil via physician-oriented survey. Out of insurance coverage, no commercialized drug, and high cost were main barriers restricting the consumption of trastuzumab. In our study, trastuzumab was not covered by the national health insurance system until July 2017. From 2012 to 2016, the average

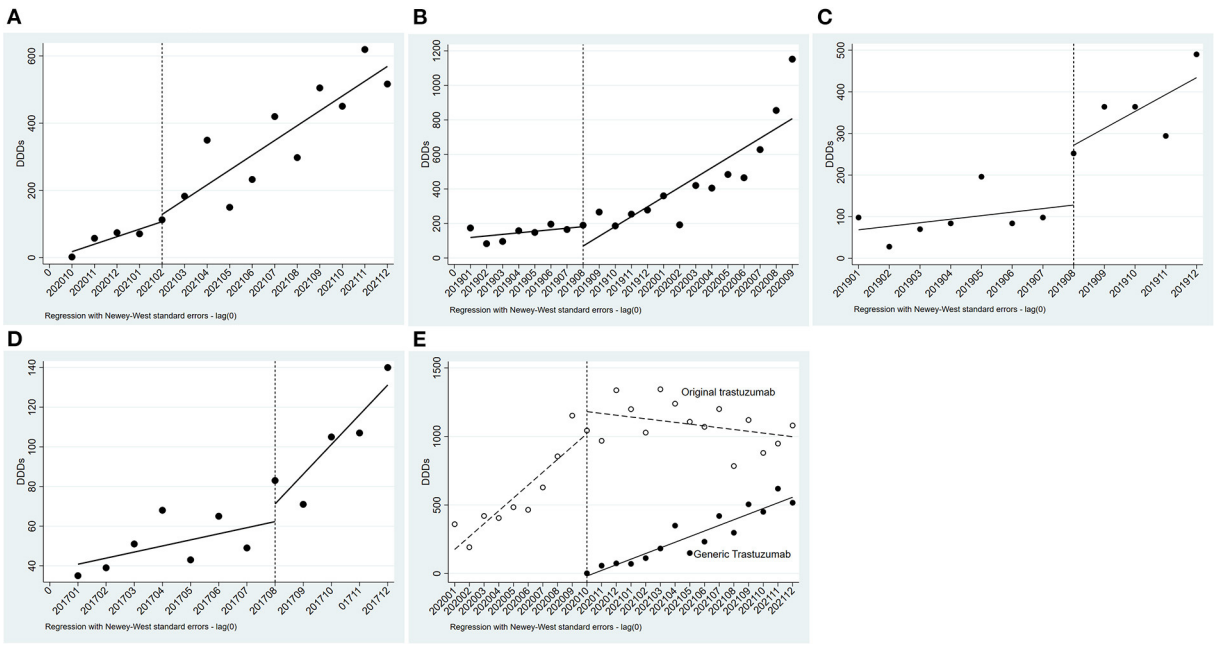

FIGURE 5
Results of the regression analysis of DDDs before and after policy implementation. **(A)** Regression analysis of DDDs of generic trastuzumab before and after insurance coverage; **(B)** Regression analysis of DDDs of original trastuzumab before and after insurance coverage and price negotiation; **(C)** Regression analysis of DDDs of original trastuzumab before and after price negotiation; **(D)** Regression analysis of DDDs of Lapatinib before and after price negotiation; **(E)** Regression analysis of DDDs of trastuzumab before and after low-price generic replacement.

cost of trastuzumab was ¥21999.42 per cycle (21 days), which was far beyond the average household income in Nanjing during the same period (19). This may explain the low and unchanged consumption of trastuzumab in 2012–2016.

DDC has been used as an efficient indicator in nearly one third of studies about drug consumption in China (13, 15). These studies have provided valuable advice for price policy-making of pharmaceutical products on the market (13). Our previous study showed that the DDC of EGFR tyrosine kinase inhibitors significantly affect their consumption (12). Hence, the relation between DDC and DDDs was analyzed in this study. As expected, the ln value of DDC was negatively correlated with the ln value of DDDs (Figure 4). Fortunately, efforts have been taken to reduce drug cost, such as reimbursement policy, national price negotiation, generic drug replacement, low-price drug replacement.

The effect of reimbursement policy on drug consumption has been extensively researched. Policies, such as MGEN plan in French (20), pharmacare programs in Canada (21), national health insurance in Japan (22), Medicare Part D (23) and Medicaid in America (24), have increased drug consumption and decreased out-of-pocket costs. China built up its basic health insurance system in 2009, which expanded the coverage and increased drug availability. In 2017, the system was further enhanced by the price negotiation and mandatory reimbursement policies. In our study, original trastuzumab (Herceptin) and generic trastuzumab (Zercepac) ran into the NHIC in July 2017 (8) and December 2020 (10), separately. The NHIC significantly increased the consumption of trastuzumab (Figures 5A,B and Table 2).

In response to increases in drug prices during the past few decades, many countries have implemented policies of price negotiation. These polices have significantly reduce drug price and increased drug consumption in Italy, France (25), America (26), and Germany (27). The Chinese government has implemented this policy in 2017, the DDC of the 15 targeted anticancer drugs dropped from US$169.24 to US$71.21 (28). Price negotiations have reduce DDC and increased the DDDs of anti-HER2 drugs in China (Figures 5B–D and Table 2).

Low-price generic or biosimilar drug replacement can reduce the cost and increase the consumption. A study has been conducted to compare the costs of biosimilars and innovator biologics (five cycles in total) in India, estimating that the use of biosimilars would save about 843 million U.S. dollars yearly (29). Likewise, introducing generics and biosimilars may overcome the barriers limiting the use of trastuzumab. In our study, available generic trastuzumab (Zercepac) significantly decreased the DDC and increased the total consumption of trastuzumab in Nanjing (Figure 5E and Table 2).

There are some limitations in our study. First, the term "consumption" meant the quantity of drugs prescribed, but not drugs administered. Second, the prevalence of HER2-positive cancer was not available, so the association of increased consumption with cancer prevalence needs further analysis.

Third, we did not analyze the prescription switch between anti-HER2 drugs after reimbursement and price negotiation. Fourth, we studied the consumption trend of the drugs without treatment efficacy.

Conclusion

The consumption of anti-HER2 drugs has increased significantly since 2017 in Nanjing, mainly due to the implementation of NHIC, price negotiation, or low-price generic drug replacement. Further efforts are needed to translate the higher consumption of anti-HER2 drugs into clinical benefits.

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

JL contributed to the initial drafting of the manuscript. HD and DD extract the data. XZ and BW made the ITS analysis. WF design this study and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.944071/full#supplementary-material

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Economic evaluation of margetuximab vs. trastuzumab for pretreated ERBB2-positive advanced breast cancer in the US and China

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Objective: To assess the economic evaluation of margetuximab plus chemotherapy over trastuzumab plus chemotherapy for women with pretreated ERBB2-positive advanced breast cancer in the United States (US) and China.

Methods: Based on the SOPHIA trial, a three-state Markov model was developed to compare the cost and efficacy of margetuximab to trastuzumab for previously treated women with ERBB2-positive advanced breast cancer. The model inputs were derived from existing literature and the US life table. Primary outcomes included lifetime costs in US dollars, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analyses were conducted to evaluate the impact of uncertainty.

Results: The base case analyses demonstrated that margetuximab plus chemotherapy had an increasing cost of $68,132 and $20,540 over trastuzumab plus chemotherapy in the US and China, respectively, with a gain of 0.11 and 0.09 QALYs both favored margetuximab. The ICERs for two treatment strategies were $260,176 in the US and $630,777 in China, resulting in a poor cost-effectiveness at their respective threshold of willingness to play. One-way sensitivity analyses showed that the results to be most sensitive to the price of margetuximab and that of trastuzumab. And an 11 and 82% price reduction of margetuximab would make this regimen cost-effective in the US and China, respectively.

Conclusion: In the US and China, margetuximab plus chemotherapy is not likely to be cost-effective for women with pretreated ERBB2-positive advanced breast cancer, whereas price reduction effectively improves insufficient cost-effectiveness.

KEYWORDS

margetuximab, trastuzumab, cost-effectiveness, breast cancer, China, the US

Introduction

Breast cancer has replaced lung cancer as the most prevalent cancer globally, with 2.26 million new cases worldwide in 2020 (1). Among women, invasive adenocarcinoma of the breast is the most common non-dermatological cancer, with the second and fourth leading cause of death in the United States (US) and China (2, 3). About 6% of breast cancer patients are diagnosed with advanced breast cancer in the US (4), while the rate is more than 20% among Chinese patients (5). Around 20 to 30% of women with breast cancer diagnoses have overexpressed Human epidermal growth factor receptor 2 (ERBB2, formerly HER2), which is associated with more aggressiveness and worse prognosis (6).

The economic burden of breast cancer is increasing rapidly with the changing treatment landscape. The 1-year treatment cost after breast cancer diagnosis increased by 2-fold within 10 years, with approximately an estimate of $20 billion by 2020 (7, 8). A tripling proportion of chemotherapy-received women (9), namely incremental use of new oncolytic drugs, contributes to increased cancer-related costs and pressure on health care budgets. Unfortunately, the higher population of patients with ERBB2-positive late-stage breast cancer will further incur higher cancer-related drug costs (10, 11). For these patients, the standard first-line treatment included trastuzumab plus taxane in the earlier years, and since 2013, the addition of pertuzumab to trastuzumab with taxane became routinely available (12, 13). Despite the marked clinical efficacy of the combination of trastuzumab, pertuzumab, and chemotherapy in patients with first-line advanced breast cancer, the vast majority of patients ultimately progress. Mounting evidence demonstrate that previous-treated patients with progression can still benefit from additional ERRB2-targeted agents, while the optimal treatment paradigm in later lines remains unsettled (14, 15).

Margetuximab, a chimeric, Fc-engineered, immune-activating anti-ERBB2 immunoglobulin G1 monoclonal antibody, shares epitope specificity and Fc-independent anti-proliferative effects with trastuzumab. Based on the SOPHIA phase three randomized open-label trial, margetuximab plus chemotherapy had acceptable safety and significant clinical benefits compared with trastuzumab plus chemotherapy in ERBB2-positive advance breast cancer after two or more prior anti-ERBB2 therapies (16). It significantly prolonged median progression-free survival (PFS) by 1.3 months (5.7 verse 4.4 months, hazard ratio (HR), 0.71; 95% confidence interval (CI), 0.58 to 0.86) and the median overall survival (OS) by 1.8 months (21.6 verse 19.8 months, HR, 0.89, IC, 0.69 to 1.13) for patients receiving margetuximab in comparison to trastuzumab. Owing to the improved efficacy, in 2020, the US Food and Drug Administration (FDA) approved margetuximab in combination with chemotherapy as the treatment of adult patients with metastatic ERBB2-positive breast cancer who have received two or more prior anti-ERBB2 regimens.

Since this treatment regimen exhibited proven effectiveness, there is an impetus for evaluating its economic value. The objective of this model-based analysis was to estimate the potential cost-effectiveness of margetuximab compared to trastuzumab, each combined with chemotherapy, for patients with pretreated ERBB2-positive advanced breast cancer in developed and developing countries, like the US and China.

Methods

Study design and setting

To estimate the effectiveness and cost outcomes of patients with pretreated ERBB2-positive advanced breast cancer, this study conducted a Markov model with a 3-week cycle length to compare margetuximab vs. trastuzumab, each with chemotherapy, in the context of the US and Chinese health care system. The base-case intention-to-treat (ITT) population was 56 years and over women who had progressive disease after two or more lines of prior ERBB2-targeted therapy (including pertuzumab), and one to three lines of non-hormonal metastatic breast cancer therapy (16). The model was evaluated based on a time horizon of the rest of a patient's life, alongside a discount rate of 3% per annum in costs and outcomes. Treatment effectiveness was assessed as life-years (LYs) and quality-adjusted life-years (QALYs). Primary economic endpoint was the projected incremental cost-effectiveness ratio (ICER). The willingness to pay (WTP) threshold of $150,000 per QALY in the US and $37,653 per QALY in China (triple GDP per capita) was used to determine cost-effectiveness.

Simulation model

The Markov model included three mutually exclusive health states: PFS, progressed disease (PD), and death (Figure 1). All pretreated patients began in the PFS state and would either remain in their assigned health state or transition to a new health state based on time-dependency transition probabilities during each 3-week cycle. The half-cycle correction was applied to all estimated costs and utilities to avoid reducing the actual cost and effectiveness of loading doses of margetuximab and trastuzumab.

Clinical data

Data from the SOPHIA trial was used to model the PFS and OS curves. Kaplan-Meier estimates beyond the observation period were extrapolated based on the standard

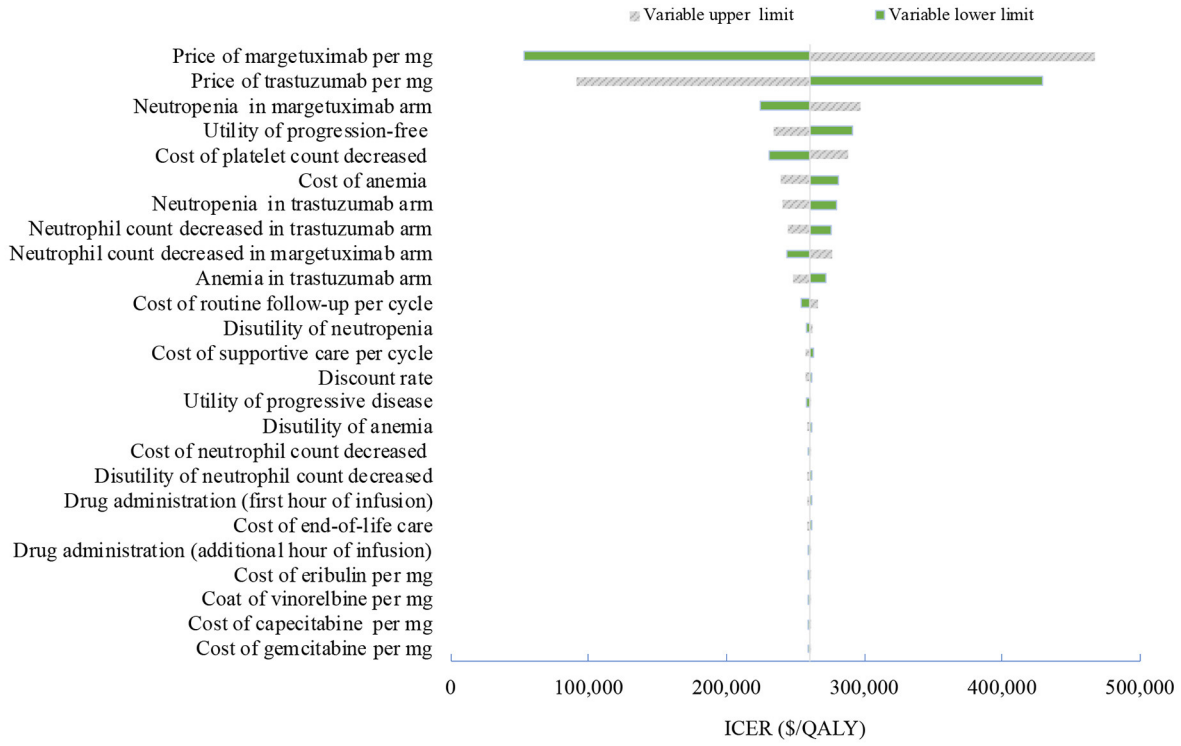

FIGURE 1
Tornado diagram of one-way sensitivity analyses of margetuximab vs. trastuzumab in the treatment of pretreated ERBB2-positive advanced breast cancer from the US perspective. QALYs, quality-adjusted life-years.

statistical analyses developed by Guyot et al. (17). The study used the GetData Graph Digitizer software (2.21 version) to gather the data points from the PFS and OS curves, fitting parametric survival functions. Multiple parametric distributions included exponential, Weibull, lognormal, gamma, log-logistic, and Gompertz. Goodness-of-fit was assessed according to Akaike Information Criterion and the Bayesian Information Criterion, combined with the visual inspection. The log-logistic distribution was adopted for PFS curves and the Weibull distribution for OS curves (Supplementary Tables S1, S2). The model estimated the mortality rate through the US and Chinese life tables. Health state utilities were sourced from the literature. Table 1 includes a summary of the utility estimates used in the model.

Patients in the SOPHIA trial received two treatment regimens, margetuximab plus chemotherapy or trastuzumab plus chemotherapy. Margetuximab was given intravenously at 15 mg/kg each cycle and trastuzumab was given intravenously at 6 mg/kg on day 1 of each cycle after a loading dose of 8 mg/kg. In the base-case analyses, the study modeled patients to remain on treatment unless they were disease-free and did not have a major toxicity event. That implied a median of six cycles for margetuximab vs. five cycles for trastuzumab. Given that, the model adjusted the PFS curve downward by applying the ratio of median time on treatment to median PFS at each cycle. There were four chemotherapy choices including vinorelbine, capecitabine, eribulin, and gemcitabine, with the relative distribution of 35.6, 26.7, 25.4, and 12.3%, respectively (16).

Costs and utilities

The analyses were conducted from the perspective of the Chinese and US health care system. Direct costs included the drug costs, drug administration, management of adverse events (AEs), best supportive care, and end-of-life care, estimated in 2021 US dollars ($1 = 6.45 Chinese yuan) according to the US and China consumer price index. Drug costs for margetuximab and trastuzumab targeted therapies were derived from projected April 2022 Average Sale Price (ASP) (Genentech data), published literature, and Chinese national drug prices. The US market price of margetuximab was used for the base-case analyses because the margetuximab has not been marketed in China. Drug dosages for margetuximab, trastuzumab, and chemotherapy were based on the SOPHIA trial. The AEs

TABLE 1 Model inputs.

Parameter	Base case	range		Distribution	Source
		Low	High		
Cost in the US ($)					
Margetuximab per mg	8.75	7.00	10.50	Gamma	2022 ASP
Trastuzumab per mg	8.64	6.91	10.37	Gamma	2022 ASP
Capecitabine per mg	0.00	0.00	0.00	Gamma	2022 ASP
Eribulin per mg	1,274.36	1,019.49	1,529.23	Gamma	2022 ASP
Gemcitabine per mg	0.02	0.02	0.02	Gamma	2022 ASP
Vinorelbine per mg	0.86	0.69	1.03	Gamma	2022 ASP
Supportive care	5,600.00	4,480.00	6,720.00	Gamma	(18)
Routine follow-up	1,890.00	1,512.00	2,268.00	Gamma	(18)
End-of-life care	21,585.00	17,268.00	25,902.00	Gamma	(18)
Drug administration					
First h of infusion	136.61	109.29	163.93	Gamma	(18)
Additional h of infusion	28.71	22.97	34.45	Gamma	(18)
Management of adverse events					
Neutrophil count decreased	10,603.70	8,482.96	12,724.44	Gamma	(19)
Anemia	146,36.53	11,709.22	17,563.84	Gamma	(19)
Neutropenia	10,603.70	8,482.96	12,724.44	Gamma	(19)
Cost in China ($)					
Margetuximab per mg	8.75	7.00	10.50	Gamma	Local price
Trastuzumab per mg	1.94	1.55	2.33	Gamma	Local price
Capecitabine per mg	0.02	0.02	0.03	Gamma	Local price
Eribulin per mg	617.15	493.72	740.58	Gamma	Local price
Gemcitabine per mg	0.09	0.07	0.10	Gamma	Local price
Vinorelbine per mg	2.38	1.90	2.85	Gamma	Local price
Supportive care	1,616.78	1,293.42	1,940.14	Gamma	(20)
Routine follow-up	162.00	129.60	194.40	Gamma	(20)
End-of-life care	1,275.03	1,020.02	1,530.04	Gamma	
Drug administration	22.00	17.60	26.40	Gamma	(21)
Management of adverse events					
Neutrophil count decreased	3,184.01	2,547.21	3,820.81	Gamma	(22)
Anemia	607.52	486.02	729.03	Gamma	(20)
Neutropenia	3,184.01	2,547.21	3,820.81	Gamma	(22)
Risks for main AEs in margetuximab arm (grade ≥3)					
Neutrophil count decreased	0.09	0.08	0.10	Beta	(16)
Neutropenia	0.20	0.18	0.22	Beta	(16)
Risks for main AEs in trastuzumab arm (grade ≥3)					
Neutrophil count decreased	0.11	0.09	0.12	Beta	(16)
Anemia	0.06	0.06	0.07	Beta	(16)
Neutropenia	0.12	0.11	0.14	Beta	(16)
Health state utility in the US					
Progression-free	0.72	0.64	0.79	Beta	(23)
Progressive disease	0.47	0.42	0.52	Beta	(23)
Health state utility in China					
Progression-free	0.85	0.77	0.94	Beta	(24, 25)
Progressive disease	0.52	0.47	0.57	Beta	(24, 25)
Disutility					
Neutrophil count decreased	0.13	0.12	0.14	Beta	(26, 27)
Anemia	0.07	0.07	0.08	Beta	(26, 27)
Neutropenia	0.13	0.12	0.14	Beta	(26, 27)
Discount rate	0.03	0	0.08	Fixed in PSA	-

ASP, Medicare Part B Quarterly Average Sales Price; PSA, probabilistic sensitivity analysis.

considered in the model were those rated at a severity of grade 3–5 and must have occurred in at least 5% of patients in the clinical trial. The mean cost of AEs for the margetuximab and trastuzumab arms was estimated by multiplying the probability of occurrence of individual AE by the cost of managing each AE. The costs of managing AEs, drug administration and supportive care were estimated based on previous literatures. The study assumed that patients in two groups received best supportive care after progression in the model. Table 1 also includes a summary of cost parameters used in the model.

Sensitivity analysis

Sensitivity analyses were performed to determine which variables would have a substantial impact on projected costs and outcomes. One-way sensitivity analyses were presented by tornado diagrams. The model also performed probabilistic sensitivity analyses to further test the robustness of the results using Monte Carlo simulation. When the level of confidence was available, variation was based on actual data; when unavailable, the ±20% ranges were assumed for costs, and ±10% for utilities and risks of AEs.

Results

Base case

Table 2 shows the detailed information of base-case results. Compared to trastuzumab plus chemotherapy, margetuximab plus chemotherapy were associated with both increased costs and improved outcomes from the US and the Chinese perspectives. From the US perspective, the patients treated with margetuximab plus chemotherapy yielded 0.55 QALYs, with additional 0.09 QALYs than those who received trastuzumab plus chemotherapy. The margetuximab plus chemotherapy costs an additional $23,540, resulting in an ICER of $160,176 compared to trastuzumab and chemotherapy. From the Chinese perspective, margetuximab plus chemotherapy therapy was associated with a mean quality-adjusted survival per patient of 0.65 QALYs, which was 0.11 QALYs longer than trastuzumab plus chemotherapy therapy. The estimated ICER was $630,777 per QALY.

Sensitivity analyses

One-way deterministic sensitivity analyses revealed that the price of margetuximab, the price of trastuzumab altered the cost-effectiveness of the regimens in the US and China (Figures 1, 2), resulting in ICERs varies from $52,913 to $467,436 and from $484,977 to $776,576, respectively. Based on the probabilistic sensitivity analyses (Figure 3), 25% of simulations generated a chance of being cost-effective for margetuximab at a WTP of $150,000, and the percentage would increase to more than 50% at a WTP threshold of $263,000 per QALY in the US. In China, the margetuximab regimen had a 0% chance to be good money for its value at a WTP of $37,653. In addition, the margetuximab regimen was cost-effective when its price was reduced by 11% in the US and 82% in China.

Discussion

The SOPHIA trial demonstrated a head-to-head advantage of margetuximab compared to trastuzumab, providing a promising option for patients with pretreated ERBB2-positive advanced breast cancer in later line treatment (16). Considering different national conditions and medical environments, this study conducted the model-based cost-effectiveness analyses of margetuximab over trastuzumab, each with chemotherapy, for pretreated ERBB2-positive advanced breast cancer population from the US and the Chinese perspective, leveraging clinical and outcomes data in the SOPHIA trial. Although margetuximab is not available on the Chinese mainland market, the results provided evidence for its pricing in China in the future. The study projected an ICER of $258,147 per QALY gained for the US patients and of $637,656 per QALY gained for Chinese patients. The results support that although margetuximab was associated with improved clinical benefit, it was not cost-effective at the common WTP thresholds of $150,000 and $37,653 in the US and China, respectively. However, it is very close to the cost-effective threshold in the US.

Although no standardized treatment strategies have been established for patients after first-line treatment with ERBB2-positive advanced breast cancer, many candidate third-line and beyond regimens were used historically, including lapatinib with capecitabine, trastuzumab with capecitabine, or other chemotherapeutics with continued trastuzumab (13, 28, 29). Current evidence indicated that the cost-effectiveness was associated with the perspective of studies, the total regimen, and the comparison strategy (30). For example, lapatinib with capecitabine was cost-effective compared to trastuzumab with capecitabine and capecitabine alone from the perspective of the United Kingdom National Health Service (31), while not superior to capecitabine from the US societal perspective (32).

More trials are assessing novel monoclonal antibodies (MoAbs), small molecule tyrosine kinase inhibitors (TKIs), and antibody drug conjugates (ADCs) as the third-line and beyond therapy for ERBB2-positive advanced breast cancer. Margetuximab, the next generation ERBB2-specific MoAbs, resulted in a 1.3-month improvement in median PFS when it replaced trastuzumab in a chemotherapy combined therapy in the third and later lines. Although the base-case analyses failed to prove its cost-effectiveness, sensitivity analyses showed that the result may be reversible when adjusting the price of margetuximab and trastuzumab. A slight decrease in the price

TABLE 2 Discounted incremental cost-effectiveness of margetuximab vs. trastuzumab.

Analysis	Total cost, $	LYs	QALYs	Incremental			ICER (incremental cost/QALY, $)
				Cost, $	LYs	QALYs	
US perspective							
Margetuximab	201,322	0.90	0.55	20,540	0.13	0.09	260,176
Trastuzumab	177,782	0.77	0.46	NA	NA	NA	NA
Chinese perspective							
Margetuximab	106,263	0.89	0.65	68,132	0.12	0.11	630,777
Trastuzumab	38,131	0.77	0.55	NA	NA	NA	NA

LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; NA, not applicable.

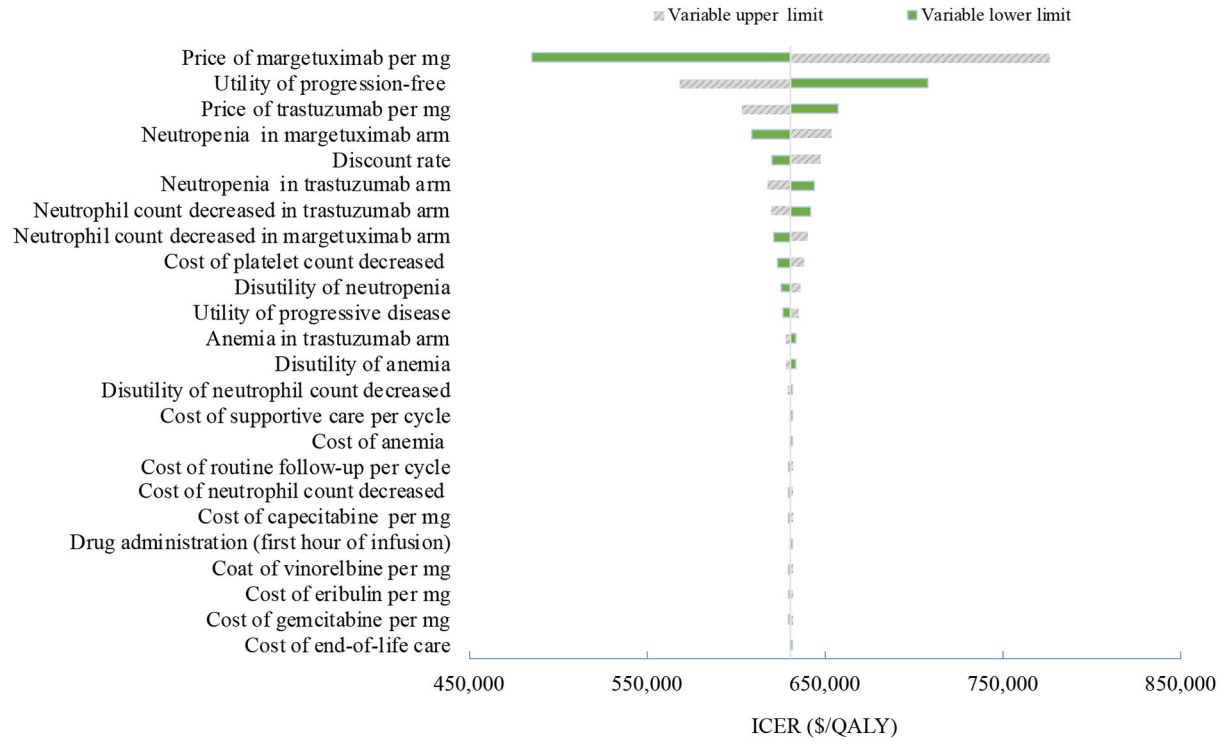

FIGURE 2
Tornado diagram of one-way sensitivity analyses of margetuximab vs. trastuzumab in the treatment of pretreated ERBB2-positive advanced breast cancer from the Chinese perspective. QALYs, quality-adjusted life-years.

of margetuximab would greatly improve its consequence on the value for money in the US. With a 26% price reduction, margetuximab would be dominant over trastuzumab, with a cost-saving and additional QALYs gained in the US, while the price reduction of making margetuximab cost-effective is up to 82% in China. In contrast, the price reduction of trastuzumab reinforces the favorable, cost-effective result itself. The price of trastuzumab in China is 4.5 times cheaper than the US price due to the recent drug negotiation. The nearly identical QALYs gained in the two regimens explained why the cost-effectiveness result is largely dependent on changes in the relative price of margetuximab and trastuzumab. However, since the unsettled optimal treatment paradigm in later lines, margetuximab provides a promising opportunity for patients with pretreated ERBB2-positive advanced breast cancer, especially for those considering the best supportive care.

Recent evidence from the NALA and TULIP trials presents another promising alternative to margetuximab, including the pan-ERBB2 TKI neratinib and ADC (vic-) trastuzumab duocarmazine (SYD985) (33, 34). Substitution of neratinib for lapatinib prolonged median PFS by 2 months (33). Compared with the physician's choice of therapy, a 2.3-month

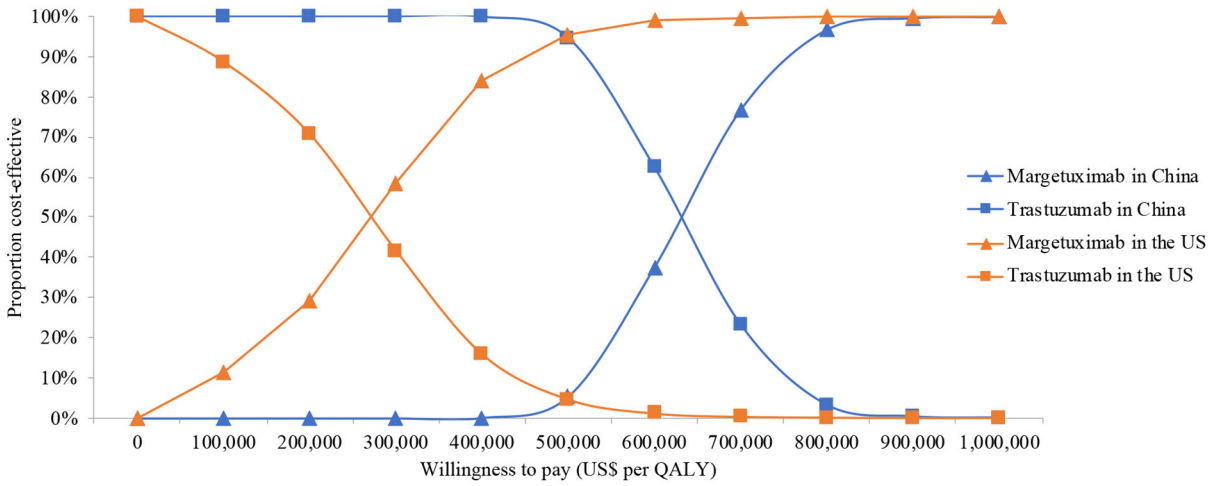

FIGURE 3
Cost-effectiveness acceptability curve for the base case analysis from the Chinese and the US perspective. QALYs, quality-adjusted life-years.

improvement in median PFS was observed for SYD985 (34). The Food and Drug Administration (FDA) approved the neratinib but not yet SYD985 in later-line setting for patients with ERBB2-positive advanced breast cancer in the US. Head-to-head comparison data between margetuximab and other alternatives, along with the cost-efficacy ratios was not available in current evidence, resulting in difficulties in determining the optimal treatment regimen. Despite that, it is reasonable to consider margetuximab as an active regimen for those who are vulnerable to toxic effects of these novel therapies.

This study is subject to limitations. A limitation inherent is reliance on data extrapolation from the clinical trial to a lifetime horizon for economic evaluation. The SOPHIA trial reported the interim analysis results of PFS and OS survival curves. The lack of final survial results reinforces the uncertainty about clinical benefits of the two regimens. If OS in SOPHIA trial is significantly greater than that projected in the present model, the cost-effectiveness of margetuximab will be likely to be improved; however, if margetuximab fails to improve OS, trastuzumab will remain cost-effective. Besides, the quality of life data were available from published literatures rather than from the SOPHIA trial, which failed to reflect the real situation despite conducting sensitivity analyses. Thus, utilities were tested with a range of ±10%, and the result showed that the results were robust.

Conclusion

The study found that, in patients with pretreated ERBB2-positive advanced breast cancer, despite acceptable safety and significant clinical benefits, margetuximab plus chemotherapy exhibited unfavorable cost-effective result over trastuzumab plus chemotherapy. The cost-effectiveness of margetuximab is very sensitive to the relative price of margetuximab to trastuzumab. The price reduction of margetuximab improves the consequence on its value for money and even makes the regimen cost-effective.

Author's note

Compared to trastuzumab plus chemotherapy, margetuximab plus chemotherapy has exhibited proven clinical benefits in patients with pretreated ERBB2-positive advanced breast cancer. However, the cost-effectiveness of this new regimen remains to be investigated.

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/s.

Author contributions

The conception and design of the study were primarily conducted by YZ and BC. The drafting of the paper was mainly the responsibility of ZT. All authors have reviewed the analysis and interpretation of the data and contributed to the drafting of the manuscript, revising the manuscript for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.942767/full#supplementary-material

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Using 5 consecutive years of NICE guidance to describe the characteristics and influencing factors on the economic evaluation of orphan oncology drugs

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Objective: Orphan oncology drugs used in this article were defined by the type of disease treated by drugs, as drugs used to treat rare diseases with a prevalence of ≤500 per million people per year. In this article, our concern was to explore focus on the economic evaluation of the National Institute for Health and Care Excellence (NICE), when orphan oncology drugs were appraised for reimbursement, and provide advice and suggestions to decision-makers.

Methods: A retrospective study was used in this study. Thirty guidance were gathered as our subject by NICE from 2016 to 2020, excluded drugs were not identified as orphan by European Medicines Agency (EMA) and orphan drugs were not used for cancer, and orphan oncology drugs were terminated at the time of data collection at NICE. Qualitative analysis, descriptive statistics, and Fisher's exact test were conducted.

Results: Of all guidance, the partitioned survival model was used most to appraise orphan oncology drugs, and every drug had a kind of commercial arrangement such as patient access scheme (PAS), managed access arrangements (MAAs), and commercial access agreement (CAAs). End of life is an important indicator that had been defined by NICE in the methods of technology appraisal in 2013, and drugs that met the criterion would be given a higher threshold of ICER. In addition, we found that potential health benefits were increasingly concerned such as drug delivery.

Conclusion: In the setting of uncertain clinical and cost efficacy, orphan oncology drugs are comprehensively evaluated in multiple additional dimensions, which include life-extending benefits, and innovation. NICE uses a combination of special considerations for incomplete data, appropriate economic models, and appropriate health technology assessment (HTA) methods during the assessment process, besides, orphan oncology drugs with

insufficiency evidence were recommended Cancer Drugs fund (CDF) to afford for patients, which would obtain more availability and accessibility, based on which, high-quality drugs for treating rare cancers can fall within the scope of affordable healthcare provided by the English medical insurance fund.

KEYWORDS

orphan oncology drugs, NICE, economic evaluation, influencing factors, technology appraisal guidance

Introduction

Rare diseases are also known as Orphan diseases, which were used to refer to some uncommon, low incidence, and often life-threatening diseases. Drugs that treat orphan diseases are called orphan drugs. Orphan drugs, or Orphan Medicinal Products (OMPs), exist for <3% of rare diseases (1). It is shown that the number of orphan drug designations assigned by the United States Food and Drug Administration (FDA) significantly increased from 1983 to 2019, most prominently in oncology (1910, 37%) (2). Another study on orphan drug approvals in Europe found that 39% of all orphan drugs that were approved by the European Medicines Agency through a centralized process were cancer-related (3). Nine of the top 10 indications for orphan drugs as specified by the European Medicines Agency/European Mes Aedicingency (EMA) were for cancer (including acute myeloid leukemia, non-Hodgkin's lymphoma, glioma, pancreatic cancer, ovarian cancer, multiple myeloma, renal cell carcinoma, liver cancer, and chronic lymphocytic leukemia) (4).

There were two definitions of orphan drugs used in oncology. Take the European Union as an example, one is defined by the type of disease treated by drugs, such as orphan drugs in oncology, oncology drugs with orphan designation, medicines for orphan indications in oncology, oncology Orphan drugs (ODs), which were defined as drugs used to treat rare diseases with a prevalence ≤500 per million people per year. They are usually referred to by the following terms: orphan drugs in oncology, oncology drugs with an orphan designation, medicines for orphan indications in oncology, and oncology ODs. This article focuses on this definition, using "orphan oncology drugs." An alternative definition defines orphan drugs as those used to treat cancers with an incidence of ≤60 per million people/year, and refers to them as rare tumor drugs. There are about 200 rare tumors in Europe, which account for 20–24% of all tumor diagnoses (5). These drugs are usually referred to by one of the following terms: rare cancers, rare tumors, rare neoplastic disorders, and oncology drugs in the treatment of rare diseases.

Providing equal access to affordable drugs across countries is high on the political agenda in many countries, even though it is far from being achieved (6). Consequently, all countries are exploring ways and methods that suit their own country to provide access to affordable drugs, and some have already had special and well-established HTA agencies (7), such as the National Institute for Health and Care Excellence (NICE) in the UK, the Scottish Medicines Consortium (SMC) in Scotland (8), the Dental and Pharmaceutical Benefits Board (TLV) in Sweden and the Haute Autorité de santé (HAS) in France (9).

There is still a big distance in the average number between non-orphans and orphan drugs (10). Even though rare disease has a low incidence, drugs for rare diseases offer important health benefits and continue to challenge traditional health technology assessment (HTA) (11). But on account of the high treatment cost, a small number of subjects, uncertain clinical effects, social value, and other problems, it is difficult to appraise orphan oncology drugs, and conventional appraisal methods were not applicable anymore. It is necessary to explore multiple appraisal methods when evaluating orphan oncology drugs, including the use of alternative indicators, incomplete data processing, and social value factors.

National Institute for Health and Care Excellence/NICE in the UK has a separate process through which certain drugs for rare diseases are reviewed from the outset (12), which made an important role in producing evidence-based guidance and advice for health, public health, and social care practitioners. They did technology appraisal guidance (TAG, beginning in 2000) and highly specialized technologies (HST, beginning in 2015, which was only used to consider drugs for very rare conditions) to make recommendations on the clinical and cost-effectiveness of drugs (13), which were used to help to ensure that the NHS uses its resources fairly and effectively. Drugs were appraised based on a review of clinical and economic evidence. And there are 5 types (recommended, optimized, Cancer Drugs Fund, not recommended, only in research) of recommendations after appraisal, which they can make. Appraisal recommendations are prepared by independent committees, which provides a good reference for us to appraise orphan oncology drugs.

This study evaluates the guidance of orphan oncology drugs appraised by NICE from 2016 to 2020 and focuses on the economic assessment of these drugs in order to explore concerns on the economic evaluation of NICE when orphan oncology drugs were appraised for reimbursement, which was

TABLE 1 Orphan oncology drugs guidance from 2016 to 2020.

Year	Guidance no. of HTG and TAG	Guidance no. of orphan drugs	Guidance number of orphan oncology drugs			
			Total	Recommend to NHS	Recommend to CDF	Not recommend
2016	53	2	1	1	0	0
2017	63	12	7	5	0	2
2018	57	17	15	8	6	1
2019	60	18	8	2	3	3
2020	53	13	7	5	0	2
Total	**286**	**62**	**38**	**21**	**9**	**8**

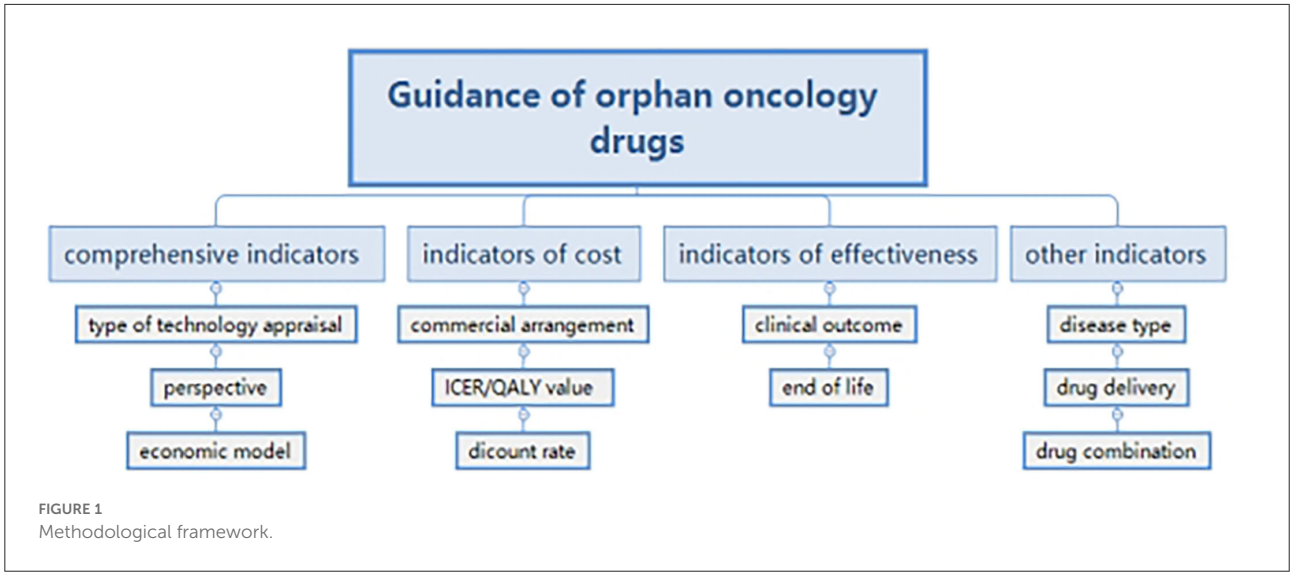

FIGURE 1
Methodological framework.

aimed to generalize findings and provide advice and suggestions to decision-makers.

Materials and methods

Sampling and inclusion criteria for HTA agencies and drugs

We conducted a retrospective study on guidance published on the website of the National Institute for Health and Care Excellence/NICE from 2016 to 2020 (https://www.nice.org.uk/guidance/published?ndt=Guidance&ndt=Quality%20standard.NICE) was chosen for four reasons: (i) it is well-established, (ii) its guidance had been publicly available, (iii) it made a very important role in the final reimbursement decision in the UK, (iv) and its guidance had been reported in a language understood.

For the included drugs, we first collected drug guidance from the guidance program of highly specialized technologies (HST) and technology appraisal guidance (TAG) (14) on the website of NICE. Second, Human medicine European public assessment reports on the European Medicines Agency (EMA) webpage (15) were used to identify if drugs were designated as orphan drugs and authorized for use in the European Union. There were 286 drugs that have been published from 2016 to 2020, including 11 from the HST guidance program and 275 from the TAG program, 62 of which received an orphan EMA designation. Those were excluded because indications were not on oncology and appraisal were terminated at the time of data collection at NICE. Finally, a total of 30 guidance of orphan oncology drugs were selected (Table 1).

Study design and methodological framework

We paid attention to the economic analysis of guidance and formulated a framework with the method of thematic analysis (16). Indicators in guidance were extracted and classified into four groups. Comprehensive indicators

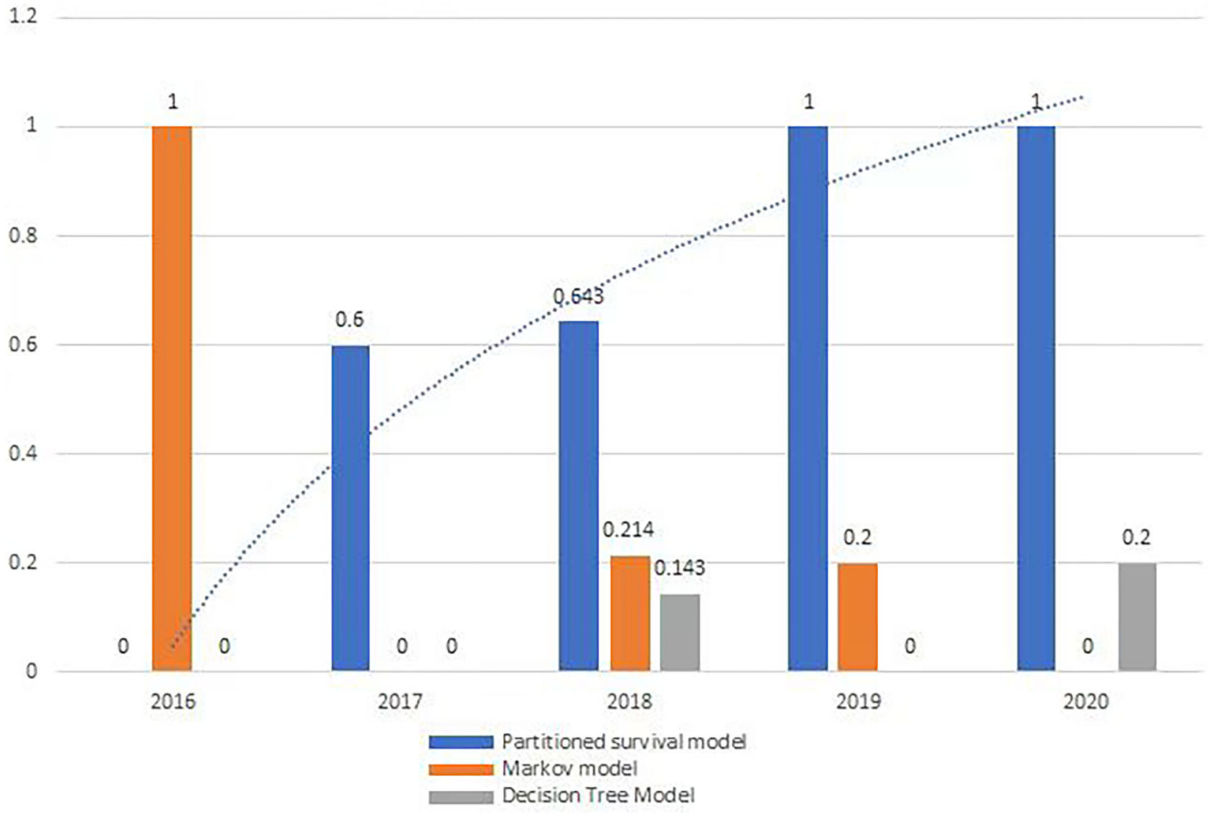

FIGURE 2
The usage of partition survival model.

included: technology appraisal; perspective and economic model; indicators of cost such as a commercial arrangement; Incremental cost effectiveness ratio (ICER)/QALY (quality-adjusted life year) value and discount rate; indicators of effectiveness, such as clinical outcome and end of life; and other indicators such as disease type, drug delivery, and drug combination (Figure 1). Because of the qualitative decisions (17), the research did not aim at quantitative indicators, but to generalize findings and supply suggestions for the government.

Results

There were 30 orphan oncology drug guidance between 2016 to 2020 on the NICE website were chosen in this study. And among the 30 orphan oncology drugs, 21 were recommended to NHS, and 9 were recommended to CDF. The content of guidance of 30 orphan oncology drugs would be described in four sections as the framework.

Comprehensive indicators

From 2016 to 2020, all orphan oncology drugs were appraised by Single Technology Appraisal (STA), except in 2018. There was a growing trend in the usage of partition survival models (Figure 2), but no significant trend on indicators of comprehensive indicators.

Type of technology appraisal

Of the 30 recommended orphan oncology drugs, 27 (90%) were appraised *via* Single Technology Appraisal (STA) and 3 (10%) were appraised *via* Multiple Technology Appraisal (MTA). A single technology appraisal (STA) covers a single technology for a single indication. A multiple technology appraisal (MTA) normally covers more than one technology or one technology for more than one indication. The three orphan oncology drugs appraised by MTA were lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumors, cabozantinib for treating medullary thyroid cancer, and lenvatinib and

sorafenib for treating differentiated thyroid cancer after radioactive iodine, all of whose guidance was published in 2018 (Table 2).

Perspective

Of the guidance that presented a specific and clear perspective, 8 (26.7%) analyses were conducted from the perspective of the NHS and Personal Social Services (PSS), and 5 (16.7%) from the perspective of the NHS without PSS. A total of 16 drugs did not formulate a perspective in their guidance (Table 2). The scope described by NICE usually advocates that the company or ERG should provide an NHS and PSS perspective to study the drug. However, because of the small number of patients with a specific orphan disease, it is difficult to perform a clinical trial. The company or ERG therefore only did their study from the NHS or payer perspective.

Data analysis

Qualitative analysis was used in the first stage of the research. On the basis of the framework, all the relevant information at each step of the decision process was identified. Then, the data collected was exported into excel for analysis. Descriptive statistics were conducted to determine the types and frequencies of indicators. A Fisher's exact test was used to measure associations between recommendation and ICER/end of life/drug delivery/drug combination.

Economic model

From 2016 to 2020, a partitioned survival model was used to perform a cost-effectiveness analysis for 22 orphan oncology drugs (73.3%), a Markov model for 5 (16.7%), and a decision tree model for 3 (10%). Four orphan oncology drugs did not document the type of economic model used in their guidance (Table 2).

Several economic models were combined for the cost-effectiveness analysis of four drugs. The economic model for Pomalidomide, a treatment for multiple myeloma that was previously combined with lenalidomide and bortezomib, in 2017 was a semi-Markov partitioned survival structure. In 2018, Tisagenlecleucel was evaluated using a partitioned-survival model, semi-Markov, and decision tree model. Blinatumomab, which was appraised in 2019 for treating acute lymphoblastic leukemia in remission with minimal residual disease activity, was analyzed using a partitioned-survival model and a semi-Markov model. Gilteritinib, which was appraised in 2020 as a treatment for relapsed or refractory acute myeloid leukemia, was assessed using a decision-tree structure followed by partitioned survival models.

Indicators of cost

Commercial arrangement

All 30 orphan oncology drugs have commercial arrangements. A total of 21(70%) had a patient access scheme (PAS) *via* a simple discount, 7 (23.3%) had a managed access arrangement (MAA), and 2 (6.7%) had a commercial access agreement (CAA) (Table 3).

ICER/QALY value

The ICER/QALY value of 2 orphan oncology drugs (6.7%) was below £20,000, 11 orphan oncology drugs (36.7%) were between £20,000 and £30,000, while that of 16 orphan oncology drugs (53.3%) was above £30,000. One drug's ICER/QALY value was not published. And there was no significant difference between ICER/QALY value and recommendations ($p = 0.238$) (Table 3).

Discount rate

The discount rate of pharmaceuticals is generally between 3 and 5% (18). The discount rates for orphan oncology drugs from 2016 to 2020 were 1.5% (10% of drugs) and 3.5% (40% of drugs), which are the same as the UK standard obtained in ISPOR (19). The discount rates of 15 orphan oncology drugs were not published because of commercial privacy (Table 3).

Indicators of effectiveness

Clinical outcome

The most common clinical indicator was overall survival (OS), which was included in the economic models of 29 of the 30 recommended orphan oncology drugs. The second most frequent was progression-free survival (PFS), which was included in 83.3%. Other indicators included complete response (CR, 30%), response rates (RR, 26.7%), and event-free survival (EFS, 20%). Less common indicators included objective response rate (ORR, 10%), disease-free survival (DFS, 10%), time to next treatment (10%), relapse-free survival (RFS, 6.7%), overall remission rate (ORR, 6.7%), minimal residual disease (MRD, 6.7%), and duration of response (DoR, 6.7%). The clinical outcome indicator of response time was used only once in 2016 for Panobinostat (Table 4).

End of life

The majority of the published guidance on drugs in our study (28, accounting for 93.3%) included a separate paragraph to discuss evidence regarding end-of-life and orphan oncology

TABLE 2 Details of comprehensive indicators in guidance from 2016 to 2020.

Indicators *No.(%)*	Total condition from 2016 to 2020			2016			2017			2018			2019			2020		
	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total
Comprehensive indicators																		
Type of technology appraisal																		
Single technology appraisal/STA	18(60%)	9(30%)	27(90%)	1(100%)	0(0%)	1(100%)	5(100%)	0(0%)	5(100%)	5(35.7%)	6(42.9%)	11(78.6%)	2(40%)	3(60%)	5(100%)	5(100%)	0(0%)	5(100%)
Multiple technology appraisal/MTA	3(10%)	0(0%)	3(10%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	3(21.4%)	0(0%)	3(21.4%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Perspective																		
National health service/NHS	3(10%)	2(6.7%)	5(16.7%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	0(0%)	1(7.1%)	1(7.1%)	2(40%)	1(20%)	3(60%)	0(0%)	0(0%)	0(0%)
NHS and PSS	5(16.7%)	3(10%)	8(26.7%)	1(100%)	0(0%)	1(100%)	2(40%)	0(0%)	2(40%)	0(0%)	1(7.1%)	1(7.1%)	0(0%)	2(40%)	2(40%)	2(40%)	0(0%)	2(40%)
Unspecified	13(43.3%)	4(13.3%)	16(53.3%)	0(0%)	0(0%)	0(0%)	2(40%)	0(0%)	2(40%)	7(50%)	4(28.6%)	11(78.6%)	0(0%)	0(0%)	0(0%)	3(60%)	0(0%)	3(60%)
Economic model																		
Partitioned survival model	15(50%)	7(23.3%)	22(73.3%)	0(0%)	0(0%)	0(0%)	3(60%)	0(0%)	3(60%)	5(35.7%)	4(28.6%)	9(64.3%)	2(40%)	3(60%)	5(100%)	5(100%)	0(0%)	5(100%)
Markov model	4(13.3%)	1(3.3%)	5(16.7%)	1(100%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	2(14.3%)	1(7.1%)	3(21.4%)	1(20%)	0(0%)	1(20%)	0(0%)	0(0%)	0(0%)
Decision tree model	1(3.3%)	2(6.7%)	3(10%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	2(14.3%)	2(14.3%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)
Unspecified	3(10%)	1(3.3%)	4(13.3%)	0(0%)	0(0%)	0(0%)	2(40%)	0(0%)	2(40%)	1(7.1%)	1(7.1%)	2(14.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)

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TABLE 3 Details of cost indicators in guidance from 2016 to 2020.

Indicators *No.(%)*	Total condition from 2016 to 2020			2016			2017			2018			2019			2020		
	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total
Cost indicators																		
Commercial arrangement																		
Patient access schemes/PAS	19(63.3%)	2(6.7%)	21(70%)	1(100%)	0(0%)	1(100%)	4(80%)	0(0%)	4(80%)	7(50%)	2(6.7%)	9(30%)	2(40%)	0(0%)	2(40%)	5(100%)	0(0%)	5(100%)
Commercial access agreement/CAA	2(6.7%)	0(0%)	2(6.7%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	1(7.1%)	0(0%)	1(7.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Managed access arrangement /MAAs (Contains PAS, CAA)	0(0%)	7(23.3%)	7(23.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	4(28.6%)	4(28.6%)	0(0%)	3(60%)	3(60%)	0(0%)	0(0%)	0(0%)
ICER/QALY value																		
≤£20,000	1(3.3%)	1(3.3%)	2(6.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	1(7.1%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)
£20,000-£30,000	10(33.3%)	1(3.3%)	11(36.7%)	1(100%)	0(0%)	1(100%)	1(20%)	0(0%)	1(20%)	5(35.7%)	1(7.1%)	6(42.9%)	2(40%)	0(0%)	2(40%)	1(20%)	0(0%)	1(20%)
≥£30,000	10(33.3%)	6(20%)	16(53.3%)	0(0%)	0(0%)	0(0%)	4(80%)	0(0%)	4(80%)	3(21.4%)	3(21.4%)	6(42.9%)	0(0%)	3(60%)	3(60%)	3(60%)	0(0%)	3(60%)
Unspecified	0(0%)	1(3.3%)	1(3.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	1(7.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Discount rate																		
1.50%	2(6.7%)	1(3.3%)	3(10%)	1(100%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	1(7.1%)	1(7.1%)	2(14.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
3.50%	8(26.7)	4(13.3%)	12(40%)	0(0%)	0(0%)	0(0%)	3(60%)	0(0%)	3(60%)	1(7.1%)	1(7.1%)	2(14.3%)	1(20%)	3(60%)	4(80%)	3(60%)	0(0%)	3(60%)
Unpublished	11(36.7%)	4(13.3%)	15(50%)	0(0%)	0(0%)	0(0%)	2(40%)	0(0%)	2(40%)	6(35.7%)	4(28.6%)	10(71.4%)	1(20%)	0(0%)	1(20%)	2(40%)	0(0%)	2(40%)

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TABLE 4 Details of indicators of effectiveness in guidance from 2016 to 2020.

Indicators *No.(%)*	Total condition from 2016 to 2020			2016			2017			2018			2019			2020		
	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total
Indicators of effectiveness																		
Clinical outcome																		
Overall survival/OS	20(66.7%)	9(30%)	29(96.7%)	1(100%)	0(0%)	1(100%)	5(100%)	0(0%)	5(100%)	8(100%)	6(42.9%)	14(100%)	1(20%)	3(60%)	4(80%)	5(100%)	0(0%)	5(100%)
Progression-free survival/PFS	16(53.3%)	9(30%)	25(83.3%)	1(100%)	0(0%)	1(100%)	4(80%)	0(0%)	4(80%)	5(35.7%)	6(42.9%)	11(78.6%)	2(40%)	3(60%)	5(100%)	4(80%)	0(0%)	4(80%)
Objective response rate/ORR	2(6.7%)	1(3.3%)	3(10%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	0(0%)	1(7.1%)	1(7.1%)	1(20%)	0(0%)	1(20%)	0(0%)	0(0%)	0(0%)
Complete response/CR	7(23.3%)	2(6.7%)	9(30%)	0(0%)	0(0%)	0(0%)	2(40%)	0(0%)	2(40%)	1(7.1%)	2(14.3%)	3(21.4%)	1(20%)	0(0%)	1(20%)	3(60%)	0(0%)	3(60%)
Relapse-free survival/RFS	1(3.3%)	1(3.3%)	2(6.7%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	0(0%)	1(7.1%)	1(7.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Disease-free survival/DFS	3(10%)	0(0%)	3(10%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	3(21.4%)	0(0%)	3(21.4%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Event-free survival /EFS	5(16.7%)	1(3.3%)	6(20%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	3(21.4%)	1(7.1%)	4(28.6%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)
Overall remission rate/ORR	2(6.7%)	0(0%)	2(6.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	0(0%)	1(7.1%)	0(0%)	2(40%)	2(40%)	1(20%)	0(0%)	1(20%)
Minimal residual disease/MRD	1(3.3%)	1(3.3%)	2(6.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	1(7.1%)	1(20%)	1(20%)	2(40%)	0(0%)	0(0%)	0(0%)
Response rates/RR	5(16.7%)	3(10%)	8(26.7%)	1(100%)	0(0%)	1(100%)	2(40%)	0(0%)	2(40%)	2(14.3%)	2(14.3%)	4(28.6%)	0(0%)	1(20%)	1(20%)	0(0%)	0(0%)	0(0%)
Duration Of response/DoR	2(6.7%)	0(0%)	2(6.7%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)
Time to next treatment	1(3.3%)	2(6.7%)	3(10%)	1(100%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	2(14.3%)	2(14.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Time to response	1(3.3%)	0(0%)	1(3.3%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
End-of-life																		
Meet criterion, sufficient evidence	7(23.3%)	3(10%)	10(33.3%)	0(0%)	0(0%)	0(0%)	4(80%)	0(0%)	3(60%)	2(14.3%)	1(7.1%)	3(21.4%)	0(0%)	2(40%)	2(40%)	1(20%)	0(0%)	2(40%)
Meet criterion, insufficient evidence	6(20.0%)	0(0%)	6(20%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	3(21.4%)	0(0%)	3(21.4%)	0(0%)	0(0%)	0(0%)	2(40%)	0(0%)	1(20%)
Not meet criterion	7(23.3%)	5(16.7%)	12(40%)	1(100%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	3(21.4%)	4(28.6%)	7(50%)	2(40%)	1(20%)	3(60%)	1(20%)	0(0%)	1(20%)
Unspecified	1(3.3%)	1(3.3%)	2(6.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(7.1%)	1(7.1%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)

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TABLE 5 Details of indicators of effectiveness in guidance from 2016 to 2020.

Indicators	Total condition from 2016 to 2020			2016			2017			2018			2019			2020		
No.(%)																		
	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total	To NHS	To CDF	Total
Orter indicators																		
Disease type																		
Blood and bone marrow cancers	17(56.7%)	7(23.3%)	24(80%)	1(100%)	0(0%)	1(100%)	4(80%)	0(0%)	4(80%)	5(35.7%)	4(28.6%)	9(64.3%)	2(40%)	3(60%)	5(100%)	5(100%)	0(0%)	5(100%)
Liver cancers	1(3.3%)	0(0%)	1(3.3%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Head and neck cancers	0(0%)	1(3.3%)	1(3.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	1(7.1%%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Metastases	1(3.3%)	0(0%)	1(3.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	0(0%)	1(7.1%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Ovarian cancer	0(0%)	1(3.3%)	1(3.3%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(7.1%)	1(7.1%%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Thyroid cancer	2(6.7%)	0(0%)	2(6.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	2(6.7%)	0(0%)	2(6.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Drug delivery																		
Oral	8(26.7%)	2(6.7%)	10(33.3%)	1(100%)	0(0%)	1(100%)	3(60%)	0(0%)	3(60%)	3(21.4%)	2(14.3%)	5(35.7%)	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)	1(20%)
Infusion	13(43.3%)	7(23.3%)	20(66.7%)	0(0%)	0(0%)	0(0%)	2(40%)	0(0%)	2(40%)	5(35.7%)	4(28.6%)	9(64.3%)	2(40%)	3(60%)	5(100%)	4(80%)	0(0%)	4(80%)
Drug combination																		
Yes	8(26.7%)	2(6.7%)	10(33.3%)	1(100%)	0(0%)	1(100%)	1(20%)	0(0%)	1(20%)	1(7.1%)	2(14.3%)	3(21.4%)	1(20%)	0(0%)	1(20%)	4(80%)	0(0%)	4(80%)
No	13(43.3%)	7(23.3%)	20(66.7%)	0(0%)	0(0%)	0(0%)	4(80%)	0(0%)	4(80%)	7(50%)	4(28.6%)	11(78.6%)	1(20%)	3(60%)	4(80%)	1(20%)	0(0%)	1(20%)

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drugs. A total of 10 orphan oncology drugs met NICE's criteria for being considered a life-extending treatment and had sufficient evidence, 12 orphan oncology drugs did not meet NICE's criteria, and 6 orphan oncology drugs were considered a life-extending treatment but had uncertain cost-effectiveness estimates. 2 orphan oncology drugs had unspecified end-of-life guidance (Table 4).

Other indicators

Disease type and indication

It is shown that 80% of indications of disease were blood and bone marrow cancers, including multiple myeloma, large cell lymphoma, Philadelphia chromosome-negative acute lymphoblastic leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), CD30-positive Hodgkin lymphoma, follicular lymphoma, large B-cell lymphoma, and chronic lymphocytic leukemia (CLL), followed by thyroid cancer (6.7%), which included medullary thyroid cancer. liver cancers, metastases, head and neck cancers, and ovarian cancer were the target for 3.3% of treatment each (Table 5).

Of all the 30 drugs, 4 (13.3%) were used for treating diseases at least 2 previous treatments, 8 (26.7%) were used for relapsed or refractory disease, 9 (30%) were used for treating acute disease, and 4 (13.3%) were used for treating untreated disease. Most drugs were used for adults, except Kymriah (Tisagenlecleucel), which was used to treat relapsed or refractory B-cell acute lymphoblastic leukemia in people aged up to 25 years.

Drug delivery

Of all of the recommended drugs, 33.3% were taken orally and the rest (66.7%) were administered by intravenous infusion. And the difference between drug delivery and recommendation found has no significance ($p = 0.675$) (Table 5).

Drug combination

Drug combinations were recommended for 33.3% of orphan drugs. Daratumumab, which is used for CD30-positive cutaneous T-cell lymphoma, was recommended as a treatment option after the failure of at least one systemic therapy in adults when combined with bortezomib and dexamethasone. Carfilzomib, used for treating multiple myeloma in adults, was only recommended following the failure of at least one systemic therapy when combined with either lenalidomide and dexamethasone or dexamethasone alone. Polatuzumab vedotin was indicated for treating relapsed or refractory diffuse large B-cell lymphoma when combined with rituximab and bendamustine. There were no significant differences between drug combination and recommendation ($p = 0.675$) (Table 5).

Discussion

Drugs recommended to CDF may obtain more availability and accessibility

Orphan oncology drugs can be recommended to the NHS or CDF. The guidance of the drugs that were recommended to the NHS will be reviewed after 2 or 3 years. Drugs were usually recommended for use as an option for the Cancer Drugs Fund because of uncertain cost-effectiveness estimates, immature survival data, an uncertain impact of the treatment on patient life expectancy, and in incomplete compliance with end-of-life standards. Drugs recommended to the CDF would not impede patient use while more evidence is collected for a final NICE review and a final recommendation regarding NHS use. To some degree, orphan oncology drugs recommended to CDF may obtain more availability and accessibility, a study showed that there is greater availability and accessibility of orphan medicines in England where most of the 68 OMPs were reimbursed because they were included in the NHS England specialized commissioning list [32] or the Cancer Drugs Fund [13], compared with Scotland and Wales (20). This kind of dynamic management mechanism is important to learn.

Partitioned survival model was increasingly used to appraise orphan oncology drugs

The most useful economic model for orphan oncology drugs in all the guidance was the partitioned survival model, and there was an increasing trend from 2016 to 2020 (Figure 2), which is in line with the work by Williams et al. (21) and others (22, 23). Partition survival models are often used in the economic evaluation of drugs in oncology mostly depending on the fact that it does not have to calculate the metastatic probability of the disease, and also do not require a large number of model assumptions, closer to the actual observed data; The survival curve can be directly applied to obtain the proportion of patients with different health statuses (22), and the complex risk function can be directly reconstructed by extrapolation (23).

Patient access schemes (PAS) and CAAs were broadly used to control the price, and MAAs were used to provide a vital alternative route for patients to access these treatments

Every orphan oncology drug has at least one commercial arrangement. Drugs recommended to the NHS usually have

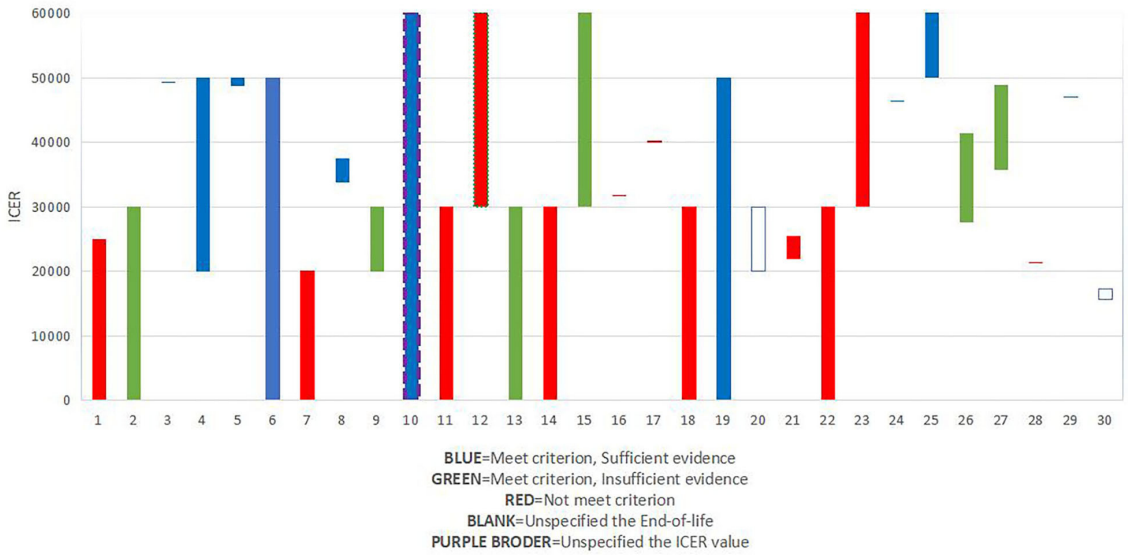

FIGURE 3
Relationship between end of life and ICER of orphan oncology drugs.

PAS, which entails a simple discount. However, it is a pity that we cannot ascertain the amount that was discounted due to commercial confidentiality.

Managed access arrangements (MAAs) are an agreement between NHS England and a company. Some drugs cannot be recommended due to uncertainty about their value for money, MAAs were used by the time to collect more evidence to address the uncertainties. Usually, without managed access, NICE might not be able to recommend patients have access to these promising new drugs at that time. Managed access provides a vital alternative route for patients to access these treatments. In our study, MAAs were all used for drugs recommended to the CDF, which include a Data Collection Agreement (DCA), and Commercial Access Agreement (CAA), with a simple discount PAS. However, CAAs were also unpublished because of commercial confidentiality. Drugs were funded through the CDF for a limited period of time (up to 2 years), during which MAAs will be maintained in accordance with (1) the results that need to be collected to address uncertainty in key clinical areas, and (2) the cost of the drug regulatory access agreement. The drug will then undergo rapid reconsideration to decide if it is recommended for use in the NHS (24).

In conclusion, PAS are pricing agreements proposed by pharmaceutical companies to enable patients to access high-value drugs. MAAs are data collection protocols added to CAAs (25). In 2016 the NHS introduced CAAs and MAAs, both of which are simpler compared to the complex PAS process (26).

Some alternative indicators were used as clinical trial evidence

Except for overall survival/OS and progression-free survival/PFS, some other indicators such as progression-free survival/PFS, objective response rate/ORR, complete response/CR, relapse-free survival/RFS, disease-free survival/DFS, event-free survival /EFS, overall remission rate/ORR, minimal residual disease/MRD, response rates/RR, duration of response/DoR, time to next treatment, time to response were also used to evaluate the clinical outcome of drugs. Even though overall survival remains/OS (27) and progression-free survival/PFS (28) are the gold standard and commonly used outcomes for drugs, it has been proved that many oncology drugs do not provide benefits of PFS and OS (29). Therefore, along with the requirements for drug accelerated and medical reimbursement, more and more alternative indicators were used to evaluate the clinical outcomes, which were also applied to the complexity and specificity of orphan diseases.

Potential association among recommendation, ICER/QALY value, and end of life

National Institute for Health and Care Excellence (NICE) typically defines a price of £20,000 to £30,000 per unit of QALY as cost-effective (30–32). In our study, the percentage of

ICER/QALY values above £30,000 (53.3%) was higher than the percentage of ICER/QALY values below £30,000 except for drugs appraised in 2018. This suggests that the threshold ICER/QALY values are increasing to some degree.

The guide to the methods of technology appraisal had been published in 2013, and the purpose of the guide is to ensure that all interests should be considered when evaluating a treatment designed to prolong life. The guidance details that a "life-extending treatment at the end of life" treatment should satisfy two criteria (i) the treatment is indicated for patients with a short life expectancy, normally < 24 months, and (ii) there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. Besides, they should satisfy the two criteria and the evidence should be sufficient, and the assumptions used in the reference case economic modeling should be plausible, objective, and robust (33), if it has been considered as a drug that is a life-extending treatment, it would be given greater weight to QALYs achieved in the later stages of terminal diseases.

Besides, we explored the association between recommendation, ICER/QALY value, and end-of-life (Figure 3). Results showed that of all the 10 drugs that met the criterion of end of life and had sufficient evidence, 2 drugs were given a threshold of more than £50,000, and 8 drugs were given a threshold between £30,000 to £50,000, which might prove the importance of "end-of-life."

Drug delivery and other potential health-related benefits would be a new concern

Of all the 10 oral medications, 8 drugs (80%) were recommended to the NHS. This rate of recommendation was higher than that of drugs that needed to be administered *via* intravenous infusion. NICE takes into account not only the economics and effectiveness of the medication, but also the characteristics of the drug itself such as its delivery to patients, and it proved that some hidden factors had been given increasing attention, which would give more convenience for patients and their family, reduce non-medical costs and enhance the quality of life.

Conclusion

The selection and appraisal process of NICE for orphan oncology drugs is important and also provides a good reference for other decision-makers. Attribute to the high treatment cost, small population, insufficient evidence of orphan oncology drugs, in order to solve the problem of a small number of subjects for validated trials and the uncertainty of clinical outcomes related to drug treatment, alternative indicators, special treatment of incomplete data, and appropriate economic models and HTA methods were used to estimate cost-effectiveness. Clinical evidence and cost-effectiveness are the basis of NICE's appraisal of orphan oncology drugs, but they also take into account factors such as the potential health-related benefits, its life-extending effects, and the impact of the medication on patient quality of life. Within the limits of affordable national medical insurance, how to improve the availability and accessibility of orphan oncology drugs became a global problem instead of a matter for any individual country, researchers should do their best to maximize the usage of orphan oncology drugs within limited resources.

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

DS, LZ, and ZN were responsible for data collection and analysis. ZW, YY, LJ, and YN were responsible for data collection. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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Cost analysis of implementing a vial-sharing strategy for chemotherapy drugs using intelligent dispensing robots in a tertiary Chinese hospital in Sichuan

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Introduction: Chemotherapy drug wasting is a huge problem in oncology that not only results in excessive expenses on chemotherapy drugs but also increases the cost of disposing of chemotherapy waste and the risk of occupational exposure in the environment. The main objective of this study was to evaluate the potential for hospitals in China to employ a real-time vial-sharing strategy that can save drug costs.

Method: This study was conducted retrospectively at Pharmacy Intravenous Admixture Services (PIVAS), People's Hospital of Sichuan Province, China, from September to November 2021. Data on prescription drugs wasted were collected from the Hospital Information System (HIS). To assess the real-time vial-sharing strategy, we estimated drug wastage and drug waste costs using intelligent robots that dispense multiple prescriptions simultaneously.

Results: 24 of the 46 wasted drugs were cost-saved. The vial-sharing strategy saved 186,067 mg of drugs, or ~59.08% of the total amount wasted, resulting in savings of 150,073.53 China Yuan (CNY), or 47.51% of the cost of the total waste.

Conclusion: Our investigation established that employing a real-time vial-sharing strategy using an intelligent robot to dispense multiple prescriptions simultaneously is cost-effective. Additionally, this approach presented no safety issue concerns, such as the introduction of impurities to sterile compounding *via* repeated interspersing or the incorrect registration of information during drug storage, often encountered with traditional vial-sharing strategies.

KEYWORDS

chemotherapy drug, amount of waste, cost savings, vial-sharing, intelligent dispensing robots

Introduction

According to a recent statistical finding, the number of new tumor cases worldwide reached 19.3 million in 2020 (1). Cancer is among the leading causes of human death. Globally, the cost of cancer treatment is usually very high because treatment is long-term and drugs are very expensive, and providing affordable health care becomes a huge challenge. Increasing health care costs are putting a huge strain on patients and the health insurance system. The drastic increase in the use of chemotherapy drugs has led to an upsurge in the amounts of intravenous chemotherapy drugs left in vials after use due to individualized dosing, resulting in significant drug waste. From an economic point of view, the value of drugs discarded as waste is high, and disposing of the waste is equally expensive. Therefore, reducing drug waste in this part of oncology is essential for resource and cost savings.

Several studies have assessed the amount and cost of wasted chemotherapy drugs around the world (2–6). Investigations revealed that patients incurred vast drug waste-related economic consequences because they paid for both the dosages used and discarded. Ibrahim suggested that dose rounding of chemotherapy drugs could result in theoretical cost savings of about 10%, with potential annual cost savings of $192,800 (7). Vandyke et al. (8) made cost savings of nearly $200,000 in 1 year through automated dose rounding administered by pharmacists. Heinhuis et al.'s (9) implementation of fixed-dosing led to a significant reduction in the number of vials used for almost all monoclonal antibodies. Measures such as dose-banding and fixed-dosing also increased the possibility of recycling unused drugs during their expiration date. In the US study (10), Bendamustine and Bortezomib, were used as examples to assess the impact of different packaging methods on single-dose vials, and the results showed that drug waste can be significantly reduced by optimizing vials. Unfortunately, implementing this method is beyond the control of medical institutions because designing vial specifications mainly depends on pharmaceutical enterprises. Jiang et al. (11) obtained a 394,536 CAD (21.1%) reduction in total drug costs over 3 years by scheduling as many patients to receive carbazole on 1 weekday as possible for combination chemotherapy. To accommodate vial sharing, some studies have also used Closed System Drug Transfer Devices (CSTD) to extend the shelf life of drugs after opening. Edwards et al. (12) saved over $96,000 over 7 weeks using CSTD, with an estimated $700,000 saved per year. Juhász et al. (13) achieved cost savings of up to 18.6% using CSTD for expensive intravenous biologics.

Based on literature studies, few investigations on the real-time vial-sharing strategy have been conducted outside of China. Few inquiries on chemotherapy drug waste and vial sharing are currently available in China. Vial-sharing in previous studies usually meant preparing each prescription drug individually and retaining the remainder of the current vial for reuse when preparing the same drug for the next prescription (12–18). There is a need to evaluate the sterile state and stability data of the product and a need to amplify efforts to preserve residual drugs, which is obviously very complex and easy to make mistakes. However, the process of preparation in our current research is based on the need to use the same drug for different prescriptions, with the intelligent dispensing robot employed to prepare all prescription doses of the same drug at once.

The objectives of this study are:

1. To determine the extent of chemotherapy drug wastage and its cost in a tertiary general hospital in China.
2. To determine the amount and cost of drug wastage that can be saved by implementing a real-time vial-sharing strategy using intelligent robots that dispense multiple prescriptions simultaneously.

Methods

Data sources

This study was conducted retrospectively at Pharmacy Intravenous Admixture Services (PIVAS) of the People's Hospital of Sichuan Province, China. Sichuan Provincial People's Hospital has the largest and most standardized, as well as technologically most advanced and mature, intravenous drug intelligent dispensing center in China, which is directly managed by the Department of Pharmacy and is fully computerized. Introducing intelligent dispensing robots can effectively reduce the exposure of chemotherapy drugs to medical staff (19). The WEINAS intelligent dispensing robots are used to prepare hazardous injectable drugs, such as antineoplastic drugs, automatically. Their operating system enables the dispensation of multiple prescriptions for the same drug simultaneously. First, multiple two-dimensional prescription information codes for the same drug and scanned, and then the drugs are placed into the compounding area at the same time according to the instructions. If any drugs remain in the vial after the dispensation of the previous prescription, they will be used immediately when distributing the next prescription, resulting in real-time sharing. The entire preparation process is continuously verified and recorded for traceability.

More than 90% of chemotherapy drug preparations in the hospital can be done directly by three intelligent robotic systems in a fully enclosed purified space. Drugs that can be shared in vials can all be set up in advance on the robot system following to the specifications of drugs and their characteristics, without the need to specify their dosage and specifications. For each new drug introduced, a robot engineer can perform experimental debugging and then enter the corresponding instructions for the robot to perform the sharing operation. As a precondition for drug sharing, the drug must be capable of being dispensed

individually using a robot. Firstly, administration by a robot does not affect the physicochemical properties of the drug, drugs that foam after shaking are not suitable. Also, drugs do not reduce the efficiency of a robot's dispensing, but drugs that must still be left to stand for a period after adding solvents to them are not appropriate. The removed drugs are shown in Table 1. Excluding these special cases, any drugs that can be dispensed using the intelligent dispensing robot can be shared.

Design of the study

This study aimed to determine the potential cost savings of implementing real-time vial-sharing in Chinese hospitals using intelligent dispensing robots at PIVAS. To realize this goal, the investigation utilized the simultaneous preparation of multiple prescriptions feature of the hospital's intelligent dispensing robots to carry out the experimental design. The intelligent dispensing robot uses a real-time vial-sharing strategy that works by placing several prescriptions for the same drug on the operating table at the same time and then using a specially designed syringe with needles on both ends, one of which is inserted into the vial and the other into the infusion bag. Upon entering a command to share a prescription, the needle in the vial is not withdrawn, but the needle in the infusion bag is withdrawn and inserted into another infusion bag, and then the remaining drug in the vial is withdrawn into the infusion bag, thus completing the process of vial-sharing. This whole process of vial-sharing can be set up in the robot system without fear of drug instability associated with the process after opening or increased risk of the rubber falling off caused by extracting the vial of liquid several times. On the contrary, as we uncovered in this paper, the procedure instead reduces the time cost.

The time interval used for real-time sharing preparation was set based on the time between one start-up and the shutdown of the intelligent dispensing robots. The working hours of the robots are the same as the staff working hours every day: the robots work during two periods, from 8:00 a.m. to 12:00 a.m. and from 2:00 to 5:00 p.m. By calculating the amount and cost of wasted chemotherapy drugs, we evaluated the possibility of achieving cost savings in a Chinese hospital PIVAS using a real-time vial-sharing strategy in which intelligent robots dispensed multiple prescriptions simultaneously.

Date collection and calculation

Using HIS, we retrospectively observed all drug prescriptions that potentially generated waste at PIVAS from September-November 2021. The information collected included the name of the prescribed drug, the actual dose of the drug, drug specifications, number of vials used, and unit price per vial of the drug. The amount of waste and the cost of the wasted drug were calculated based on the difference between patient usage and vial specifications. The determination of drug costs was predicated on the unit price of the drug per milligram. The amount of drug waste, the cost of drug waste, and the number of drug prescriptions that generated waste were also analyzed and compared. Finally, assuming that vial-sharing was implemented in the manner described in Table 2, the total number of vials used for each drug each time was utilized to estimate the number and cost of vials that could be saved for each drug. The savings diagram is shown in Figure 1.

Statistical analysis

Microsoft Office Professional Plus Excel 2019 was used to compile and analyze the data in this study. The amount of waste, drug waste costs, and cost saved of drugs are collated and summed. As continuous variables, they are reported as outcomes in this study. A drug waste cost is the unit price per milligram of a drug multiplied by the amount of the drug wasted. This paper contains a small sample of quantitative information for a paired design. We conducted a hypothetical test on drug waste costs, and the difference does not conform to the normal distribution by the normality test. So, using the paired t-test is not appropriate. The Wilcoxon signed-rank test should be employed instead. A p-value < 0.05 indicated statistical significance. The percentages of the amount of waste, waste costs, number of waste-generating drug prescriptions, and cost saved for each drug are displayed on the fan charts.

Results

Amount of waste

During the 3-month study period, a total of 3,509 cases of waste-generating prescriptions were collected: these included 46 different drugs that were wasted, with an average number of prescriptions per month being 1,170. Table 3 summarizes the number of prescriptions, vial specifications, the unit price per vial, amount wasted, and drug waste cost for the 46 drugs. The traditional single-dose preparation produced a total drug waste of up to 314,898.625 mg. The percentage of the amount of waste per drug is shown in Figure 2: the top five were cytarabine (42.58%), fluorouracil (7.21%), ifosfamide of 100 mg (7.18%), cyclophosphamide (6.22%), and gemcitabine of the 1000 mg from manufacturer 1 (6.10%).

Drug waste costs

The drug waste costs for the traditional single-dose preparations and the vial-sharing preparations were 315,884

TABLE 1 Drugs not considered for vial sharing by intelligent dispensing robots.

Removed drug	Manufacturer	Specification (mg)	Drug characteristic	Reason
Paclitaxel for injection (Albumin Bound)	Jiangsu hengrui medicine	100	Foaming	It foams and needs to be left to stand for a while after the addition of the corresponding solvent.
Camrelizumab for injection	Jiangsu hengrui medicine	200	Foaming	It foams
Kangai injection	Changbaishan pharmaceutical	10	None	Because the vial specification is too small, it would require a significant amount of vials per prescription and would result in inefficient dispensing by the robot.
Azacitidine for injection	Sichuan huyu pharmaceutical	100	Instability	Ready-to-use
Mesna injection	Jiangsu hengrui medicine	400	None	Administration by intravenous bolus (Not including intravenous infusion)

TABLE 2 Example of total *Oxaliplatin waste costs for traditional single-dose preparation and vial-sharing preparation options.

Preparation method	Date	Patient	Amount used (mg)	Number of vials used	Amount wasted (mg)	#Drug wasted cost (CNY)
Traditional single-dose preparations	9/1 am	Patient 1	180	2	20	¥76.27
		Patient 2	120	2	80	¥305.07
		Patient 3	150	2	50	¥190.67
	9/1 pm	Patient 4	180	2	20	¥76.27
		Patient 5	140	2	60	¥228.80
		Patient 6	150	2	50	¥190.67
	Total		920	12	280	¥1,067.75
Vial-sharing preparations	9/1 am	Total at am	450	5	50	¥190.67
	9/1 pm	Total at pm	470	5	30	¥114.40
	Total		920	10	80	¥305.07

*Oxaliplatin: the specification is 100 mg, and the unit price of the drug is ¥381.34 per vial. #Drug wasted cost (CNY) = [Unit price (CNY/vial)/Specifications (mg)] * Amount wasted (mg).

CNY and 165,810 CNY ($p = 0.0000194 < 0.05$), respectively. The percentage of wasted expenses per drug class ranged from 0.01 to 15.16%, as shown in Figure 3. The top 5 drugs accounting for more than 56% of the total drug waste costs were oxaliplatin (100 mg, 15.16%), paclitaxel (100 mg, 14.48%), cytarabine (11.21%), etoposide (40 mg, 8.91%), and calcium folinate (7.05%).

Number of drug prescriptions

The percentage of waste-generating drug prescriptions is shown in Figure 4. The top five drugs were cisplatin (21.12%), cytarabine (10.72%), oxaliplatin (100 mg, 7.21%), calcium Folinate (6.84%), and etoposide (40 mg, 6.73%).

Cost saved

The cost savings results are shown in Table 4. Vial-sharing achieved cost savings for 24 drugs. Using the estimates from the outcome of those 24 medications, the vial-sharing strategy saved 186,067 mg of drugs, or ∼59.08% of the total amount wasted, resulting in savings of 150,073.53 CNY, or 47.51% of the cost of the total waste. The percentage of drug cost savings is shown in Figure 5: oxaliplatin (100 mg, 21.09%), cytarabine (18.21%), etoposide (40 mg, 13.09%), calcium folinate (12.17%), and paclitaxel (100 mg, 10.39%).

Discussion

In this study, chemotherapy drug wastage was substantial and caused a considerable economic burden. During the

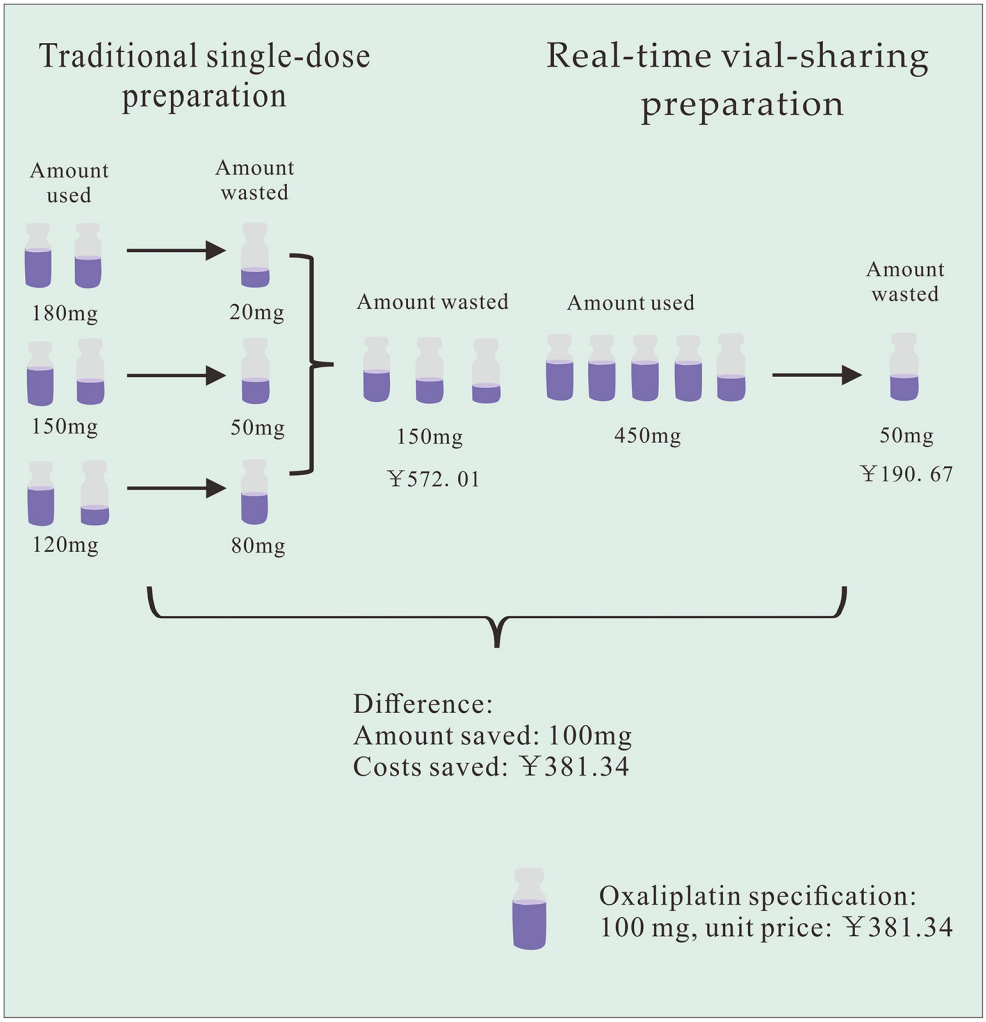

FIGURE 1
Example of cost-saving diagrams with Oxaliplatin at one time interval.

3-month inquiry, a total of 314,898.625 mg of the drugs ended up as waste, with a cost analysis of 315,884 CNY. We found the real-time vial-sharing method to have significant cost advantages over the traditional single-dose preparation. Via-sharing reduced drug waste by more than half and saved 159,807.68 CNY or 50.5% of the total drug waste costs.

Only 24 of the 46 wasted drugs were cost-saved through real-time vial-sharing. The discrepancies were mainly due to the low frequency of drug use, which resulted in no prescriptions of the same drugs being generated at the same interval, or the prescribed dose was so large that the remaining drugs could not be saved even after they were shared (e.g., if two patients need 80 mg of oxaliplatin with a specification of 100 mg, the extra servings can only produce waste and would not be shared at that interval). The possibility of saving medications through real-time vial-sharing is closely associated with the frequency of administration and the differences between common doses and vial specifications in the population. For drugs with a large amount of waste that cannot adopt the vial-sharing strategy, medical institutions can optimize drug specifications to select chemotherapy drugs with smaller sizes as much as possible during drug selection. In this study, oxaliplatin, etoposide of 40 mg, calcium folinate, and paclitaxel of 100 mg were highly cost-effective when administered using the real-time vial-sharing strategy. It is recommended that hospitals carry out the vial-sharing strategy for frequently used chemotherapy drugs, expensive drugs, and drugs that generate a huge amount of waste.

Appropriate specifications of the drug are important to reduce drug waste. It is recommended that medical institutions adjust the specifications of hospital drugs, which can also effectively reduce drug waste. Taking cisplatin as an example, we compared the information collected on drug prescriptions. We found that the specification of the drug vial was 30 mg, while the

TABLE 3 Summary of information on waste-generating prescribed chemotherapy drugs at PIVAS.

No.	Drug	Specifications (mg)	Unit price (CNY/vial)	Number of prescriptions	Number of vials used		Amount wasted (mg)		Drug wasted cost (CNY)	
					Traditional single-dose preparations	Vial-sharing preparations	Traditional single-dose preparations	Vial-sharing preparations	Traditional single-dose preparations	Vial-sharing preparations
1	Oxaliplatin	100	¥381.34	253	527	444	12,558.86	4,258.86	¥47,891.96	¥16,240.74
2	Paclitaxel	100	¥780.00	174	708	688	5,869.5	3,869.5	¥45,782.10	¥30,182.10
3	Cytarabine	500	¥132.00	376	418	211	134,075	30,575	¥35,395.80	¥8,071.80
4	Etoposide	40	¥251.95	234	509	431	4,469	1,349	¥28,149.11	¥8,497.01
5	Calcium folinate	100	¥124.20	240	316	169	17,939.3	3,239.3	¥22,280.61	¥4,023.21
6	Pemetrexed disodium	100	¥789.00	58	400	395	2,315	1,815	¥18,265.35	¥14,320.35
7	Gemcitabine/manufacture 1	1000	¥710.00	45	83	82	19,220	18,220	¥13,646.20	¥12,936.20
8	Methotrexate	10	¥174.89	89	172	133	647.125	257.125	¥11,317.57	¥4,496.86
9	Loplatin	50	¥1,766.70	33	35	34	315	265	¥11,130.21	¥9,363.51
10	Irinotecan	40	¥489.34	45	298	295	754	634	¥9,224.06	¥7,756.04
11	Cisplatin	30	¥19.12	741	1,556	1,174	12,929.4	1,469.4	¥8,240.34	¥936.50
12	Vincristine	1	¥195.00	86	147	130	42.04	25.04	¥8,197.80	¥4,882.80
13	Bevacizumab	100	¥1,500.00	8	38	38	420	420	¥6,300.00	¥6,300.00
14	Calcium levofolinate	50	¥124.20	70	112	78	2,401.8	701.8	¥5,966.07	¥1,743.27
15	Ifosfamide	1000	¥204.80	50	127	121	22,600	16,600	¥4,628.48	¥3,399.68
16	Oxaliplatin	50	¥2,100.00	6	24	24	106	106	¥4,452.00	¥4,452.00
17	Fluorouracil	250	¥49.00	189	1,199	1,150	22,697	10,447	¥4,448.61	¥2,047.61
18	Docetaxel/manufacturer 1	20	¥297.16	22	130	128	216	176	¥3,209.33	¥2,615.01
19	Oxaliplatin	50	¥236.80	29	101	95	595	295	¥2,817.92	¥1,397.12
20	Cyclophosphamide	200	¥24.15	194	734	688	19,590	10,390	¥2,365.49	¥1,254.59
21	Epirubicin/manufacturer 1	10	¥86.25	51	306	305	255	245	¥2,199.38	¥2,113.13
22	Trastuzumab	440	¥5,500.00	2	2	2	160	160	¥2,000.00	¥2,000.00
23	Pemetrexed disodium	500	¥2,735.83	2	4	4	350	350	¥1,915.08	¥1,915.08
24	Paclitaxel/manufacturer 1	30	¥228.00	20	137	137	250	250	¥1,900.00	¥1,900.00
25	Loplatin	10	¥438.04	9	39	39	42	42	¥1,839.77	¥1,839.77
26	Gemcitabine/manufacturer 1	200	¥122.61	24	92	92	2,570	2,570	¥1,575.54	¥1,575.54
27	Ifosfamide	500	¥39.10	67	312	306	16,050	13,050	¥1,255.11	¥1,020.51
28	Paclitaxel/manufacturer 2	30	¥137.65	23	164	162	352	292	¥1,615.09	¥1,339.79

(Continued)

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TABLE 3 (Continued)

No.	Drug	Specifications (mg)	Unit price (CNY/vial)	Number of prescriptions	Number of vials used		Amount wasted (mg)		Drug wasted cost (CNY)	
					Traditional single-dose preparations	Vial-sharing preparations	Traditional single-dose preparations	Vial-sharing preparations	Traditional single-dose preparations	Vial-sharing preparations
29	Docetaxel/manufacturer 2	20	¥1,300.00	2	12	12	20	20	¥1,300.00	¥1,300.00
30	Ratitrexed	2	¥669.00	4	10	10	3.2	3.2	¥1,070.40	¥1,070.40
31	Homotrimoxaline	1	¥96.00	17	39	39	8.5	8.5	¥816.00	¥816.00
33	Etoposide	100	¥7.79	223	239	165	9,976.6	2,576.6	¥777.18	¥200.72
34	Bortezomib	1	¥298.95	7	16	16	2.3	2.3	¥687.59	¥687.59
34	Bleomycin	15	¥119.00	7	14	14	70	70	¥555.33	¥555.33
35	Rubidomycin	20	¥26.88	34	64	64	402.8	402.8	¥541.36	¥541.36
36	Gemcitabine/manufacturer 2	1000	¥205.63	5	10	10	2,250	2,250	¥462.67	¥462.67
37	Actinomycin D	0.2	¥119.00	6	18	18	0.7	0.7	¥416.50	¥416.50
38	Carboplatin	50	¥30.35	28	191	188	619.5	469.5	¥376.04	¥284.99
39	Dextrazoxane	250	¥336.01	5	7	7	230	230	¥309.13	¥309.13
40	Docetaxel/manufacturer 3	20	¥54.12	8	45	45	70	70	¥189.42	¥189.42
41	Nedaplatin	50	¥326.70	2	6	6	20	20	¥130.68	¥130.68
42	Nedaplatin	10	¥55.00	4	55	55	17	17	¥93.50	¥93.50
43	Gemcitabine/manufacturer 2	200	¥59.98	2	7	7	200	200	¥59.98	¥59.98
44	Doxorubicin	10	¥22.92	6	15	15	17	17	¥38.96	¥38.96
45	Mesna	400	¥8.63	6	12	10	1,200	400	¥25.89	¥8.63
46	Epirubicin/manufacturer 2	10	¥122.00	1	14	14	2	2	¥24.40	¥24.40
			Total	3,509	9,464	8,250	314,898.625	128,831.625	¥315,884.00	¥165,810.47

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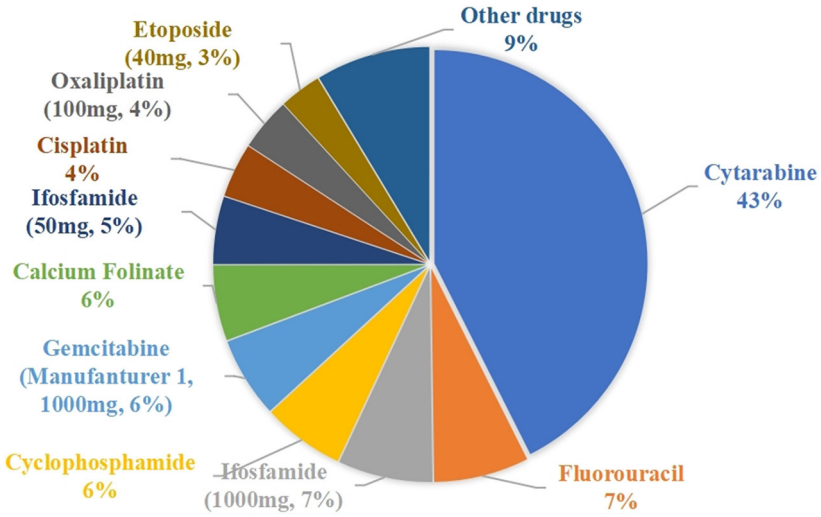

FIGURE 2
Percentage of drug wastage.

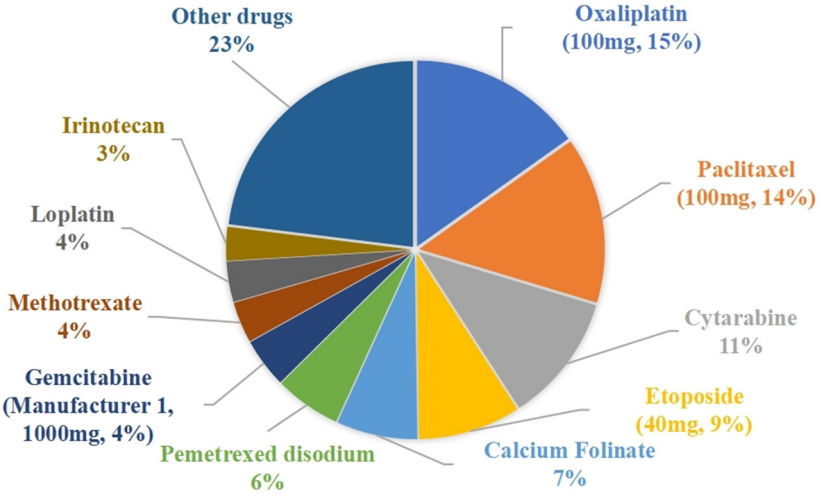

FIGURE 3
Percentage of drug waste costs.

common doses for the population were mostly 40 mg or 50 mg, which is why the number of drug prescriptions that generated waste was so high (741, 21.12%). This is a very clear indication that pharmaceutical companies must redesign or increase the specifications for this drug and that medical institutions should base their drug purchases on doses commonly used in the population. Redesigning the vial specification will make it easier to match the doses commonly used by the population and inevitably reduce the amount of drug waste currently in play.

The biggest percentage of wasted costs was oxaliplatin at 100 mg in the pre-study period, as it was only available in a single larger specification. In the course of the study, the country conducted a new round of centralized purchasing of 50 mg of oxaliplatin. Therefore, during the latter part of the trial data collection (from November 15), the hospital started supplying 50 mg of oxaliplatin. In our comparison of the number of prescriptions and drug waste, we found that a total of 253 prescriptions of 100 mg of oxaliplatin produced wastes of up to 12,553.86 mg, an average waste

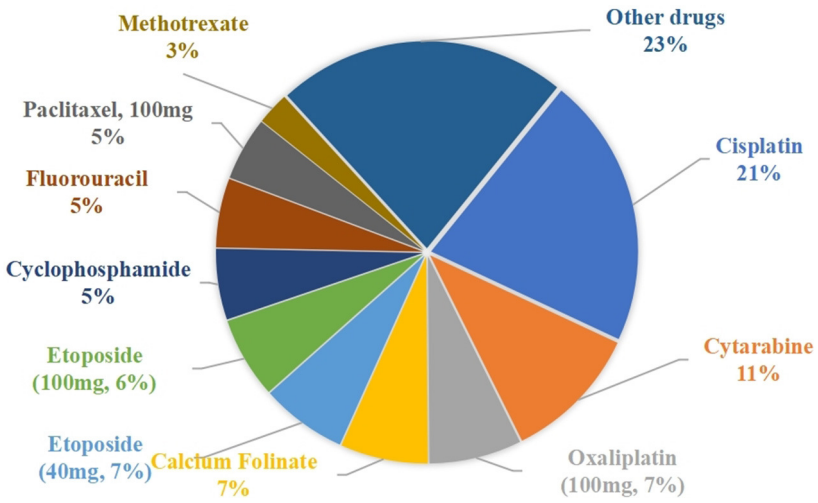

FIGURE 4
Percentage of waste-generating drug prescriptions.

TABLE 4 Wasted drugs and costs saved through vial-sharing preparations.

No.	Drug	Specifications (mg)	Unit price (CNY/vial)	Number of vials saved	Amount saved (mg)	Cost saved (CNY)
1	Oxaliplatin	100	¥381.34	83	8,300	¥31,651.22
2	Cytarabine	500	¥132.00	207	103,500	¥27,324.00
3	Etoposide	40	¥251.95	78	3,120	¥19,652.10
4	Calcium folinate	100	¥124.20	147	14,700	¥18,257.40
5	Paclitaxel	100	¥780.00	20	2,000	¥15,600.00
6	Cisplatin	30	¥19.12	382	11,460	¥7,303.84
7	Methotrexate	10	¥174.89	39	390	¥6,820.71
8	Calcium levofolinate	50	¥124.20	34	1,700	¥4,222.80
9	Pemetrexed disodium	100	¥2,735.83	5	2,500	¥3,945.00
10	Vincristine	1	¥195.00	17	17	¥3,315.00
11	Fluorouracil	250	¥49.00	49	12,250	¥2,401.00
12	Loplatin	50	¥1,766.70	1	50	¥1,766.70
13	Irinotecan	40	¥489.34	3	120	¥1,468.02
14	Oxaliplatin	50	¥236.80	6	300	¥1,420.80
15	Ifosfamide	1000	¥204.80	6	6,000	¥1,228.80
16	Cyclophosphamide	200	¥24.15	46	9,200	¥1,110.90
17	Gemcitabine/manufacturer 1	1000	¥710.00	1	1,000	¥710.00
18	Docetaxel/manufacturer 1	20	¥297.16	2	40	¥594.32
19	Etoposide	100	¥7.79	74	7,400	¥576.46
20	Paclitaxel/manufacturer 2	30	¥137.65	2	60	¥275.30
21	Ifosfamide	500	¥39.10	6	3,000	¥234.60
22	Carboplatin	50	¥30.35	3	150	¥91.05
23	Epirubicin/manufacturer 1	10	¥86.25	1	10	¥86.25
24	Mesna	400	¥8.63	2	800	¥17.26
			Total	1214	186,067	¥150,073.53

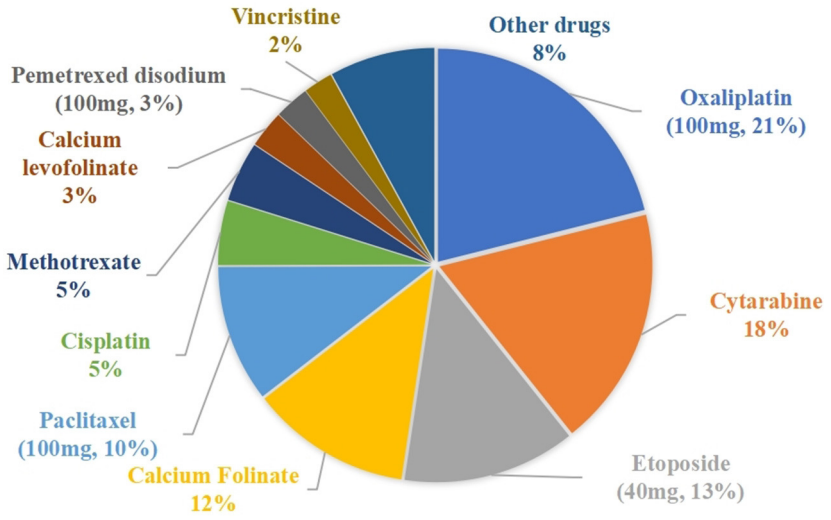

FIGURE 5
Percentage of drug costs saved.

of 49.62 mg per prescription. While 29 prescriptions of 50 mg of oxaliplatin only generated 595 mg of waste, an average waste of 20.5 mg per prescription, indicating that the proportion of wasted oxaliplatin is significantly lower for smaller specifications than for larger ones. This finding also suggests that drug procurement by medical institutions based on population dose requirements can be effective in limiting drug waste and that the amount of drug wastage is much lower with the provision of smaller specifications than with larger ones.

Due to differences in the health insurance system, few studies on the economics of vial-sharing have been conducted in China. Regrettably, medical institutions do not pay attention to the chemotherapy drugs left in vials, and patients are charged for the total amount of drug per vial rather than the actual dose received. However, investigations in the UK (20) and Japan (21) have shown that using leftover vials results in significant cost-saving, especially for molecularly targeted drugs. In the UK and Japanese inquiries, vials were reused for 7 and 1 day, respectively. However, our estimates were based on the number of vials needed to achieve half-day sharing. Therefore, the proportion of potential economic savings in China may exceed the results we have obtained in this study. Under China's drug cost methodology, implementing vial-sharing means that the cost of using a CSTD or intelligent dispensing robots will be borne by medical institutions. While medical institutions using intelligent dispensing robots for drug preparation will still charge patients for preparations, the cost will be much less than the expenses on wasted drug; so if this aspect is applied to the actual process, then patients, medical institutions, and national health insurance agencies will all benefit. Additionally, it will reduce the risk of exposing medications to healthcare workers during the process of chemotherapy drug dispensing (19) as well as the cost of disposing of waste fluids in healthcare facilities (17). To implement the vial-sharing strategy more effectively, we need to get the support of professional pharmacy organizations and government bodies. Government departments should provide guidelines for the application of partially used vials and guidelines on compounding to offer recommendations for assigning the beyond-use dating (BUD) on compounded sterile injectable products. The Society of Hospital Pharmacists should support the practice of vial-sharing in specialized pharmacy aseptic manufacturing sites and licensed compounding facilities following rigorous governance frameworks and professional standards of practice. The National health system should provide opportunities for achieving financial savings. It should have appropriate reimbursement plans for these drugs. In addition, medical institutions can also use The Closed system transfer devices (CSTDs) to optimize vial sharing, which can prevent contamination of drug products and has the potential to allow the extended BUD of single-use vials.

This study is the first to propose the concept of real-time vial-sharing. Notably, the aseptic condition and stability data of the drug composite product are key factors influencing the use of the vial-sharing strategy. Using CSTD will introduce some new risks, and traditional vial-sharing will also require manual intervention for their

storage, which could result in the incorrect writing of information or dose miscalculation or omission altogether (21). Rather than use CSTDs to store drugs for reuse in the same period (22), we prepared them simultaneously by employing an intelligent dispensing robot. Therefore, the introduction of an intelligent robot capable of dispensing multiple prescriptions simultaneously to run a real-time vial-sharing strategy in this investigation encountered not the traditional approach-related safety issue concerns, such as the introduction of impurities due to repeated interspersing or recording drug information incorrectly. Using our method will also provide other benefits, including simplicity of the process, reduced risk of errors, and more accurate dosing, rendering its application highly safe and feasible.

While the outcome of this study was impressive, the investigation had its limitations. The cost analysis was performed using data collected from a single facility and only for 3 months, albeit a tertiary general hospital in China. More hospitals should be included in future projects for a more generalizable outcome. Due to the limitations of the health insurance system and national policies, the multi-prescription real-time vial-sharing strategy using intelligent dispensing robots was not practically applied. This paper only presented a theoretical basis for conducting this strategy, and, therefore, in subsequent research, we will aim to examine the practical feasibility of this strategy. In addition, the cost of introducing an intelligent dispensing robot was not discussed in this study. The purchase and maintenance of robots and the use of special blending devices that assist in sharing are expensive, whereas manual operations do not have this expense. What is more, there is currently no way to avoid the wastage of chemotherapy drugs caused by the use of intelligent dispensing robots; however, we can minimize this wastage, for example, by scheduling the same prescribed drugs for the same period whenever possible. Lastly, drugs that are shared using intelligent dispensing robots are not currently charged exactly for the actual dose used, with the resulting cost of wasted drugs borne by patients. In practice, health institutions typically charge patients for the actual number of prescription vials first. During the dispensation process, if vials are shared between prescriptions, there is a corresponding saving in drugs and costs (the intelligent dispensing robot will scan each dispensed prescription, and the system can monitor and record it in real-time). This saving can subsequently be refunded to the patient's account according to the actual status of prescriptions. To ensure that this strategy works, the health insurance department must also be looped in for agreement. This strategy will also save corresponding costs for the medical insurance department. Theoretically, it will be a win-win-win situation for the patient, the health institution, and the medical insurance department.

Conclusion

This inquiry, as far as documented evidence is concerned, is the first study from China on reducing waste and cost savings in chemotherapy. It is also the first time that the concept of a real-time vial-sharing strategy has been proposed. According to our estimates, an oncology drug waste reduction to control costs is feasible and economically beneficial. Notably, medical institutions with PIVAS can achieve waste reduction and cost savings by introducing intelligent dispensing robots to share drug vials in real-time for multi-prescription dispensing of chemotherapy drugs. This not only saves medical resources and reduces exposure risks but also eases the huge burden on patients, medical institutions, and the national medical insurance system. This certainly is a multi-win situation. Additionally, with real-time sharing, the aseptic condition and stability data of the drug composite product can be easily assured. Based on our findings, we also recommend that medical institutions prioritize scrutinizing drugs in terms of their unit price, frequency of use, prescription dose, and common population dose to determine which medications are appropriate for a real-time vial-sharing strategy.

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/s.

Author contributions

HL and JY conceived and designed the study. HL, JY, LZ, and YS collected and analyzed the data. HL wrote the first draft of the manuscript. HL, JY, and LZ critically revised it. All authors checked the data and made contributions to this study.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.936686/full#supplementary-material

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Government drivers of breast cancer prevention: A spatiotemporal analysis based on the association between breast cancer and macro factors

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Background: Currently, breast cancer (BC) is ranked among the top malignant tumors in the world, and has attracted widespread attention. Compared with the traditional analysis on biological determinants of BC, this study focused on macro factors, including light at night (LAN), PM2.5, per capita consumption expenditure, economic density, population density, and number of medical beds, to provide targets for the government to implement BC interventions.

Methods: A total of 182 prefecture-level cities in China from 2013 to 2016 were selected as the sample of the study. The geographically and temporally weighted regression (GTWR) model was adopted to describe the spatiotemporal correlation between the scale of BC and macro factors.

Results: The results showed that the GTWR model can better reveal the spatiotemporal variation. In the temporal dimension, the fluctuations of the regression coefficients of each variable were significant. In the spatial dimension, the positive impacts of LAN, per capita consumption expenditure, population density and number of medical beds gradually increased from west to east, and the positive coefficient of PM2.5 gradually increased from north to south. The negative impact of economic density gradually increased from west to east.

Conclusion: The fact that the degree of effect of each variable fluctuates over time reminds the government to pay continuous attention to BC prevention. The spatial heterogeneity features also urge the government to focus on different macro indicators in eastern and western China or southern and northern China. In other words, our research helps drive the government to center on key regions and take targeted measures to curb the rapid growth of BC.

KEYWORDS

breast cancer scale, light at night, macro factors, geographically and temporally weighted regression model, temporal and spatial heterogeneity

Introduction

Cancer is the killer of human life (1). With the rapid development of medical technology, human beings are still unable to eliminate the pain of cancer and loss of life (2, 3). In all patterns of cancer, breast cancer (BC) incidence and mortality both lie on top of malignant tumors (4, 5). According to the International Agency for Cancer Research (IARC) of the World Health Organization (WHO), BC morbidity (11.7%) ranked first and mortality (6.9%) ranked fifth among all cancers in 2020 (6); BC has been a heavy burden on the global population (7). Additionally, the metastasis of BC cells will lead to the pathology of other organs (8, 9). Patients suffer from both physical pain and mental depression (10); thus the demand for health and longevity cannot be satisfied (11, 12). The exact carcinogenic factors of BC are not yet clear (13), so reducing the disease risk also faces difficulties. Today, the whole world is focusing on "converging attacks" from the two aspects of prevention and treatment of BC (14, 15) to break through the "BC dilemma." In this study, an in-depth exploration and multidimensional analysis of the potential macro influences on BC provides a theoretical evidence-based basis for BC intervention.

Based on the theory of social determinants of health, the occurrence of disease is the result of multidimensional factors. Currently, the analyses of carcinogenic factors of BC focus on the following three aspects: congenital inheritance (5, 15–18), lifestyle and psychological pressure (15, 19–22), and physical environment (natural environment and social environment, etc.) (15, 23–26). In addition, the mechanism by which light at night (LAN) blocks melatonin formation and triggers BC has attracted much attention (27–33). Xiao et al. used the Cox proportional hazards models to estimate the hazard ratio of BC and found that different tumor stages and ethnic differences would cause different results in the effect of LAN on BC. In black women, the relationship between LAN and increased BC risk was observed for localized BC only, whereas in white women, the relationship was observed for regional/distant stages (32). Al-Naggar et al. applied a linear regression method to demonstrate a significant association between artificial light at night and diseases such as BC in protected areas (27). Lamphar et al. studied 25,025 breast cancer cases and found that cumulative light pollution was positively associated with BC and persisted after age standardization (31). These studies fully demonstrate the important role of remote sensing light in BC.

With the continuous innovation of research methods, the research analyzing the spatial characteristics of cancers has become more and more abundant. This is the key to taking targeted preventive measures in different regions based on the differential distribution of diseases in space, and is also the basis for efficient promotion of human health. Amin et al. used SaTScan software to identify significant BC spatial clusters in the United States and propose high emphasis on areas of spatial clustering of BC (34). Using the geographically weighted regression (GWR) method, in the study by Pes et al., a hotspot of gastric cancer mortality was detected in the central mountainous area of Sardinia among males, positively associated with goiter, and the practice of sheep-rearing, whereas there was a negative association with the diet score (35). Imounga et al. examined spatial trends in cervical cancer in French Guiana, reminding policymakers to focus on remote areas (36).

There is an increasing number of studies on the determinants of BC, but there are still some limitations. First, the research scale is mostly focused on the national scope, while the spatial distribution characteristics of BC are not described more precisely and are not conducive to targeted intervention. Second, although these studies have considered light impacts on BC, they pay more attention to the behavioral habits and physiological characteristics at the individual level. The study of the impacts of LAN on BC under the economic level, medical condition, and air quality lacks attention. However, macro factors play significant roles. For example, people in developed countries tend to have a high intensity of LAN, leading to a higher incidence of BC. The BC incidence in developed countries (71.7/100 thousand) is higher than that in less developed countries (29.3/100 thousand) (4). Additionally, a comprehensive early examination schedule, reasonable medical service supply and appropriate late treatment plan can effectively reduce the morbidity and mortality of BC (37). Furthermore, air pollution from a high level of fine particulate matter will increase breast density and raise the risk of BC. The emission density of PM2.5 in downtown Atlanta is 4.6 times higher than that in rural Georgia, and the average incidence of BC is 16.62% higher than that in rural Georgia (38). Third, most articles use statistical methods to process panel data and lack attention to spatial heterogeneity and time span. This may reduce the estimation efficiency, biased results, and lack of continuous changes in the data, which is too different from the real situation of BC.

In such a context, our study has some outstanding innovations. Considering the importance of the scale effect on spatial research, avoiding the roughness of large scale research at the global-level and unobservable small scale studies at the county-level, this study adopted an intermediate scale in prefecture-level cities and focused on the impacts of macroeconomic indicators on BC from a sustainable development perspective. In addition, to emphasize a spatiotemporal perspective, this study applied the geographically

Abbreviations: BC, Breast Cancer; LAN, Light at Night; GTWR, Geographic and Time Weighted Regression; IARC, International Agency for Cancer Research; VIIRS/DNB, Visible Infrared Imaging Radiometer Suite Day/Night Band; CNRDS, Chinese Research Data Services Platform; OLS, Ordinary Least Squares; GWR, Geographically Weighted Regression; TWR, Time Weighted Regression.

TABLE 1 The test of sample size.

Output parameters	Values
Non-centrality parameter δ	3.6228448
Critical t	1.9714347
Df	208
Sample size group 1	105
Sample size group 2	105
Actual power	0.9501287

and temporally weighted regression (GTWR) model (39). By constructing a spatiotemporal dependent stereo model, we can obtain more accurate results (40) and consequently display different factors attributed to BC from various regions, for further targeted intervention measures. This will provide a theoretical reference for the prevention of BC in countries or regions with high incidence and has great significance for promoting human health.

Materials and methods

Variable selection and data source

This study considered China's prefecture-level cities or municipalities directly under the central government as the research objects. After sorting out the data fully, 182 research units were retained. The specific sampling method can be described in three steps. First, among all prefecture-level cities in China, 216 cities with established cancer surveillance centers were screened. Second, to ensure the spatial continuity of the panel data, we took 2013 as the base year and deleted the surveillance centers added later. Therefore, 182 prefecture-level cities were retained. Third, we collected data for each explanatory variable, matched them with the above 182 prefecture-level cities, and thus finalized the 182 prefecture-level cities.

Additionally, we also verified the sample size to ensure rigor. The minimum sample size was calculated by applying G*power 3.1.9.7 developed by Heinrich Heine University Düsseldorf. We chose the two-sided t-test and the difference between two independent means (two groups) as the test type and measured variable. The significance level is 5%, and the test power is 95%. Table 1 shows that the minimum sample size is 105. It is much smaller than the 182 in this study. So, the sample size in this paper meets the requirements for research reliability.

In the process of building the model, we selected the number of BC cases (the BC scale) as the explained variable. These data were from the *China Cancer Registry Annual Report (2013–2016)*, published in 2017–2020. In addition, considering the significant geographic differences in disease morbidity and mortality (41–44), it is only through appropriate spatial methods that the spatial heterogeneity of disease can be displayed thoroughly, and targeted policies can be made accordingly. Ignoring spatial heterogeneity can lead to many problems, such as loss of estimation efficiency, biased estimation, and saliency of errors. Therefore, we analyzed the factors related to the spatial distribution pattern of BC as follows:

(1) Light at night. The light data is obtained through spatial technology, so it is easy to match the regional geographic location (31). Light changes alter our circadian rhythm, especially the normal cycle of melatonin. This leads to early menarche and elevated circulating estrogen and prolactin, sex hormones that increase the risk of BC (28, 30, 32, 45). We include the LAN data in the explanatory variables. It uses Visible Infrared Imaging Radiometer Suite Day/Night Band (VIIRS/DNB) image data, which is one of the ways to collect light images at night and it has higher spatial resolution and a wider radiation detection range. The data was obtained from the Chinese Research Data Services Platform (CNRDS).

(2) Environmental pollution. Aromatic hydrocarbon receptors in polluted environments mediate the effects of many endocrine disruptors and have implications for BC in young or premenopausal women (46–48). There is little literature on the effects of environmental pollution on BC from a spatial perspective. Under the constraints of data availability, we finally chose "PM2.5" as a proxy variable for environmental pollution. PM2.5 can potentially affect breast density by interfering with the growth of breast cells and increasing the relative amount of fibrous tissue (48, 49), thereby greatly enhancing the risk of BC. The data was obtained from the atmospheric composition analysis group of Dalhousie University.

(3) Economic development and wealth level. From a spatial perspective, economic development and wealth level vary by geographic location (50). Considering the availability of data and the quality of variables, "economic density" and "per capita consumption expenditure" are chosen as proxies for economic development and wealth levels. In general, the higher the level of economic development or the higher the economic and social status of people, the greater attention they pay to BC prevention and screening (51, 52). Additionally, BC prevention and treatment are at a high level in terms of supply and demand. This came from the *China City Statistical Yearbook (2014–2017)* or the *Economic and Social Development Statistical Bulletin (2013–2016)*.

(4) Population. To integrate the characteristics of population and area, we chose "population density" as the proxy variable. The occurrence of BC ultimately manifests in the individual. When the population base is large, the possibility of BC increases (53). The data were obtained from the *China City Statistical Yearbook (2014–2017)* or

the *Economic and Social Development Statistical Bulletin (2013–2016)*.

(5) Medical resources and medical service level. Based on the availability of data, "number of medical beds" was used as a proxy variable. If a region has abundant medical resources and a high level of medical services, the screened BC cases are very close to the actual number of patients, and a relatively high BC scale would be detected (54). The data was obtained from the *China City Statistical Yearbook (2014–2017)*.

(6) Education level. We chose "average years of education" and "number of students in higher education" for each region as proxy variables. Higher education groups are more likely to accept the relevant knowledge and treatment process of disease prevention (55). Therefore, the prevention and treatment of BC are more effective among them.

(7) Political background. Each region has experienced unique changes thus far, and these political changes will also have a certain impact on BC (56).

We attempted to find relevant data on "education level," but unfortunately, they are too scarce due to covering 182 prefecture-level cities from 2013 to 2016. So, in the end, we have to exclude this factor. In addition, political factors have little impact on BC in China from 2013 to 2016, and are not easy to quantify. The "political background" was also excluded.

Stata, GeoDa, and ArcGis10.2 are adopted to process the data. Table 2 shows a specific description of these variables.

Research methods

Ordinary least squares (OLS)

The OLS model needs to select a set of linearly independent functions in advance, and obtain the closest result to the real situation by setting the undetermined coefficients and solving them. The condition of OLS is to use the least square method to obtain the unknown data and minimize the square sum of the error, that is, to minimize the square sum of the distance from all observations on the scatter diagram to the regression line. Its calculation formula is as follows:

$$y_i = \beta_0 + \sum_k \beta_k x_{ik} + \varepsilon_i$$

In the formula, i is the prefecture level city number, y_i represents the BC scale in city i, x_{ik} represents the k-th explanatory variable of the i-th city, and β_0 indicates the expected value of BC cases in different regions when all explanatory variables do not work. β_k is the k-th regression parameter of the control variable which indicates that the BC scale fluctuates with the change in explanatory variables. ε_i is a random error term.

Geographically weighted regression (GWR)

This method extends the traditional OLS from a global to a local framework by incorporating the spatial location into the parameters and using a locally weighted least squares method for point-by-point parameter estimation. The estimated parameters will change depending on geospatial location, thus visualizing the spatial heterogeneity of the study object. Its calculation formula is as follows (57):

$$y_i = \beta_0(u_i, v_i) + \sum_k \beta_k(u_i, v_i) x_{ik} + \varepsilon_i$$

(u_i, v_i) represents the centroid coordinates of city i. Unlike the spatial "fixed" coefficient estimates in the global model, this model allows the parameter estimates $\beta_k(u_i, v_i)$to vary with space, so it can capture local effects. It is critical to select an appropriate weight matrix for estimating the parameters of GWR. The spatial weights can be estimated by a spatial kernel function, also called a distance-decay function. According to whether the bandwidth is varied, the 2 basic types of spatial kernels are fixed and adaptive kernels, which use fixed bandwidth and a fixed number of nearest neighbors within an adaptive bandwidth, respectively. Further, this method was chosen because quadratic kernel function had the best (smallest) AICc for fitting the GWR model to the data. So, this study selected the adaptive bandwidth quadratic kernel function commonly used in academia as the distance weight function. Its formula is:

$$w_{ij} = \begin{cases} \left[1 - \left(\frac{d_{ij}}{b_i}\right)^2\right]^2 & if\ d_{ij} < b_i \\ 0 & otherwise \end{cases}$$

Where w_{ij} is the weight of the impact of city i on city j, $d_{ij}$is the distance between city i and city j, and b_i is the bandwidth specific to location i.

Geographically and temporally weighted regression (GTWR) and temporally weighted regression (TWR)

GTWR is an extended model of GWR. It not only considers the spatial non-stationarity of geographic data but also adds the time effect in the model to improve the goodness of fit of the model (58). Its formula is:

$$y_i = \beta_0(u_i, v_i, t_i) + \sum_k \beta_k(u_i, v_i, t_i) x_{ik} + \varepsilon_i$$

Where i(u_i, v_i, t_i)represents the spatiotemporal coordinates of city i, u_i, v_i represents the projected spatial coordinates, and t_i is the projected temporal coordinates. Unlike the global regression model with "fixed" coefficients, GTWR allows parameter estimation $\beta_k(u_i, v_i, t_i)$ to

TABLE 2 Description of various variables.

Variable	Interpretation	Unit
The BC scale	Total number of male and female BC cases in each region	Person
LAN	The sensors on the satellite can detect the light information of the earth at night, representing the data of human activities	DN total value/number of grids
PM2.5	The higher the concentration of particles with aerodynamic equivalent diameter <2.5 microns in the ambient air, the more serious the air pollution is	$\mu g/m^3$
Permanent population	The population who often lives here or has lived here for more than 6 months throughout the year	10,000 people
Area size	Total area of a region	km^2
GDP	The final value of production activities of all resident units in an area within 1 year	10,000 yuan
Per capita consumption	Total expenditure of residents to meet the daily consumption of families	Yuan/person
Economic density	GDP per unit area	100 million yuan/km^2
Population density	Population per unit area	10,000 people/km^2
Number of medical beds	The number of medical beds in each region, representing the medical resources of a region	1,000 sheets

vary across space and time. Therefore, this method can capture spatiotemporal changes at the same time. The estimated value of its parameters $\beta_k(u_i, v_i, t_i)$ can be expressed as:

$$\hat{\beta}_k(u_i, v_i, t_i) = \left[X^T W(u_i, v_i, t_i) X\right]^{-1} X^T W(u_i, v_i t_i) Y$$

where $W(u_i, v_i, t_i)$ is the space-time weight matrix, and its diagonal elements are the weight values of city i and its adjacent city j, GTWR defines w_{ij} as a weight matrix constructed by the adaptive Gaussian distance attenuation function. This makes the weight of data points closer to observation point i higher than that of data points farther from observation point i in a spatiotemporal coordinate system. In addition, in the GTWR model, the ${d_{ij}}^{ST}$ used in the weight matrix—the spatiotemporal distance between city i and city j—is defined as a linear combination of spatial and temporal distances:

$${d_{ij}}^{ST} = \sqrt{\lambda\left[(u_i - u_j)^2 + (v_i - v_j)^2\right] + \mu\,(t_i - t_j)^2}$$

Where λ and μ are the scale parameters of equilibrium space and time, respectively. In particular, when $\lambda = 0$, the spatiotemporal distance degenerates into the distance in the TWR model; when $\mu = 0$, the spatiotemporal distance degenerates into the distance in the GWR model (59).

Results

Spatial variation characteristics of the BC scale from 2013 to 2016

The scale of BC in 182 prefectural-level units in China from 2013 to 2016 is shown in Figure 1. From a spatial perspective, the Liaodong Peninsula, Shandong Peninsula, and Beijing-Tianjin-Hebei area are located in the Bohai Rim and some cities in the Yangtze River Delta are areas with a high scale of BC. They also have a higher degree of BC clustering. Overall, there are eight prefecture-level cities with an average annual scale of BC exceeding 1,000. They are Beijing (2,597), followed by Tianjin (2,544), Shanghai (2,243), Hangzhou (1,550), Nantong (1,461), Shenyang (1,385), Guangzhou (1,223), and Wuhan (1,113). From the time perspective, compared with the former 2 years, the scale of BC in 2015 and 2016 is much lower, and 92.86% of prefecture-level cities have a lower scale of BC than the previous 2 years. In addition, the scale of BC in 2015 was lowest, so to reflect the continuous changes in the scale of BC more effectively, it was necessary to study both the spatial effects and time effects of the scale of BC.

Results from OLS model

OLS regression is first used to explore the relationship of the scale of BC and LAN, PM2.5, per capita consumption

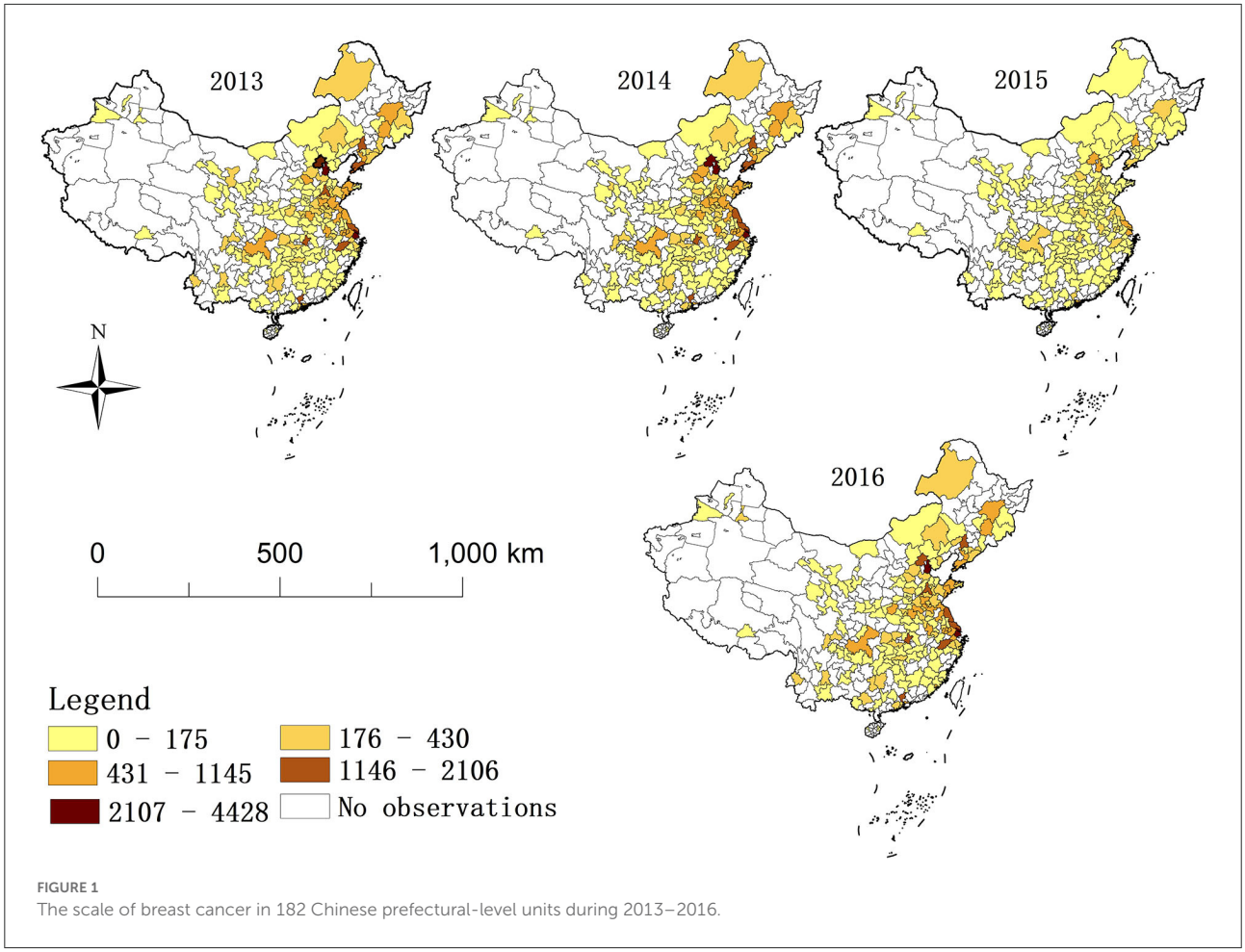

FIGURE 1
The scale of breast cancer in 182 Chinese prefectural-level units during 2013–2016.

expenditure, economic density, population density, and number of medical beds. This model can be used as a benchmark for comparison with local regression model results. Table 3 shows the estimated results of OLS. The R^2 was 0.581, which indicated that OLS can explain at least 58.1% of the total variation in the scale of BC and has statistical significance. Additionally, the variance inflation factor (VIF) values were lower than 3, verifying that the choice of explanatory variables can avoid the problem of collinearity. According to the results in Table 3, the scale of BC had a strongly positive correlation with LAN, PM2.5, per capita consumption expenditure and number of medical beds (p-value < 0.1) and a negative correlation with population density (p-value < 0.05).

Results from GTWR model

Furthermore, the GTWR model was also adopted to verify the relationship between the scale of BC and the above explanatory variables. Compared with OLS, the fitting results of GTWR are significantly improved in terms of the R^2 and AICc values. Table 4 shows five statistics, including each estimated parameter's minimum (Min), lower quartile (LQ), mean, upper quartile (UQ) and maximum (Max). For variable LAN, the Min and Max values of the coefficients are −6.161 and 44.114 respectively, indicating that the correlation between the scale of BC and LAN has obvious spatial-temporal variation. With LQ = 4.994 > 0, negative relationships exist for some spatial units or time frames, and positive relationships are dominant overall. Similarly, the coefficients of other variables also show apparent space-time variation; the differences between the maximum and minimum PM2.5, per capita consumption expenditure, economic density, population density, and number of medical beds are 4.489, 81.325, 236.969, 1,491.394, and 22.225, respectively.

Performance comparison of different models

To illustrate the applicability of GTWR to this study, GWR and TWR are also tested on the same dataset, and

TABLE 3 Parameter estimate summaries of OLS on the entire data set.

Variable	Co-ef.	St. err.	*t*-statistic	*P*-value	VIF
Intercept	−84.312	30.924	−2.73	0.007***	–
LAN	12.862	6.671	1.93	0.054*	2.75
PM2.5	2.185	0.544	4.02	0.000***	2.45
Per capita consumption expenditure	13.586	6.262	2.17	0.030**	1.78
Economic density	10.771	9.177	1.17	0.241	1.53
Population density	−219.122	89.962	−2.44	0.015**	1.28
Number of medical beds	17.206	0.753	22.86	0.000***	1.1
R^2			0.581		
AICc			10,316.301		

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

TABLE 4 Parameter estimate summaries of GTWR on the entire data set.

Variable	Min	LQ	Mean	UQ	Max
Intercept	−167.39	−119.262	−84.366	−39.809	32.025
LAN	−6.161	4.994	21.169	34.296	44.114
PM2.5	−0.683	1.034	1.716	2.098	3.86
Per capita consumption expenditure	−12.122	5.918	23.018	45.439	69.203
Economic density	−209.127	−65.206	−35.143	12.93	27.824
Population density	−277.394	−231.967	94.174	239.197	1,214
Number of medical beds	4.136	14.823	17.509	24.077	26.361
R^2			0.747		
AICc			10,008.2		

Table 5 presents the fitting results of these models. The TWR model performs better than the GWR model, indicating that the fluctuation during 2013–2016 was greater than its spatial discrepancy. Namely, the time non-stationarity was greater than the spatial non-stationarity. GTWR exhibited the best performance, including the highest R^2, lowest RSS and lowest AICc. It is worth mentioning that the comparison has two contributions to the whole thesis. It can prove that the GTWR model is more suitable for BC scale local effects. Also, our research content needs to eliminate one-by-one traditional methods (OLS, GWR, and TWR) and methodological upgrades. The research topic of this study was the temporal and spatial differences of the BC scale in 182 prefecture-level cities in China from 2013 to 2016 and the macro factors driving its changes, capturing both temporal and spatial local effects. Undoubtedly, this is something that a global model such as OLS cannot achieve. Therefore, this article selects the GTWR model to further describe the correlation between various influencing factors and the scale of BC.

Temporal variation of estimated coefficients

Figure 2 illustrates the variation in selected variable coefficients during 2013–2016 in Beijing, Guangzhou, Hangzhou, Nantong, Shanghai, Shenyang, Tianjin, and Wuhan (the scale of BC in the selected cities exceeds 1,000). In the Figures 2A–F denote LAN, PM2.5, per capita consumption expenditure, economic density, population density, and number of medical beds, respectively. In summary, the estimated coefficients of each variable in the selected cities have the same trends over time, which can be divided into two categories. One is the three-stage fluctuation mode, namely, the trend of coefficients in each city from 2014 to 2015 is opposite to that in the previous and subsequent periods, and (A), (B), (C) and (D) all show this characteristic. Taking LAN as an example, its fluctuation feature over 4 years is "rise-fall-rise," and the positive impact fluctuates repeatedly. It is worth mentioning that the economic density has an opposite impact on the scale of BC. In 2013–2014 its increase effectively reduced the scale

TABLE 5 Performance comparison of four models on the entire data set.

	OLS	GWR	TWR	GTWR
Neighbor		235	237	244
RSS	59,645,963	45,486,100	37,244,200	36,034,100
R-square	0.5811	0.6811	0.7388	0.7473
AICc	10,316.301	10,180.6	10,021	10,008.2

of BC, but in the next 2 years, it showed the promotion to the scale of BC. The other is the two-stage fluctuation mode. The change in the coefficient of population density and the number of medical beds over time is consistent with this model. The former showed a rise followed by a fall, while the latter showed the opposite. The trend of population density changes from a strengthening promoting effect to a strengthening inhibiting effect. In contrast, the impact of the number of medical beds is always positive and decreases year by year until 2015, only to pick up in 2016. In conclusion, the inclusion of time effects can reflect the influencing trend of various factors and be beneficial to clarify the direction and focus of BC prevention.

Spatial variation of estimated coefficients

To show the effect of each factor on the spatial distribution of the BC scale more clearly, we will describe them through the spatial distribution characteristics map.

As shown in Figure 3, the average coefficient for LAN displays a pattern in which "the positive correlation increases from west to east." In other words, the positive impact of LAN on the BC scale is strengthening in eastern China but weaker in western China, which shows consistency with our hypothesis.

In Figures 4A–E represent the spatial distribution of the average coefficients of the GTWR model for the five explanatory variables, PM2.5, per capita consumption expenditure, economic density, population density, and the number of medical beds, respectively, during 2013–2016. According to the spatial patterns, we can summarize them into three forms: (1) Patterns in the north-south direction. The contribution of PM2.5 to the BC scale increases from north to south. In most southern cities, the BC scale was more positively influenced by PM2.5 concentrations, with regression coefficients ranging from 1.79 to 1.84 in the highest rank. (2) The degree of the positive impact shows an increasing pattern from west to east. The variables of per capita consumption expenditure, population density, and number of medical beds all fall into this category. In other words, the BC scale increases less with increasing per capita consumer spending, population density, and number of medical beds in western cities relative to those in the east. (3) The degree of the negative impact also shows an increasing pattern from west to east. The coefficient of economic density is consistent with this pattern. Concretely, a one-unit increase in economic density reduces the BC scale more in eastern cities than in western cities. In addition, the results of population density and economic density in the GTWR model are contrary to the previous OLS, which illustrates the necessity to consider the spatial perspective.

Discussion

Our study has important implications. First, China is the largest developing country and is representative of the vast regional disparities in economic development and the clustering status of the BC scale. The corresponding policy recommendations can provide lessons for other regions with high BC pathogenesis. Second, compared with the classical regression models (e.g., OLS, GWR, and TWR), the GTWR model, shows the best performance in studying the problem of this study. This result proves the validity of the GTWR model in modeling the spatiotemporal heterogeneity at the BC scale. It also precisely portrays the spatiotemporal leap trajectory of the impact of each explanatory variable on the BC scale, mainly LAN (60). Third, this study focused on the macro factors of the BC scale. It is an innovative exploration compared with previous studies that investigated only from the biogenetic perspective. This study captured the characteristics of macro elements based on their influence on the BC scale. Additionally, it provides an evidence-based foundation for the differentiated implementation of regional health policies. At the same time, it strengthens the government's initiatives in the two dimensions of time and space.

How can governments break the stalemate over the timing of the rise in the BC scale?

The gradual upward trend of the BC scale has intensified over time. From the perspective of governments, to curb or mitigate this trend, they should first focus on the macro factors that affect the BC scale. Governments should not only continue to promote the development of protective factors but also try to curb the deterioration and recurrence of risk factors over time.

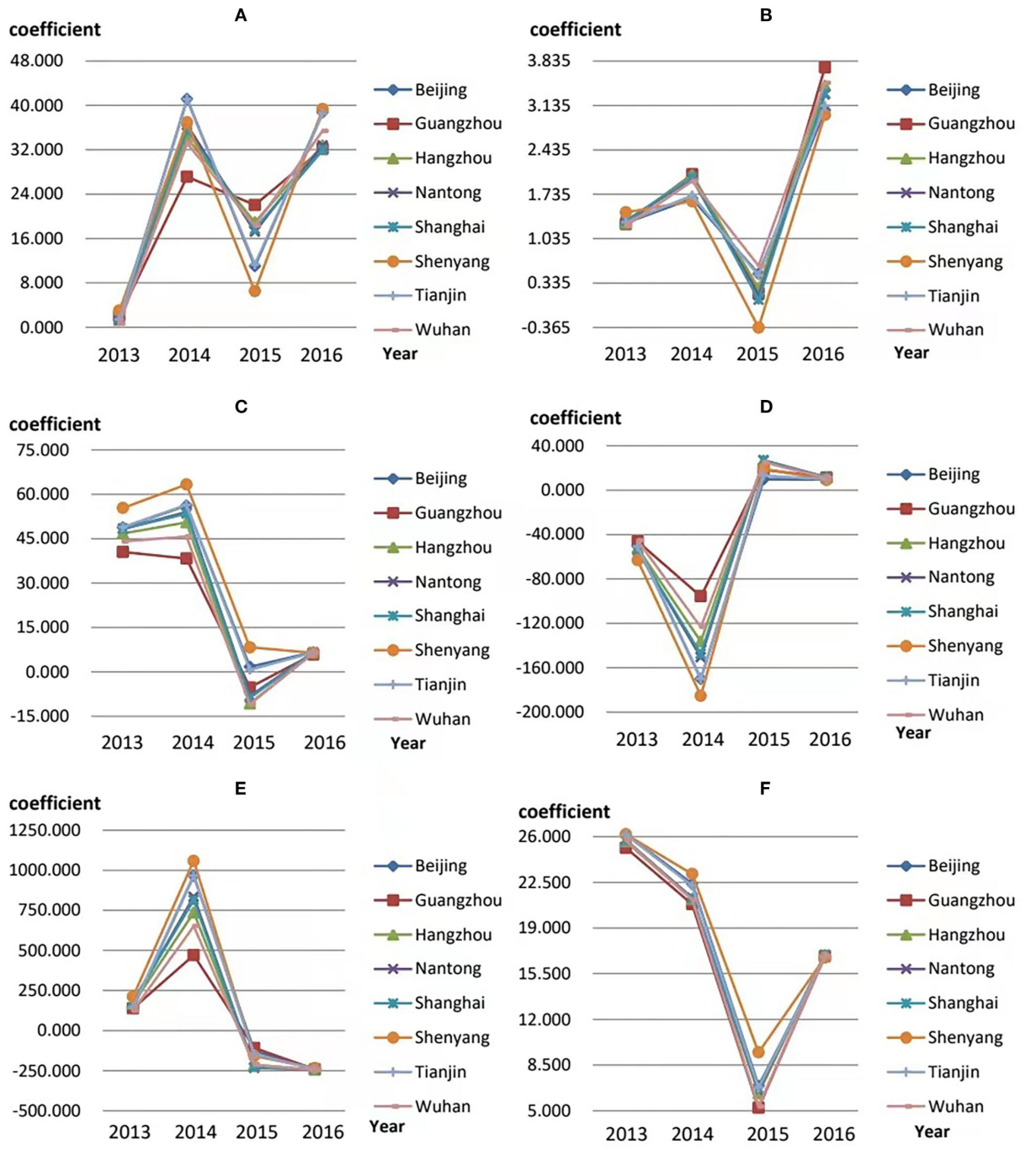

FIGURE 2
Temporal variation in the estimated coefficients. **(A–F)** represent the coefficient variations of LAN, PM2.5, per capita consumption expenditure, economic density, population density, and number of medical beds, respectively.

First, LAN and PM2.5 always appear to be risk factors for BC. The coefficients for both show an overall increasing time trend (except in 2015), indicating that they have a growing degree of influence on the scale of BC. Therefore, the government needs to take initiatives to reduce overall LAN and PM2.5 in the city, minimize large-scale forms of nighttime operations and continue to impose strict regulations on factory exhaust and vehicle emissions. Second, per capita consumption expenditure and economic density have changed from risk factors to protective factors over time. Spending power and economic density increases indicate that the population is wealthier, and disease prevention is more effective among them

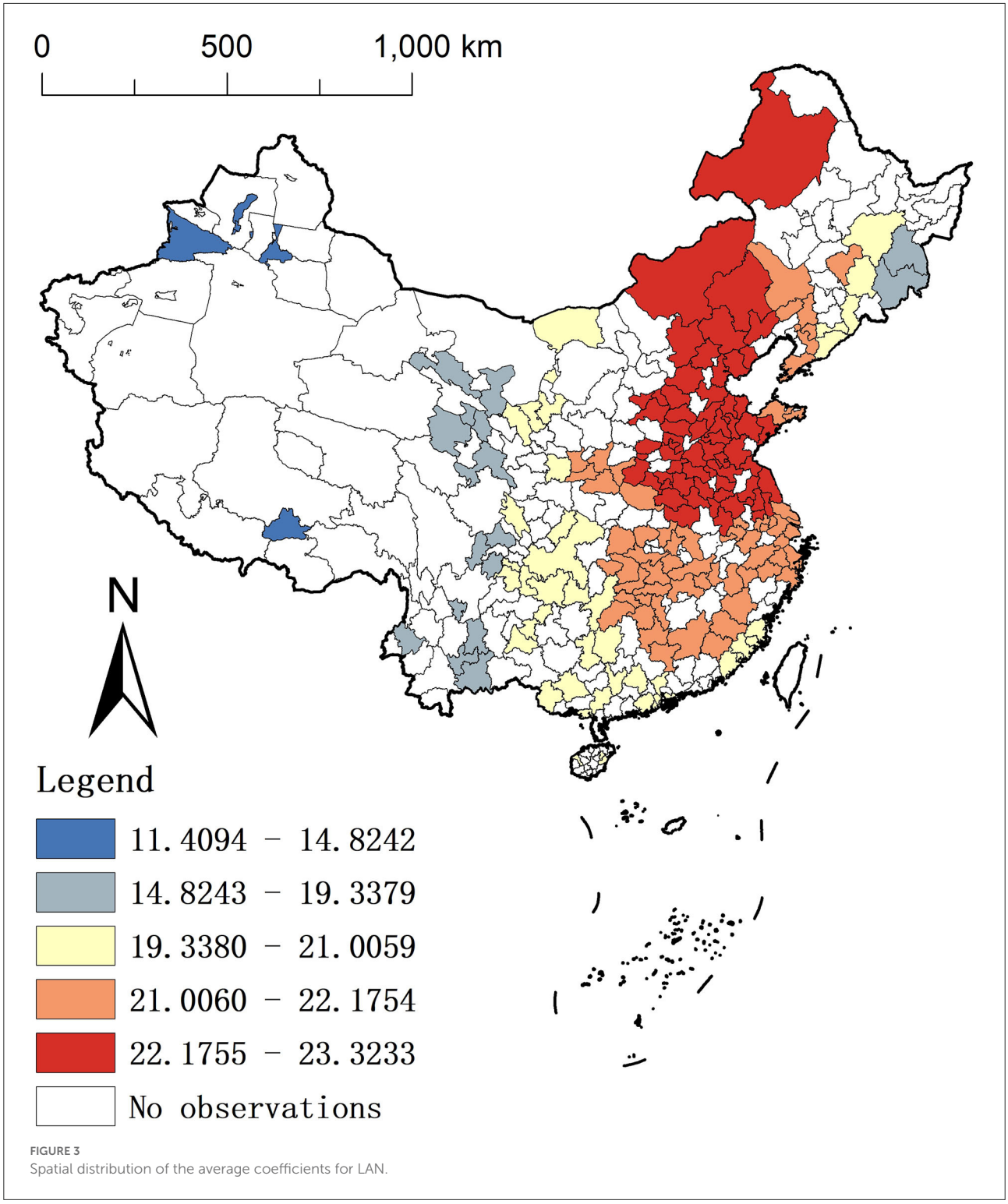

FIGURE 3
Spatial distribution of the average coefficients for LAN.

(61), which can explain its suppressive impact on BC. Third, the positive impact of the number of medical beds and population density played a more prominent role in increasing the BC scale in 2015–2016. Specifically, the dangerous degree of the number of medical beds first decreased and then rebounded in 2016. Due to the progress of society, abundant medical resources have led to a significant increase in cancer detection rates. In addition, the improvement of medical testing and the enhancement of people's health awareness have played a vital role in slowing down the occurrence of diseases. However, the situation may be worse (62, 63) if we do not consistently reinforce the level of medical care and health awareness.

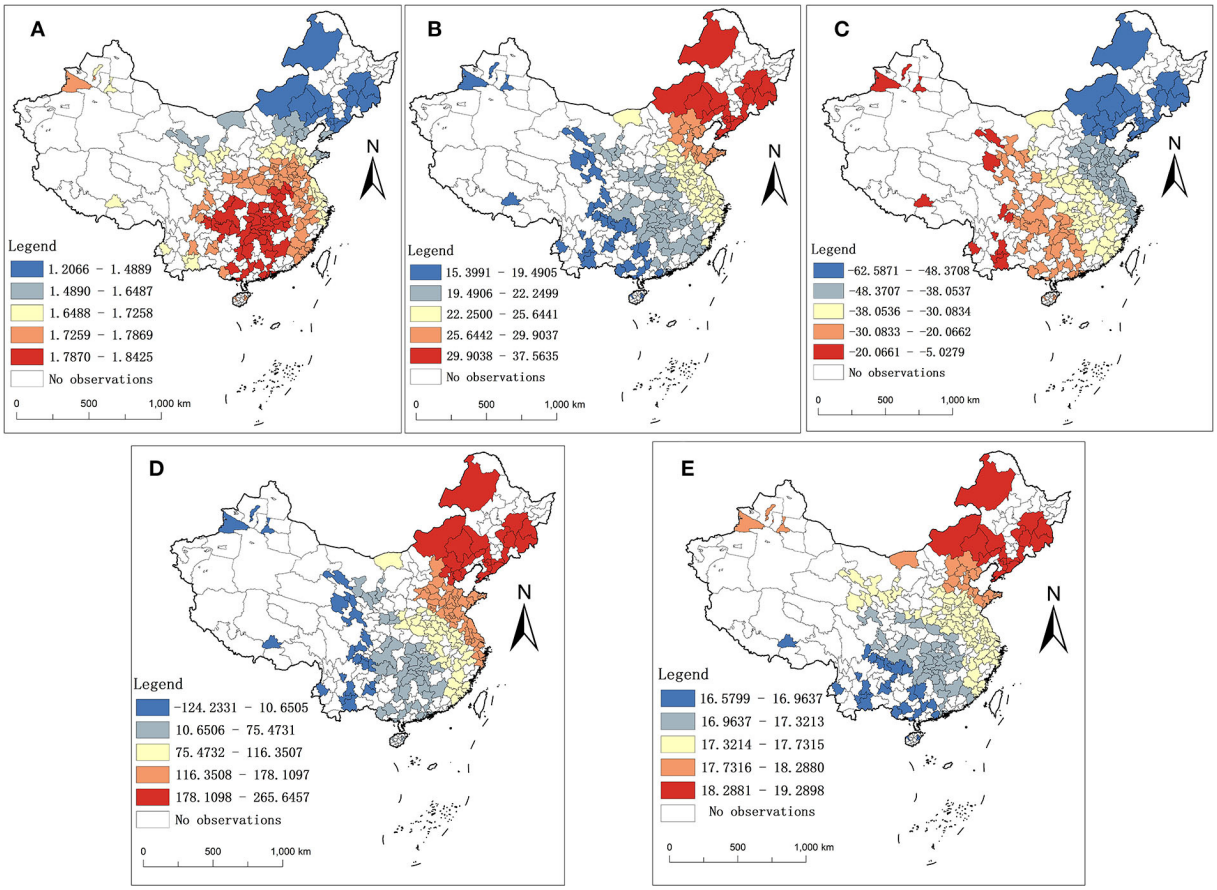

FIGURE 4
Spatial distribution of the average coefficients for other explanatory variables. **(A–E)** represent the spatial distribution of the average coefficients of PM2.5, per capita consumption expenditure, economic density, population density, and number of medical beds, respectively.

Population density manifested as a transition from protective factors to risk factors. The increasing life expectancy of the elderly and the liberalization of the two-child policy in 2016 have brought a new round of increase in population density. The increase in the population base leads to an increase in population density, which in turn expands the BC scale. If the government can continue to optimize the "birth policy" and "pension policy," the development of a healthy population structure in China is just around the corner, and the problem of population density will be solved.

How can governments respond to the spatial heterogeneity of the BC scale?

In epidemiological studies, **in addition to** people and time, location is also a vital dimension (64). The reasons for the heterogeneity in the spatial distribution of the BC scale are diverse (34, 65). Therefore, the government also needs to change the spatial heterogeneity pattern of the BC scale based on multiple macro perspectives and different regions; otherwise, it will be challenging to achieve a breakthrough in "restraining the rapid growth of the BC scale" in the short term.

(1) Considering that lights can directly reflect the local industrialization level, urbanization level, and population concentration (66), its distribution pattern is consistent with China's economic development gradient from west to east, which is relatively reasonable. There is no doubt that LAN extends our leisure, entertainment, office, and study time and makes great contributions to improving our quality of life. However, this is also a hazard. It limits the brightening effect of the stars at night. Additionally, it artificially increases energy consumption, breaks the balance of the natural environment, increases the BC scale, and even seriously damages human life and health. How can we, with government's help, both enjoy the fun of LAN and reduce its health hazards? The eastern region, where the coefficient of LAN is higher, should pay more attention to the management of LAN. The government should focus on setting the lighting source control and lighting limit technical requirements in some

developed eastern cities. For example, mitigation can be achieved by investigating the actual needs to provide the minimum lighting level required for walking, driving, and by setting street lights to avoid targeting residential areas. In addition, local governments should implement zoning management for residential, commercial, traffic road, industrial, and landscape areas according to their development (67) and reduce lighting in public spaces to the lowest acceptable level. Furthermore, it is necessary to improve the transparency of information. In the current situation where people lack knowledge about the hazards of light pollution, the government should monitor health warnings and other content on the sales packaging of lighting objects to protect consumers' right to know. Finally, it is worth mentioning that although light pollution control methods emerge in an endless stream, the control process also requires the government to comprehensively consider the local population size, economic development, characteristics of human health development, and the carrying capacity of the medical and health system.

(2) High regression coefficients of PM2.5 were largely concentrated in southern cities of China. Many developed enterprises will emit waste gas because of the pursuit of rapid development. In recent years, although China has strictly monitored the goals of "energy saving, emission reduction, and emission standards," there are still "fish that slip through the net." Moreover, low rainfall and wind speed in winter, exogenous imported pollution from northern cities, and high motor vehicle exhaust (68, 69) all contribute to the concentrations of PM2.5 and further lead to higher human breast density and consequently a larger BC scale. Therefore, the southern regions' governments should speed up air pollution management. In the face of air pollution caused by enterprises, it is necessary to carefully approve the site selection of the enterprise, especially the location upwind of the city, and to increase the cost of exhaust emissions through environmental protection tax, etc., and encourage enterprises to eliminate outdated processes and equipment and use more clean energy such as wind energy and solar energy. It is also crucial for the government to continuously strengthen green management in construction as well as vehicle transport management (70, 71). In addition, the government should call on people to prepare necessary protective equipment outdoors, such as masks, to reduce the harm of some inhalable particles.

(3) The regression coefficients of per capita consumption expenditure, population density, number of medical beds, and economic density all have significant regularity in the east-west direction. The specific performance is that the promotion effect of the first three is gradually increasing from west to east, and the latter is the opposite. This reflects, for one thing, the drawbacks of excessive economic development in developed regions, such as people's anxiety due to more significant life stress (72), leading to a greater degree of influence of various risk factors. In addition, it reflects the imbalance of economic resources, population size, and medical resources between the eastern and western regions of China. Therefore, local governments cannot simply pursue economic benefits at the expense of regional population health. The development process of China's eastern and western regions is relatively complex, and the two are at different stages of economic development. The western region is limited by harsh climate and terrain conditions, and the development of various fields lags. However, the eastern region has entered a new stage of focusing on individual characteristics by mapping high technology in the medical field and gathering medical talent. Therefore, the developed eastern region should pay more attention to mental health, while the western region needs to invest in medical resources to alleviate the rapid increase in the BC scale. The government can make significant progress in BC prevention by eliminating the "one size fits all" policy approach across the country.

Limitations

This study also had some limitations. The spatial units involved in this study include only 182 prefecture-level cities, which may lead to insufficient spatial non-stationarity. In larger spatial regions, spatial heterogeneity features are usually more significant. In addition, based on the availability of data, the BC scale was used as the dependent variable instead of using BC morbidity. Although we added population density as an explanatory variable to the model later, there are still limitations in describing the morbidity status of BC. Last, due to the constraints of data and spatial research methods, our explanatory variables do not include micro-level influencing factors such as lifestyle and genetic inheritance, nor do we have macro-level variables covering all fields to achieve a perfect fit with reality. In the future, we will still pay further attention to the shortcomings of these aspects, with the aim of providing a more detailed and realistic description of the effects, the scope of influence, and the degree of influence on BC.

Conclusion

This study evaluated the spatial and temporal associations between the scale of BC and macroscopic factors in 182 prefectural Chinese cities by using the GTWR model. Regardless of the time dimension or the space dimension, the macro factors show obvious differences. If the government cannot take differentiated and targeted measures based on multiple

perspectives and different regions, this will seriously restrict the integration of health into all policies. Additionally, it will also make people in different regions lack equity in BC prevention, further exacerbating the unequal development of the region.

We put forward some targeted policy recommendations. First, the control of LAN should focus on the developed cities in the east, especially to set the lighting source control and lighting limit technical requirements and to warn consumers of light hazards. Second, the control of environmental pollutants such as PM2.5 should be led by southern cities. Not only must strict requirements be placed on the source of pollutant emissions, such as restrictions on exhaust emissions from enterprises and automobiles but also the concentration of pollutants must be reduced by increasing the green area. The eastern region in the mature stage of economic development should focus on individual situations, such as immense psychological pressure. The western region, which is relatively lagging in economic development, should focus on economic development and be ready to undertake the transfer of developed medical technology from the eastern region. Last but not least, policies formulated by the government on strengthening economic development and consumption capacity or weakening LAN, PM2.5, etc., must ensure the continuity of time, and continue to progress in the process of "implementation-optimization."

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

XB is responsible for writing original draft and revision. XZ is responsible for visualization. HS, YLi, and YC are responsible for writing review and editing. GG, BW, YLa, WX, and YW are responsible for data collection and literature retrieval. BS is responsible for framework design and supervision. YLi is responsible for supervision. 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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Cost-effectiveness analysis of drug-eluting beads and conventional transarterial chemoembolization in the treatment of hepatocellular carcinoma

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Objective: To conduct a cost-effectiveness analysis of drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) and conventional transcatheter arterial chemoembolization (cTACE) for first-line treatment of hepatocellular carcinoma (HCC) from the perspective of the Chinese healthcare system.

Methods: Based on the real-world clinical data of HCC patients receiving interventional therapy, a partitioned survival model was constructed for cost-effectiveness analysis. The model period is 1 month, and the research time limit is 10 years. The incremental cost-effectiveness ratio (ICER) is used as the evaluation index. One-way sensitivity analysis and probabilistic sensitivity analysis were used to analyze the uncertainty of parameters to test the stability of the model results.

Results: The ICER of the DEB-TACE group was 11,875.62 $/QALYs, which was lower than the willingness to pay threshold (WTP) of 31,499.23 $/QALYs. One-way sensitivity analysis suggested that the utility value of progression-free survival (PFS) in the DEB-TACE group had the greatest impact. Probabilistic sensitivity analysis showed that at the level of WTP of 31,499.23 $/QALYs, DEB-TACE had a cost-effective probability of 92%.

Conclusion: Under the current economic level in my country, DEB-TACE is more cost-effective than cTACE in the treatment of HCC patients.

KEYWORDS

DEB-TACE, cTACE, partition survival model, cost-effectiveness analysis, hepatocellular carcinoma

Introduction

Primary Hepatic Carcinoma (PHC) is a malignant tumor of the digestive system with a high mortality rate worldwide. Global Cancer Statistics 2020 is a statistical report on cancer worldwide, published jointly by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO). The report pointed out that in 2020, there were 19.3 million new cancer cases worldwide and 10 million deaths. Among them, primary liver cancer accounts for approximately 906,000 new cases and 830,000 deaths, making it the sixth most common malignancy and the third leading cause of death worldwide (1). In 2015, a cancer statistic about China showed that liver cancer had the fourth highest incidence rate and the second highest mortality rate (after lung cancer), with an estimated 370,000 new cases and 326,000 cancer-related deaths (2). Hepatocellular carcinoma (HCC) is the main type of PHC, accounting for about 75–85% of all cases. In Northeast Asia and Southeast Asia, including China, Indonesia and South Korea, Hepatitis B is the most important factor in causing HCC (3). In particular, as the country with the heaviest hepatitis B burden in the world, nearly half of the new cases of liver cancer patients in the world come from my country. The annual cost is 43,310.148 yuan. With the increase of laboratory fees, operation fees and inspection fees, the treatment costs of patients are increasing year by year, causing a heavy economic burden to patients (4).

Radical therapy such as surgical resection is the main treatment for early stage HCC, while hepatic artery embolization, systemic chemotherapy, and molecular targeted therapy are the main treatments for intermediate and advanced HCC (5, 6). Because the onset of HCC is relatively insidious and has no obvious early signs, it is often diagnosed at an advanced stage. At this time, the most traditional treatment methods such as surgical resection have not achieved the best results, and the prognosis is poor and the mortality rate is high (7). Transcatheter arterial chemoembolization (TACE) is currently the most widely used clinical interventional method for mid-stage HCC (8). In 2020, the Chinese Society of Clinical Oncology pointed out in the *"Guidelines for the Diagnosis and Treatment of PHC 2020"* that TACE can be used as a first-line therapy for advanced unresectable HCC. According to the different embolic agents, TACE is divided into conventional TACE (cTACE) and Drug-eluting Beads TACE (DEB-TACE) (9). cTACE is an emulsion made of lipiodol as an embolic agent, and a mixture of chemotherapy drugs and lipiodol is injected into the artery supplying the tumor. Simultaneous embolization of blood vessels, treatment of tumor necrosis through cytotoxicity and ischemia (10). However, due to the fluidity of lipiodol, the chemotherapeutic drugs cannot be accurately released around the tumor, which reduces the local effective concentration and action time of the chemotherapeutic drugs (11). DEB-TACE is a new embolization technology using drug-loaded microspheres as embolizing agent, which can accurately and permanently embolize arterial vessels and target cancer cells. It uses the ion exchange mechanism to controllably and slowly release chemotherapeutic drugs to achieve continuous drug delivery and permanent embolization, and to increase the local intratumoral drug concentration. Thus, the concentration of chemotherapeutic drugs in the systemic blood circulation is reduced, and the systemic toxicity to the human body is reduced (12).

Compared with cTACE, the drug-loaded microspheres used in DEB-TACE are expensive. In 2016, Cucchetti A et al. constructed a Markov model to compare the cost of treatment and the therapeutic effect obtained by patients after cTACE and DEB-TACE treatment, respectively (13). The results show that DEB-TACE is more cost-effective than cTACE. However, no incremental analysis of costs and effects was conducted in the study, and the results obtained have certain limitations. Currently, there is no economic evaluation of these two treatments in China. Therefore, from the perspective of the medical and health system, this paper conducts a cost-effectiveness analysis of DEB-TACE and cTACE in the treatment of HCC, and provides decision-making suggestions for the treatment of clinical HCC.

Materials and methods

Clinical data

A total of 89 patients with HCC who met the inclusion criteria in the interventional treatment department of the Cancer Hospital Affiliated to the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) from 2019 to 2020 was retrospectively analyzed, including 40 in the DEB-TACE group and 49 in the cTACE group. The experimental group was treated with drug-loaded microsphere embolic agent for DEB-TACE, and the control group was treated with lipiodol for cTACE.

Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with liver cancer by imaging and pathological examinations; (1) aged ≥18 years; (3) Barcelona Clinic Liver Cancer (BCLC) stages A to C; (4) liver function Child-Pugh grade is A or B; (5) Eastern Cooperative Oncology Group performance status (ECOG PS) score is 0–2; (6) No other disease affecting survival, survival >3 months; (7) No other treatment was performed before surgery.

Exclusion criteria: (1) Child-Pugh C grade of liver function; (2) Multiple tumor metastases throughout the body; (3) The existence of hepatic artery-portal venous fistula and hepatic artery-hepatic venous fistula.

The baseline characteristics of the patients are shown in Table 1.

TABLE 1 Baseline characteristics of the patient.

	DEB-TACE	cTACE	P
Patient (case)	40	49	
Gender (Male/Female)	12905	14855	0.474
Age (years)	56.0±9.24	59.15±9.40	0.15
Pathological diagnosis			
HBV	30	30	0.594
Others	10	10	
Child-Pugh			
A	35	47	0.266
B	4	2	
BCLC			
A	0	13	1
B	31	31	
C	9	6	
ECOG PS			
0	13	24	0.116
1	27	25	

HBV, Hepatitis B; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.

Interventions

Relevant tests and examinations were performed before admission, including biochemistry, blood routine, coagulation routine, quantitative detection of hepatitis B virus DNA amplification, tumor marker screening materials, CT and MR. Interventional therapy was performed after the patient signed the informed consent to exclude the contraindication of interventional therapy.

In the DEB-TACE group, microspheres loaded with epirubicin or raltitrexed were selectively injected into the blood vessels of the tumor for embolization. When the tumor diameter was <7 cm, drug-loaded microspheres of 100–300 μm were used; when the tumor diameter was >7 cm Then use 300–500 μm drug-loaded microspheres. Drug-loaded microspheres are divided into domestic Calli Spheres drug-loaded microspheres and imported DCB drug-loaded microspheres. In the cTACE group, epirubicin or raltitrexed emulsion mixed with lipiodol was injected under fluoroscopy monitoring for embolization. In addition to receiving interventional therapy for intervention, patients can take targeted therapy drugs as needed. If tumor progression is found, targeted drugs need to be replaced for second-line targeted drugs or immunotherapy.

Survival analysis

The primary endpoints in the survival analysis were PFS and OS. During the follow-up period, PD and death were observed as the outcomes of PFS and OS, respectively, and the outcomes of patients lost to follow-up were listed as censored. The time of outcome events in the two groups was counted. In the DEB-TACE group, 16 patients had disease progression and 10 died. The longest survival time was 26.23 months and the shortest was 2.67 months. In the cTACE group, a total of 26 patients had tumor progression and 16 patients died, of which the longest survival time was 28.47 months and the shortest was 4.27 months.

The Kaplan-Meier (K-M) method was used to perform survival analysis of the outcome and event schedules of patients in the DEB-TACE and cTACE groups (Supplementary Tables 1, 2) using SPSS. According to the calculation, the median PFS of patients in the DEB-TACE group was 14.20 months (95% CI 13.316–15.084), and it was 14.43 months (95% CI 9.162–19.698) in the cTACE group. There was no significant difference in disease progression ($P = 0.728$). In addition, the mean survival time of DEB-TACE group and cTACE group were 19.18 ± 1.34 and 20.82 ± 1.42 months, respectively, and the median OS was 21.27 months (95% CI 15.718–26.822) and 24.6 months (95%), respectively, CI 17.607–31.593), and the Log-Rank test showed that there was no significant difference in the overall survival rate between the two groups ($P = 0.411$). The K-M curves of PFS and OS of the two groups of patients are shown in Figures 1, 2, respectively.

Model structure

Partition survival models (PSM) belong to the category of Markov models and are often used for economic evaluation of tumors. Compared with the Markov model, the PSM does not require a hypothetical estimate of the transition probability from one healthy state to the next, but by partitioning the raw survival data or the progression-free survival curve and the overall survival curve, Obtaining the specific number or proportion of individuals in each health state avoids the influence of model assumptions on research results (14). Therefore, the PSM is used for cost-effectiveness analysis. The PSM is usually divided into three health states: PFS, disease progression (PD), and Death, as shown in Figure 3 (15). Based on real-world clinical data, this paper can directly obtain the number of patients with HCC in the three health states of PFS, PD and death, and then obtain the corresponding health output and cost. Assuming that all patients were in the PFS stage at the start of the study, the final status of all patients was death. Building a partition survival model for cost-effectiveness analysis is to make decisions based on the results of incremental analysis, mainly calculating the Incremental Cost Effectiveness Ratio (ICER), using ICER to represent the cost of each additional quality-adjusted life years (QALY) (16). Calculated as follows:

$$ICER = \frac{C_1 - C_2}{E_1 - E_2} \quad (1)$$

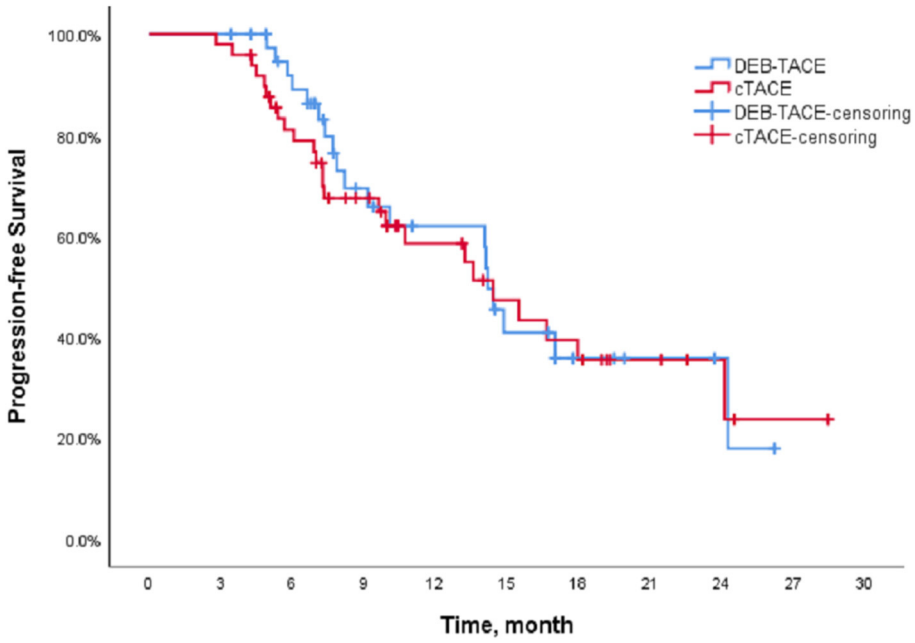

FIGURE 1
Progress free survival of the DEB-TACE and cTACE groups.

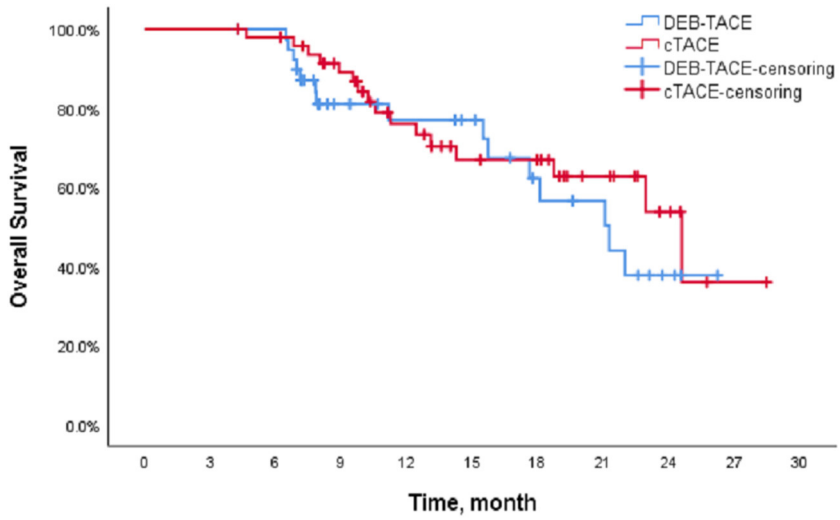

FIGURE 2
Overall survival of the DEB-TACE and cTACE groups.

Through follow-up, the disease progression and survival of patients during the follow-up period can be known. In order to simulate the entire life cycle of patients, it is necessary to fit the survival of patients. The individual patient data were analyzed using the surveyHE data package in the R language, and the Log-normal parameter distribution was obtained as the best fitting model (17). The parameters of the log-normal parametric distribution were calculated to yield the meanlog (μ) and sdlog (σ) (18) (Table 2). Then, the μ and σ values calculated by the two groups of PFS and OS were substituted into the survival function of the Log-normal parameter distribution for fitting calculation. Calculations found that when the simulation time was 10 years, the mortality rate of patients in both groups exceeded 98%, so the study time was set to 10 years.

FIGURE 3
Partition survival state transition model.

TABLE 2 Parameter values of Log-normal parameter distribution.

Group	PFS		OS	
	μ	σ	μ	σ
DEB-TACE	2.741576	0.786687	3.227158	0.742339
cTACE	2.59371	0.804045	3.11888	0.719892

The partition survival model (PSM) was constructed using Microsoft EXCEL.

Model parameters

Cost

Costs were collected by going to the Interventional Radiology Department of Cancer Hospital Affiliated to the University of Chinese Academy of Sciences. The costs of treatment during the follow-up period of the 89 patients included were collected one by one. The required direct medical costs include registration fees, diagnosis and treatment fees, inspection fees, hospitalization fees, interventional surgery fees (DEB-TACE and cTACE and other treatment methods), drug fees and other costs. After interventional surgery, daily liver protection drugs and anticancer drugs need to be taken orally; if they have HBV, they need to take anti-HBV drugs continuously; Sorafenib and lenvatinib are mainly used for first-line treatment, and regorafenib and tislelizumab are used for second-line treatment, all of which belong to drug costs. In addition to this, the management costs of adverse reactions of grade 3 to 4 after treatment need to be considered, as shown in Table 3.

There are certain differences in the frequency or dosage of interventional therapy and the use of targeted drugs and/or immunotherapy for each patient. The cost of treatment and medication and the management cost of adverse reactions were integrated for the two groups of patients with PFS and PD, respectively. These adverse reactions were alleviated by drug treatment, therefore, this cost was only considered in the first cycle in the partitioned survival model.

However, the sample size of the two groups of patients is small. If the cost is directly calculated to take the mean or median, the applicability of the cost cannot be objectively reflected. Therefore, the bootstrap method was used here to calculate the total cost of 1,000 samples consumed by patients in PFS and PD health status, and the corresponding cost mean and 95% confidence interval were obtained (19). The sampling results show that the PFS cost of a single cycle DEB-TACE group is 599.97 $, the PD cost is 162.75 $, and the AEs management cost is 3.28 $. The PFS cost, PD cost and AEs management cost of cTACE group were 353.88, 247.64 and 3.84 $, respectively.

TABLE 3 The main unit cost.

Medical project	Unit cost/$
Admission check/follow-up check	162.11
Basic hospital expenses	25.8
Interventional treatment costs	
DEB-TACE	5592.4
cTACE	2624.4
Post-operative maintenance costs	75.97
Drug cost	
Bicyclool	9.59
Ganfule capsule	14.62
Compound Glycyrrhizin Tablets	4.17
Ci Dan capsule	21.3
Tenofovir Disoproxil Fumarate Tablets	1.7
Sorafenib	204.19
Renvatinib	483.26
Regorafenib	720.33
Tislelizumab	325.16
Adverse event management costs	
Morphine Hydrochloride Injection	0.53
Metoclopramide hydrochloride injection	0.35
Ondansetron Hydrochloride Tablets	15.8
Indomethacin suppository	0.94
Lactulose Oral Solution	4.77
Nitroglycerin Sublingual Tablets	0.59

Utility

In this study, the EQ-5D-5L questionnaire was distributed to investigate the health utility value of patients in PFS and PD health status and treated with DEB-TACE or cTACE. A total of 152 questionnaires were collected (20). Among them, the DEB-TACE group had 35 PFS health status and 29 PD health status; the cTACE group had 56 and 32 PD health status, respectively. During the investigation, the negative effect of postoperative adverse reactions has been reflected in the questionnaire results, so it will not be considered again. Use the health utility score system suitable for the Chinese population studied by Luo et al. to calculate the utility value, and then use bootstrap to sample 4 groups of samples 1,000 times (21). Similarly, for small sample sizes, bootstrap is used to sample 1,000 samples from 4 groups.

TABLE 4 Summary of costs and utility values.

Parameter	Value	Lower	Upper	Distribution
C_DEB-TACE_PFS	6339.96	5071.96	7607.95	Gamma
C_DEB-TACE_PD	3154.42	2523.54	3785.31	Gamma
C_cTACE_PFS	5528.42	4422.74	6634.1	Gamma
C_cTACE_PD	2274.2	1819.36	2729.04	Gamma
C_DEB-TACE_AE	3.28	2.62	3.93	Gamma
C_cTACE_AE	3.84	3.07	4.61	Gamma
U_DEB-TACE_PFS	0.1271	0.1144	0.1399	Beta
U_DEB-TACE_PD	0.1192	0.1073	0.1312	Beta
U_cTACE_PFS	0.1177	0.106	0.1295	Beta
U_cTACE_PD	0.1145	0.103	0.1259	Beta
U_Dead	0	0	0	Beta
Discount	0.75%	0.30%	1.20%	

The mean utility values for PFS and PD in the final output DEB-TACE group were 0.8773 (95% CI: 0.8410, 0.9109) and 0.8228 (95% CI: 0.7902, 0.8536), respectively. The mean utility values for PFS and PD health status in the cTACE group were 0.8123 (95% CI: 0.7911–0.8345) and 0.7898 (95% CI: 0.7560–0.8197), respectively.

Discount

In order to compare and analyze the cost and health output at the same time node, according to the suggestion on the value of the discount rate in the evaluation of pharmacoeconomics in my country, the cost and health output will be discounted at an annual discount rate of 5.2% from the second year (22). All parameter values are shown in Table 4.

Sensitivity analysis

Considering the uncertainty of medical cost, we assumed the upper and lower bounds of medical cost to be ±20%. According to literature reports, the discount rate should be in the range of 2.1% to 8.3% for sensitivity analysis (22). One-way sensitivity analysis and probabilistic sensitivity analysis were used to explore the influence of each parameter on the model. Substitute the upper and lower limits of each parameter into the model for One-way sensitivity analysis and calculation; Probabilistic sensitivity analyses were performed using Monte Carlo simulations (N = 1,000 iterations) to analyze which drugs had a cost-effectiveness advantage at a willingness-to-pay (WTP) threshold. And the cost-effectiveness acceptability curve was used to estimate the optimal treatment measures in different WTP ranges. According to the recommendation of the *"China Pharmacoeconomic Evaluation Guidelines (2020)"*, the ICER value is compared with the per capita gross domestic product (GDP) three times that of my country in 2020. Statistics from the National Bureau of Statistics show that my country's per capita GDP in 2020 will be 10,499.74 $. Therefore, WTP is set to 31499.23 $/QALYs.

TABLE 5 Result of cost-effectiveness analysis.

Group	Cost/$	Utility/QALY	Incremental cost/$	Incremental Utility/QALY	ICER
DEB-TACE	94901.92	14.1032			
cTACE	73823.61	12.4058	43792.46	1.6975	11875.62

Result

Cost-effectiveness analysis

The partition survival model was simulated for 10 years. The results are shown in Table 5. The cumulative cost of the DEB-ATCE group was 94,901.92 $, and the cumulative effect was 14.1032 QALYs; the cumulative cost and cumulative effect of the cTACE group were 73,823.61 $ and 12.4058 QALYs, respectively. Compared with the cTACE group, the incremental cost of the DEB-TACE group was 43,792.46 $, and the incremental effect was 1.6975 QALYs. The ICER was calculated to be 11,875.62 $/QALYs, which was lower than the WTP threshold (31,499.23 $/QALYs), indicating that DEB-TACE treatment of HCC patients is economical.

Sensitivity analysis

One-way sensitivity analysis

It can be seen from Figure 4 that the PFS utility value of the DEB-TACE group and the cTACE group is the biggest factor affecting the stability of the model. The cost changes of the other two groups of PFS states also have a certain impact, and the changes of other parameters have little effect. Among them, the change of the PFS utility value of the DEB-TACE group makes the output EV maximum value of 38678.29 $/QALY, which is greater than the WTP threshold (31499.23 $/QALYs).

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed using 1,000 iterative Monte Carlo simulations, and Monte Carlo scatter plots and cost-effectiveness acceptability curves were drawn. It can be seen from Figure 5 that the incremental cost-effect scatter points are distributed on both sides of the WTP threshold. Comparing it with the WTP threshold, 92% of the incremental cost-effect scatter points are located on the lower right side of

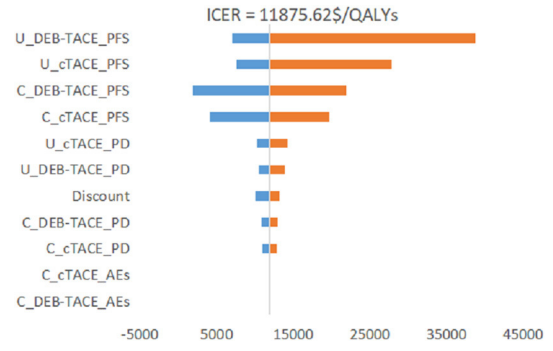

FIGURE 4
Tornado chart of one-way sensitivity analysis.

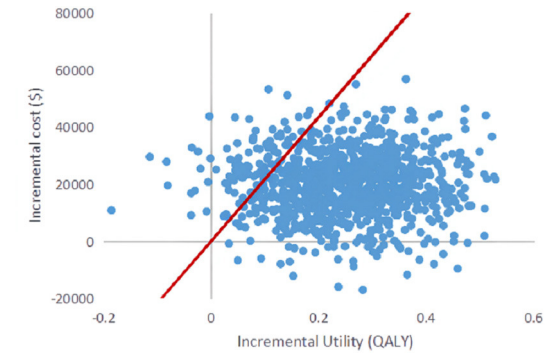

FIGURE 5
Scatter plot of incremental cost-effectiveness.

the WTP threshold. That is to say, the probability of DEB-TACE treatment of HCC patients is more cost-effective than 92%. In addition, the probability of the cost-effectiveness of the cTACE group gradually decreased with the increase of the WTP threshold. When the WTP value was <32,609.25 $/QALY, the cTACE group was more cost-effective than the DEB-TACE group. With the increase of the WTP threshold, the DEB-TACE group has an increasing probability of cost-effectiveness. When the WTP value is >65,218.50 $/QALY, the DEB-TACE group has a cost-effective probability of close to 90% (Figure 6).

Discussion

The results of basic cases show that the BCLC staging of patients in the DEB-TACE group and the cTACE group is significantly different, and doctors usually recommend patients in stage A or B to choose cTACE for treatment. However, because the lipiodol treated by cTACE is liquid, it cannot completely block the blood flow, and the lipiodol in the tumor will gradually decrease with the blood flow, which cannot achieve the best therapeutic effect. The drug-loaded microspheres in DEB-TACE can be injected into the tumor feeding artery through the catheter to achieve sustained release of chemotherapeutic drugs, and permanently embolize the hepatic artery to obtain a higher tumor response rate (23). Therefore, when the patient's tumor condition is poor and the BCLC stage is B or C, DEB-TACE treatment is preferentially recommended. This may be the reason why the DEB-TACE group has no advantage in median PFS and median OS.

The cumulative cost and cumulative utility of the DEB-TACE group were greater than those of the cTACE group, with the cumulative cost of the two groups being 94,901.92 and 73,823.61 $, respectively; the cumulative utility was 14.1032 QALYs and 12.4058 QALYs, respectively. From this, it can be concluded that the incremental cost is 43,792.46 $, and the incremental effect is 1.6975 QALYs. Through the cost-effectiveness analysis method, the ICER value can be obtained to be 11,875.62 $/QALYs. In this paper, the willingness to pay threshold is set to be three times the per capita GDP of my country, that is, WTP is 31,499.23 $/QALYs. Comparing the ICER value with the WTP threshold, ICER<WTP indicates that the DEB-TACE group is economical.

Cucchetti A et al. (13) included 5 randomized controlled trials and 11 observational studies with a total of 1,860 patients with hepatocellular carcinoma and constructed a Markov model to assess the cost and efficacy of cTACE and DEB-TACE from a healthcare provider's perspective. The study results showed that the total cost of cTACE treatment was 10,389 euros, and the effect was 3.3 QALY; the total cost of DEB-TACE treatment was 11,418 euros, and the effect was 4.0 QALY. DEB-TACE is more cost-effective than cTACE when around 2,000–3,500 EUR/QALY is the minimum willingness to pay. This result is similar to that of our study, but ICER was not calculated and a sensitivity analysis was missing.

Since there are uncertainties in the methodology, cost, utility value, and discount rate in the model, sensitivity analysis is required for these uncertainties. Through the One-way sensitivity analysis, it can be seen that the two factors that have the greatest impact on the model are the utility value of the PFS health status of the DEB-TACE group and the cTACE group, followed by the cost of the PFS health status stage of the two groups. It can be seen from the incremental effects of the two groups that the DEB-TACE group has no obvious advantage in the utility value of the PFS health state. When the utility value is at the lowest value within the fluctuation range, the ICER value increases to 38,678.29 $/QALYs is greater than the WTP threshold, That is to say, it is not economical to perform DEB-TACE intervention if the patient is in a healthy state of PFS without good health. In addition, the ICER of the cTACE group PFS health status and the cost of the two groups of PFS health statuses within the set value range are smaller than WTP, which will not affect the stability of the model. In addition, using probability sensitivity analysis to sample the uncertainty

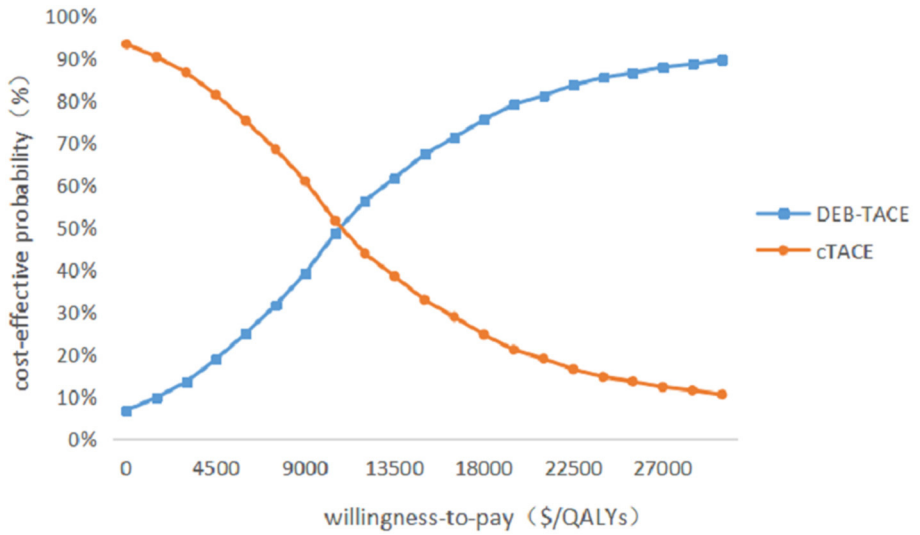

FIGURE 6
Cost-effectiveness acceptability curve.

parameters for 1,000 iterations of Monte Carlo simulation, and output the incremental cost-effect scatterplot, we can see that when the WTP is 31,499.23 $/QALYs, DEB-TACE is effective in the treatment of HCC. The probability of being economical is 92%. According to the cost-effectiveness acceptable curve, when the WTP is <32,609.25 $/QALYs, the cTACE group is more cost-effective than the DEB-TACE group; when the WTP is >32,609.25 $/QALYs, the DEB-TACE group increases with the WTP. The probability of being cost-effective gradually approaches 90%. Therefore, DEB-TACE is more economical while ensuring the health of patients.

The limitations of this paper have the following three points. First, on the screening of clinical patients. In this paper, the cases of real-world patients are collected as data, but retrospective screening will have a certain bias, and patients may have incomplete case reports during the real treatment process, which will have a certain impact on the results. Therefore, bias needs to be reduced by expanding the sample size. Second, on the fitting of survival data. In this paper, in order to simulate the 10-year survival of patients, the actual progression-free survival and overall survival of the patients were analyzed by parametric method, and the survival data were fitted according to the optimal fitting parameter distribution model. There are some discrepancies in the data. Therefore, it is necessary to obtain specific survival data of patients through long-term follow-up. Third, about the measurement of utility value. In this paper, the EQ-5D-5L health scale is used to measure the health utility value of patients in the form of a questionnaire. However, due to insufficient sample size, bootstrap is used to perform 1,000 round-trip sampling to obtain the final value, which has a certain impact on the research results. Therefore, more scales need to be collected to be representative.

Conclusion

In practical clinical applications, DEB-TACE is a treatment method that is preferentially recommended for patients with advanced hepatocellular carcinoma. Although the drug-loaded microspheres used in DEB-TACE are more expensive for embolization, the cost-effectiveness analysis can conclude that DEB-TACE is a more economical treatment option.

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/s.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GuolS provided resources and was in charge of project management. JW was in charge of data investigation and original text writing. XZ was in charge of data processing and validation. GuojS and ZD provided methodology, with GuojS overseeing the progress of the project. ZD was responsible for the final

original review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.963058/full#supplementary-material

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Factors associated with health care utilization and catastrophic health expenditure among cancer patients in China: Evidence from the China health and retirement longitudinal study

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Background: Cancer, the leading cause of mortality in China, is a significant burden on patients, their families, the medical system, and society at large. However, there is minimal data on health service utilization and catastrophic health expenditure (CHE) among cancer patients in China. The objective of this study was to identify factors associated with health care utilization and CHE in Chinese cancer patients.

Methods: The 2018 wave of a nationally representative dataset, the China Health and Retirement Longitudinal Study, was used in our study. Of 18,968 respondents recruited for the analysis, 388 were clinically diagnosed with cancer. CHE was defined as household health expenditure that exceeded 40% of non-food household expenses. A binary logistic regression model was used to identify the risks of cancer exposure among all participants, along with the likelihood of CHE in households with cancer patients at the 40% threshold. A negative binomial regression model was used to identify determinants of health service utilization among cancer patients.

Results: Contracting a family physician (incidence rate ratio IRR: 2.38, 1.18–4.77), Urban Employee Basic Medical Insurance (IRR: 4.02, 1.91–8.46, compared to the uninsured), Urban and Rural Resident Basic Medical Insurance (IRR: 3.08, 1.46–6.49, compared to the uninsured), and higher per-capita household consumption were positively associated with inpatient service utilization. Patients with a college education and above reported a greater number of outpatient visits (IRR: 5.78, 2.56–13.02) but fewer inpatient hospital days (IRR: 0.37, 0.20–0.67). Being diagnosed with a non-cancer chronic non-communicable disease was associated with an increased number of outpatient visits (IRR: 1.20, 1.10–1.31). Of the 388 participants, 50.1% of households had CHE, which was negatively correlated with a larger household size (odds ratio OR: 0.52, 0.32–0.86) and lower socioeconomic status [for quintile 5 (lowest group) OR: 0.32, 0.14–0.72].

Conclusions: The socioeconomic characteristics of cancer patients had a considerable impact on their healthcare utilization. Individualized and targeted strategies for cancer management should be implemented to identify high-risk populations and trace the utilization of care among Chinese cancer patients. Strategic purchasing models in cancer care and social health insurance with expanded benefits packages for cancer patients are crucial to tackling the cancer burden in China.

KEYWORDS

health care utilization, catastrophic health expenditure, factors, cancer, China

Introduction

Cancer is a leading cause of mortality worldwide and a substantial impediment to an optimal expected lifespan (1). There were an estimated 4.5 million new cancer cases and 3 million cancer mortalities in 2020 in China, which with the largest population in the world accounts for the highest percentage of total new cancer cases (∼23.7%) and mortalities (30.2%) worldwide (2). Cancer incidence and mortality have been rapidly rising in China (2) due to an aging population and cancer-associated lifestyle behaviors (3). Cancer represents a significant burden on patients, their families, the medical system, and society at large.

Aiming to alleviate the burden of non-communicable diseases including cancer, China initiated comprehensive healthcare reform in 2009 committed to delivering equitable accessibility to primary healthcare services with appropriate quality and financial risk protection for all citizens by strengthening healthcare infrastructure, broadening public health insurance coverage, and reforming the healthcare delivery system (4). The Urban Resident Basic Medical Insurance (URBMI) and New Rural Cooperative Medical Scheme (NRCMS) were merged into the Urban and Rural Resident Basic Medical Insurance (URRBMI) in early 2016, which enhanced the health insurance system's ability to pool financial risks for cancer patients (5). Universal Health Coverage improved the availability and utilization of health services (6), although deficiencies remain in quality, efficiency, spending, and patient satisfaction (4). Cancer patients experienced inequitable access to cancer care due to inequalities in health financing, particularly in rural China (7).

Accessing healthcare services can improve patient health but potentially lead to catastrophic health expenditure (CHE), which we defined as the proportion of out-of-pocket (OOP) spending exceeding 40% of household non-food expenses (8). Delivering high-quality care and protecting families from CHE are widely accepted desirable objectives of the healthcare system. These objectives assume that we understand what health system characteristics benefit patients and the factors that affect health service use and CHE. The demand for cancer care spans from the time of diagnosis to the terminal phase of life, making cancer patients particularly susceptible to CHE. Identifying particularly vulnerable groups *via* susceptibility factors and household characteristics may steer cancer patients to utilize appropriate healthcare services and prevent CHE attributable to cancer care.

Previous studies have highlighted issues related to health service use and economic burden among patients with non-communicable diseases, such as hypertension, diabetes, as well as patients with multiple chronic diseases (9–12). However, factors associated with cancer care utilization and CHE in China remain unclear. Health service use reflects individual behaviors related to obtaining health services to meet their health demands. Existing literature has shown that health service use is affected by individual demographic and socioeconomic factors such as age, gender, marital and employment status, education level, insurance, income (13), and health care system characteristics such as the availability, affordability, and accessibility of drugs and healthcare services (14). Previous studies have reported that health service use among cancer patients differs by sex, age, residence, employment, education, health insurance, household income, tumor site, and tumor stage (15–18). A study of rural-urban disparities among Chinese cancer patients found that rural cancer patients utilized fewer screening and treatment services than urban patients, and that care disparities were significantly influenced by socioeconomic and clinical characteristics (15). Another study on socioeconomic disparities in cancer treatment in China found that a higher proportion of patients with high socioeconomic status underwent surgery and chemotherapy than those with low socioeconomic status (19). Further, socioeconomic status was identified as the most important determinant of treatment modalities for esophageal cancer (16). Evidence from Beijing, China indicated that inpatient costs were 58.6% of total cancer treatment costs, with anti-cancer medication costs accounting for the majority of this burden. Total costs were highly associated with age, tumor type, hospital level, and payment system (20). More than 75% of cancer patients were reported to experience death and catastrophic payments within 1 year in Southeast Asia,

especially those without health insurance (21). Other studies performed in China found that CHE occurred in 78.1% of the families of lung cancer patients and 66.28% of the families of breast cancer patients, representing ultra-high OOP expenditures on healthcare in these patient groups (22, 23). Health insurance is thought to be effective against OOP spending, but large disparities exist in the benefit packages between regions with different levels of economic development (24). The Urban Employee Basic Medical Insurance (UEBMI) provides the highest reimbursement cap of the available governmental options.

Reliable predictors of healthcare utilization and CHE are needed to provide further insight for policy makers. This is particularly important now as the cancer spectrum in China transitions from a developing country to a developed one due to its dynamic socio-economic development (25). Efficient cancer control and management systems should be designed and optimized to fit this transition. This work utilized a nationally representative database to investigate factors pertinent to cancer incidence, health service utilization, and CHE among cancer patients in China. Findings may be useful in the development and refinement of individualized and targeted policies to relieve the cancer burden in China.

Methods

Data source

Data used for the current study were derived from the China Health and Retirement Longitudinal Study (CHARLS) in 2018. The CHARLS is a nationwide representative longitudinal survey performed by the National Development Institute of Peking University to serve the needs for scientific and policy research on aging issues by concentrating on Chinese people aged 45 and older and their families. CHARLS included variables related to the demographics, lifestyle habits, health status, health care, household income and consumption, and health insurance of both urban and rural residents (26). CHARLS included 150 districts and 450 rural/urban communities in 28 provinces with a multiple-stage stratified random sampling method to ensure a nationally representative sample. A total of 19,507 respondents were involved in the 2018 wave, which included 392 individuals who were clinically diagnosed with cancer. We eliminated respondents with missing health information or household consumption data, leaving a sample of 18,968 individuals (388 cancer patients).

Indicators

In CHARLS, all respondents were interviewed if they self-identified as clinically diagnosed with cancer through the following question: "Have you been diagnosed with cancer or malignant tumor (excluding minor skin cancers) by a doctor?" The cancer site was recorded. Respondents with minor skin cancers were excluded from the questionnaire as their cancer survivorship care demands tended to be relatively mild (18).

The number of monthly outpatient visits and annual inpatient days were used to measure health care utilization among the cancer patients. In CHARLS, individuals self-reported their utilization of outpatient and inpatient care through the questions: "How many times did you visit/been visited by medical facilities for outpatient care during the last month?" and "How many days did you spend in the hospital during the past year?" CHARLS gathered information on self-reported medical expenditure and total household expenditure for each family. Medical expenditure referred to the patient's outpatient expenses over the past month multiplied by 12 and inpatient expenses over the past year, including OOP expenditure and the portion reimbursed by health insurance. Regarding the total annual household expenditure, we multiplied monthly household expenses on rent, food, clothing, communication, water and electricity, fuel, services, education, traveling, entertainment, beauty, donations, daily necessities, and healthcare by 12.

Annual per-capita household consumption expenditure was adopted to gauge socioeconomic status as household consumption captured the actual living situation of each household (8). We identified five socioeconomic groups using quintiles of annual per-capita household consumption expenditure. Socioeconomic quintiles were established within each county or district and then combined across all sampled counties and districts to reflect the variable level of economic development across the targeted areas.

We defined an OOP payment on health care to be catastrophic if it surpassed 40% of the household's affordability, defined as non-food household consumption spending (8). Based on previous studies, CHE is a binary variable (8). We determined if CHE occurred by calculating the *Ei*:

$$Ei = \begin{cases} 0, \frac{oop}{xi - f(x)} \leq Z \\ 1, \frac{oop}{xi - f(x)} > Z \end{cases}$$

Where *oop* denotes direct medical expenses, deducting reimbursement by health insurance, i represents various households, x is total household consumption expenditure, $f(x)$ is food expenditure, and Z is the CHE threshold, which is set at 40%.

Variables

We considered the following individual-level and household-level variables to be covariates: gender (male and female); age (45∼65 and >65 years); household registration

(agriculture and non-agriculture); education level (primary school and below, secondary school, and college and above); marital status (married, unmarried, divorced, and widowed); employment status (employed, unemployed, jobless, and retired); physical examination (yes vs. no); family physician (contracted vs. non-contracted); impoverishment status (impoverished vs. non-impoverished); household size (1∼2 and ≥3 members); sleep duration; number of chronic diseases; basic health insurance (uninsured, UEBMI, URRBMI, URBMI, NRCMS and the other); socioeconomic groups; and geographic region (east, central, west and northeast).

Statistical analysis

The sociodemographic characteristics of cancer patients were described using frequencies and percentages of categorical variables (e.g., education level, marital status, work status, health insurance, and region). A binary logistic regression model was created to identify the risks of cancer among all participants and CHE in the households of cancer patients. A negative binomial regression analysis was utilized to investigate correlations between demographic and socioeconomic variables and the number of outpatient visits and inpatient days among cancer patients. Odds ratios (OR) and incidence rate ratios (IRR) were quantified to measure the degree of correlations between each contributor and the dependent variables. A sensitivity analysis was performed to investigate the relationship between socioeconomic status quintiles and CHE exposure using the World Bank's various definitions of CHE thresholds, which were computed as OOP expenditures on healthcare of 25 and 40% of non-food household consumption expenditures (27). All statistical analyses were performed using SPSS V.26.0. A two-tailed $P < 0.05$ was considered significant.

Results

Sociodemographic characteristics of cancer patients

The descriptive sociodemographic statistics of 388 participants with clinically-diagnosed cancer in 2018 are shown in Table 1. A total of 153 (39.4%) respondents were male and 235 (60.6%) were female. Mean age was 63.9 years, with 214 (55.2%) participants 45–65 years old and 174 (44.8%) over 65 years old. Most participants were from rural areas (67.8% of total) and had only primary education or below (67.0% of total). Three hundred thirty (85.1%) participants were married, and 146 (37.6%) were employed. Regarding household size, 246 (63.4%) households with cancer patients had less than three people. The majority (372, 95.9%) of participants were enrolled in at least one type of public health insurance, with 221 (57.0%) participating in the NRCMS. A plurality (146, 37.6%) of participants were from eastern China, followed by its central (29.6%), western (26.8%), and northeastern (5.9%) regions.

TABLE 1 Sociodemographic characteristics of cancer patients in China, 2018.

Sociodemographic characteristics	Number	Percent (%)
Gender		
Male	153	39.4
Female	235	60.6
Age (years)		
45∼65	214	55.2
> 65	174	44.8
Household registration		
Agriculture	263	67.8
Non-agriculture	125	32.2
Education level		
Primary school and below	260	67.0
Secondary school	106	27.3
College and above	22	5.7
Marital status		
Married	330	85.1
Rest 1	58	14.9
Employment status		
Employed	146	37.6
Rest 2	242	62.4
Household size		
1∼2	246	63.4
≥3	142	36.6
Health insurance		
None	16	4.1
UEBMI	84	21.6
URRBMI	42	10.8
URBMI	15	3.9
NRCMS	221	57.0
Other†	10	2.6
Region		
West	104	26.8
Northeast	23	5.9
Central	115	29.6
East	146	37.6

Rest 1 denotes unmarried, divorced, and widowed; Rest 2 stands for unemployed, jobless, and retired; UEBMI, Urban Employee Basic Medical Insurance; URRBMI, Urban and Rural Residents Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance; NRCMS, New Rural Cooperative Medical Scheme; Other† represents government medical insurance.

Cancer incidence and associated factors

Overall cancer incidence among Chinese adults aged 45 and older in 2018 was 2.05% (388 of 18,968). Participants

in higher socioeconomic quintiles had a higher likelihood of reporting a cancer diagnosis compared than those with the lowest socioeconomic status [Quintile 4: OR = 2.46, 95% CI 1.69–3.59; Quintile 5 (highest): OR = 3.04, 95% CI 2.08–4.42]. The likelihood of cancer was higher among participants who lived in eastern China than those in western China (OR = 1.54, 95% CI 1.19–2.00). Compared to employed participants, those who were unemployed, jobless, or retired had a greater incidence of cancer (OR = 2.57, 95% CI 2.04–3.25). Compared with participants who had not had a physical examination, those who obtained a medical check-up had a higher probability of being diagnosed with cancer (OR = 1.32, 95% CI 1.07–1.63). The prevalence of cancer decreased among participants who slept longer (OR = 0.90, 95% CI 0.86–0.95), received a secondary education (OR = 0.76, 95% CI 0.58–0.98 compared with those who had a primary education or less), and were unmarried, divorced, or widowed (OR = 0.72, 95% CI 0.54–0.98, compared to those who were married) (Table 2).

TABLE 2 Cancer determinants among people aged 45 years and older in China, 2018.

Variables	Odds ratio (95% CI)	*P*-value
Gender (Ref. = male)		
Female	1.17 (0.94, 1.46)	0.147
Age (Ref. = 45∼65 years)		
> 65 years	0.98 (0.77, 1.25)	0.869
Household registration (Ref. = agriculture)		
Non-agriculture	1.17 (0.80, 1.71)	0.407
Education level (Ref. = primary school and below)		
Secondary school	0.76 (0.58, 0.98)	**0.037**
College and above	0.66 (0.39, 1.10)	0.107
Marital status (Ref. = married)		
Rest 1	0.72 (0.54, 0.98)	**0.036**
Employment status (Ref. = employed)		
Rest 2	2.57 (2.04, 3.25)	**< 0.001**
Sleep duration	0.90 (0.86, 0.95)	**< 0.001**
Physical examination (Ref. = no)		
Yes	1.32 (1.07, 1.63)	**0.010**
Family physician (Ref. = no)		
Yes	0.64 (0.35, 1.18)	0.151
Impoverished (Ref. = yes)		
Non-impoverished	0.84 (0.55, 1.27)	0.400
Household size (Ref. = 1∼2)		
≥3	0.97 (0.78, 1.21)	0.810
Basic health insurance (Ref. = uninsured)		
UEBMI	0.84 (0.46, 1.55)	0.584
URRBMI	0.83 (0.46, 1.50)	0.537
URBMI	0.53 (0.25, 1.14)	0.103
NRCMS	0.91 (0.54, 1.55)	0.737
Other†	1.23 (0.51, 2.97)	0.643
Socioeconomic group (Ref. = lowest)		
Quintile 2	1.38 (0.92, 2.07)	0.123
Quintile 3	1.21 (0.79, 1.83)	0.378
Quintile 4	2.46 (1.69, 3.59)	**< 0.001**
Quintile 5 (highest)	3.04 (2.08, 4.42)	**< 0.001**
Region (Ref. = west)		
Northeast	1.04 (0.66, 1.66)	0.855
Central	1.29 (0.99, 1.69)	0.064
East	1.54 (1.19, 2.00)	**0.001**

Rest 1 denotes unmarried, divorced, and widowed; Rest 2 stands for unemployed, jobless, and retired; UEBMI, Urban Employee Basic Medical Insurance; URRBMI, Urban and Rural Residents Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance; NRCMS, New Rural Cooperative Medical Scheme; Other† represents government medical insurance.

Factors associated with health care utilization

Factors associated with health care utilization and CHE among cancer patients are presented in Table 3. An increasing number of non-communicable diseases (IRR = 1.20, 95% CI 1.10–1.31) and contracting a family physician (IRR = 2.72, 95% CI 1.01–7.35) were associated with more frequent outpatient visits. Compared with those with a primary education and below, patients with college education and above reported more frequent outpatient visits (IRR = 5.78, 95% CI 2.56–13.02) but fewer inpatient hospital days (IRR = 0.37, 95% CI 0.20–0.67). Fewer inpatient hospital days were also found to be positively associated with patients who were female (IRR = 0.55, 95% CI 0.43–0.71), non-agricultural (IRR = 0.25, 95% CI 0.14–0.44), unmarried, divorced, or widowed patients (IRR = 0.57, 95% CI 0.40–0.82), and from eastern China (IRR = 0.68, 95% CI 0.49–0.93). Fewer outpatient visits were also positively associated with patients in families of more than 2 persons (IRR = 0.53, 95% CI 0.34–0.83) and those enrolled in URRBMI (IRR = 0.30, 95% CI 0.10–0.86). Longer inpatient hospital stays were positively associated with patients who were unemployed, jobless, or retired (IRR = 3.37, 95% CI 2.56–4.44), contracted with a family physician (IRR = 2.38, 95% CI 1.18–4.77), in a household of more than two members (IRR = 1.51, 95% CI 1.16–1.96), and enrolled in UEBMI (IRR = 4.02, 95% CI 1.91–8.46), URRBMI (IRR = 3.08, 95% CI 1.46–6.49). The likelihood of inpatient service use decreased substantially with economic status. The number of inpatient hospital days reported among patients in other socioeconomic quintiles were 0.23 (IRR = 0.23, 95% CI 0.16–0.33), 0.11 (IRR = 0.11, 95% CI 0.08–0.16), 0.10 (IRR = 0.10, 95% CI 0.06–0.15), and 0.07 (IRR = 0.07, 95% CI 0.05–0.11) times as many as those in the highest socioeconomic quintile, respectively.

TABLE 3 Factors associated with health care utilization and catastrophic health expenditure among cancer patients in China, 2018.

	Number of outpatient visits		Inpatient hospital days		Catastrophic health expenditure	
	Incidence rate ratio (95% CI)	*P*-value	Incidence rate ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Number of non-communicable diseases	1.20 (1.10, 1.31)	**< 0.001**	1.06 (1.00, 1.12)	0.057	1.10 (0.98, 1.24)	0.105
Gender (Ref. = male)						
Female	1.27 (0.84, 1.92)	0.265	0.55 (0.43, 0.71)	**< 0.001**	0.65 (0.39, 1.08)	0.094
Age (Ref. = 45∼65 years)						
> 65 years	1.58 (1.01, 2.47)	**0.045**	1.20 (0.90, 1.60)	0.206	1.46 (0.86, 2.47)	0.161
Household registration (Ref. = agriculture)						
Non-agriculture	0.64 (0.28, 1.48)	0.294	0.25 (0.14, 0.44)	**< 0.001**	0.46 (0.16, 1.20)	0.110
Education level (Ref. = primary school and below)						
Secondary school	1.29 (0.79, 2.13)	0.312	0.75 (0.55, 1.03)	0.075	1.24 (0.68, 2.26)	0.473
College and above	5.78 (2.56, 13.02)	**< 0.001**	0.37 (0.20, 0.67)	**0.001**	0.52 (0.15, 1.78)	0.298
Marital status (Ref. = married)						
Rest 1	0.68 (0.38, 1.22)	0.194	0.57 (0.40, 0.82)	**0.003**	1.20 (0.60, 2.39)	0.613
Employment status (Ref. = employed)						
Rest 2	1.40 (0.90, 2.18)	0.138	3.37 (2.56, 4.44)	**< 0.001**	2.68 (1.59, 4.53)	**< 0.001**
Physical examination (Ref. = no)						
Yes	0.95 (0.63, 1.44)	0.813	0.81 (0.62, 1.04)	0.098	0.80 (0.49, 1.31)	0.376
Family physician (Ref. = no)						
Yes	2.72 (1.01, 7.35)	**0.048**	2.38 (1.18, 4.77)	**0.015**	0.92 (0.23, 3.71)	0.910
Impoverished (Ref. = yes)						
Non-impoverished	1.95 (0.77, 4.93)	0.159	1.31 (0.82, 2.10)	0.265	0.43 (0.16, 1.17)	0.099
Household size (Ref. = 1∼2)						
≥3	0.53 (0.34, 0.83)	**0.006**	1.51 (1.16, 1.96)	**0.002**	0.52 (0.32, 0.86)	**0.010**
Health insurance (Ref. = uninsured)						
UEBMI	0.46 (0.16, 1.30)	0.143	4.02 (1.91, 8.46)	**< 0.001**	0.38 (0.10, 1.43)	0.153
URRBMI	0.30 (0.10, 0.86)	**0.025**	3.08 (1.46, 6.49)	**0.003**	1.61 (0.40, 6.46)	0.501
URBMI	0.42 (0.09, 1.99)	0.277	1.93 (0.74, 5.04)	0.181	0.80 (0.15, 4.39)	0.802
NRCMS	0.55 (0.23, 1.32)	0.181	1.21 (0.63, 2.32)	0.564	0.64 (0.19, 2.18)	0.472
Other†	0.21 (0.04, 1.09)	0.063	1.90 (0.64, 5.58)	0.246	0.60 (0.09, 3.86)	0.588
Socioeconomic group (Ref. = highest)						
Quintile 2	0.60 (0.35, 1.05)	0.074	0.23 (0.16, 0.33)	**< 0.001**	0.35 (0.17, 0.74)	**0.006**
Quintile 3	0.36 (0.20, 0.66)	**< 0.001**	0.11 (0.08, 0.16)	**< 0.001**	0.39 (0.19, 0.81)	**0.011**
Quintile 4	0.56 (0.30, 1.05)	0.071	0.10 (0.06, 0.15)	**< 0.001**	0.36 (0.16, 0.81)	**0.013**
Quintile 5 (lowest)	0.57 (0.31, 1.05)	0.069	0.07 (0.05, 0.11)	**< 0.001**	0.32 (0.14, 0.72)	**0.006**
Region (Ref. = west)						
Northeast	0.33 (0.10, 1.09)	0.068	1.74 (0.98, 3.09)	0.059	0.63 (0.22, 1.81)	0.391
Central	0.79 (0.48, 1.31)	0.363	1.13 (0.80, 1.61)	0.486	0.80 (0.43, 1.50)	0.488
East	0.94 (0.59, 1.49)	0.789	0.68 (0.49, 0.93)	**0.017**	0.67 (0.37, 1.22)	0.192

Rest 1 denotes unmarried, divorced, and widowed; Rest 2 stands for unemployed, jobless, and retired; UEBMI, Urban Employee Basic Medical Insurance; URRBMI, Urban and Rural Residents Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance; NRCMS, New Rural Cooperative Medical Scheme; Other† represents government medical insurance.

CHE incidence and associated factors

50.1% of households with cancer patients were considered to have CHE when a 40% threshold was used. The prevalence of CHE was greater amongst patients who were unemployed, jobless, or retired (OR = 2.68, 95% CI 1.59–4.53) than those who were employed. Compared with households of fewer than three members, a larger family size was protective from CHE

(OR = 0.52, 95% CI 0.32–0.86). Further, patients in a lower socioeconomic class had a smaller probability of reporting CHE than those in a higher socioeconomic class. There was no discernible relationship between health insurance and CHE (Table 3). A sensitivity analysis suggested that there was a non-significant correlation between economic status and CHE when the World Bank's definition of CHE at a 25% threshold was used (Supplementary Table S1), which was inconsistent with the base case analysis. In addition, the odds of CHE were lower in non-agricultural households (OR = 0.33, 95% CI 0.12–0.92, compared with agricultural households).

Discussion

This study identifies factors potentially associated with health care utilization and CHE among Chinese cancer patients using a nationwide representative longitudinal survey of the middle-aged and elderly population. These findings provide insights into health service utilization and economic burden of cancer patients. The socioeconomic characteristics (public health insurance and household consumption level) of the patients and their families appear to have significant influence on cancer care. CHE was reported by approximately half of the families of cancer patients, with it occurring more prevalently in higher-income families than in lower-income ones. We also found that cancer was more commonly reported by people with a lower educational level, who were married, unemployed, jobless, or retired, who self-reported a shorter sleep duration, who underwent regular physical examinations, who were in a higher socioeconomic group, and who resided in eastern China.

We observed that cancer was more commonly reported by respondents who were in a higher socioeconomic category. This may be because respondents living in higher-income families had greater access to better healthcare delivery and better wellness education, and therefore were more likely to have an underlying cancer diagnosed than those who lived in lower-income families (28). Individuals from the eastern region reported an increased prevalence of cancer, which likely reflects under-reporting in the western region due to the relative shortage of health resources and accessibility (29). In agreement with a previous study, sleeping for fewer hours was correlated with cancer in Chinese people, which may be the result of physiologic mechanisms (30). Given the cross-sectional nature of our data, we were only able to establish a longitudinal association between sleep duration and cancer incidence.

Health service use by cancer patients in our study was primarily driven by gender, age, household registration, education level, marital status, employment status, physical examination, family physician, household size, health insurance, per-capita household consumption (socioeconomic status), and the number of chronic non-communicable diseases. We observed that the utilization of outpatient care increased as the number of chronic non-communicable diseases increased. This is likely due to the fact that cancer patients with additional diseases are more likely to have complications, and the subsequent demand for intensified care and coordinated treatment could increase outpatient visits (31). This association has been well documented in other studies on multimorbidity (31–33). Also, in agreement with other studies, cancer patients in higher socioeconomic groups were more likely to access and utilize both outpatient and inpatient services (28, 34, 35), exposing inequalities in cancer care. If the economic struggles resulting from cancer are not addressed, its negative impact on healthcare access and utilization may contribute to the deteriorated health status of patients in lower socioeconomic categories and increased cancer mortality (36). In contrast, patients with a higher socioeconomic status had a better prognosis, which may be associated with a higher level of care or even over-medication (17). Our results also found that patients who contracted with a family physician had more frequent outpatient visits and longer inpatient stays. A plausible explanation might be that contracting with a family physician is associated with higher income levels, which could enhance patient disease awareness and treatment compliance (37). However, family physicians serve as the gatekeepers to health care, aiming to prevent chronic diseases by intervening in disease-related lifestyle behaviors in addition to delivering primary health care services that can efficiently lower the hospitalization and mortality of patients and mitigate the burden of chronic disease in China (37). The effect of family physician contracting on the outpatient and inpatient services that were utilized by cancer patients remains for consideration.

We found that individuals with a better educational background utilized more outpatient services but fewer inpatient services. There are several possible reasons for this discrepancy. First, individuals with higher levels of education tend to rank higher in socioeconomic status and capture more appropriate pathways of care (38), such as well check-ups, consultations, and outpatient visits, permitting diseases to be identified at an early stage. Second, populations with lower levels of education may have inadequate knowledge of cancer-related symptoms and signs, so if they took these lightly or lacked illness awareness, they would not approach a clinician for a timely diagnosis (39). The observation that individuals with lower levels of education are at higher risk of cancers of the esophagus, stomach, rectum, rectosigmoid colon, liver, pancreas, lung, kidney, and urinary tract has been previously reported (40), and patients with these cancers often require radiotherapy, chemotherapy, or more intensive treatment (41), requiring a longer inpatient stay.

Social health insurance plans are designed to promote nationwide access to healthcare. Our results showed that patients enrolled in UEBMI and URRBMI reported significantly longer inpatient stays compared with non-enrolled patients, whereas URBMI and NCRMS did not influence this outcome.

An explanation for this observation is that fewer inpatient services were available to people who were covered by URBMI and NCRMS due to restricted benefits packages and reduced coverage compared with other schemes (24). Cancer patients enrolled in UEBMI were more likely to spend more time in the hospital, suggesting that UEBMI is superior to URRBMI in terms of reimbursement level. Regarding outpatient visits, our findings showed that health insurance plans seemed to have minimal impact on the decision to utilize outpatient services except for the URRBMI, whose members had fewer outpatient visits compared with uninsured patients. A previous study reported that Chinese people tended to favor inpatient services over outpatient services regardless insurance type (42), and that cancer patients might have a stronger preference toward hospitalization due to their unique treatment needs.

Our study reported that the prevalence of families with cancer patients that experienced CHE was 50.1% at a 40% threshold. Compared with other cancer studies that used the same definition and threshold of CHE, our study of Chinese showed a higher prevalence of CHE than Iran (13.77%) (43) and Malaysia (47.8%) (44), which might be attributed to the disparities in the income levels and health insurance packages between these countries. The overall prevalence of CHE among the general Chinese population was only 8.94% in 2016 in China (45). The significant discrepancy indicates that OOP spending on cancer care imposes a substantial financial burden on more than half of Chinese families with cancer patients. Moreover, the calculation of OOP spending we used only captured the direct expenses of cancer care, and our statistic is therefore conservative given the exclusion of indirect expenses such as transport and accommodation. Our findings also suggest that a large household size could shelter some families with cancer patients against CHE. One potential hypothesis for this is that family members would care for each other and provide both material and psychological assistance to those with severe diseases. A larger household size may also represent increased household consumption and income, and therefore may be a protective factor when income exceeds consumption.

While it is generally acknowledged that better-off families were more capable of coping with healthcare spending than poorer families (21), our study found that households with cancer patients that were at a higher socioeconomic level had a higher probability of experiencing CHE. There are several possible explanations for this inconsistency. First, most cancer patients with a low economic status in our study were from agricultural families. They were less likely to purchase health services due to their inadequate health knowledge of the incidence of cancer and inefficient allocation of health resources to rural regions, which may reduce the incidence of CHE (39, 46). Secondly, cancer therapy is highly expensive due to the need for repetitive hospitalizations, multiple consultations, advanced laboratory examinations, chemotherapy, rare and costly drugs, surgery and radiation therapy, and other essential care (47). Cancer patients with a low economic status might therefore forgo therapy on account of the high OOP payments and the potential impact of their care on the livelihoods of other family members, making it possible for families to avert CHE but resulting in worse health outcomes. In contrast, people in higher-income classes require greater absolute levels of spending than people in lower-income classes to trigger the so-called CHE threshold. Our results suggest that higher OOP expenses could be reflective of receiving more intensive and expensive health-care services (36), or the purchase of high-quality services from private facilities by bypassing the inconvenience of public facilities. Private healthcare services are generally more expensive than public services because they are primarily driven by the demand of better-off individuals for high-quality services (48). Finally, while the improved survival of better-off cancer patients was the result of proactive therapy, post-cancer care requires sustained financial support (17), which may increase the risk of CHE. We also found that CHE had no significant association with health insurance, indicating that public health insurance failed reduce the financial risks posed by cancer to the patient's family.

Our findings add to the body of evidence that supports the development of targeted policies and strategies to address China's growing cancer burden. The occurrence of cancer among middle-aged and elderly patients is significantly affected by social variables such as education level, marital status, employment and socioeconomic status, and geography, which involve multiple societal domains. Contemporary public health strategies require cross-sectoral collaboration to improve social determinants of health and implement effective prevention strategies that target high-risk populations (49). We also observed a significant association between health care utilization and the socioeconomic characteristics of cancer patients. Policymakers should take the socioeconomic burdens experienced by cancer patients into consideration when formulating practice guidelines on cancer management so as to facilitate efficient and individualized treatment solutions. For example, a nationwide representative cancer registry with enhanced quality and targeting will facilitate the identification of treatment priorities and care utilization among Chinese cancer patients (50). To alleviate the burden of providing cancer care and improve disease prognosis, the government needs to raise screening awareness among targeted vulnerable populations and enhance the likelihood of detecting cancer at an early stage. A cancer screening and early detection network is present in 31 provinces of China as of 2015, but whole population screenings are not offered except for breast and cervical cancer (51). OOP spending is the most significant determinant of catastrophic expenditure. In China, the high OOP expenditures on healthcare may be due to fee-for-service payment mechanisms and the failure of public health insurance to bear financial risks (52). Cancer care payment model reform is required to improve the financial burden that cancer

treatment places on Chinese families. A patient-centered and value-oriented alternative payment model for oncology is recommended due to its significant associations with improved cancer care quality and reduced resource use and care costs (53). China has almost achieved universal health insurance coverage, yet catastrophic payments for cancer patients remain too high. This may be due to the restrictions of current benefit packages and the small scale of medical aid (54). Future health insurance schemes should strengthen financial protection for Chinese cancer patients in a targeted manner.

Our study had several limitations. First, given that cancer diagnosis was self-reported, the incidence of cancer in China was potentially underestimated. This assumption is even more profound in vulnerable populations who are less likely to be diagnosed with cancer at an early stage. Second, health service use and health payments among cancer patients were also self-reported. These are also prone to underestimation, especially among older adults and those with a lower education level. Third, our sample size was rather small for this type of study. A larger sample should be used in future work. Given that many of our findings indicate that better-off families were less likely to experience CHE (45), future studies should use other indicators of socioeconomic groups beyond socioeconomic status quintiles. Future work should also take into consideration variables related to mental health because of its significant impact on care-seeking behaviors (55). Finally, this research only recruited Chinese people aged 45 years and older. Future studies should consider the impact of cancer on younger cohorts.

Conclusion

The socioeconomic characteristics of cancer patients had a considerable impact on their healthcare utilization, especially health insurance and socioeconomic status. OOP spending on cancer care imposed a substantial financial burden on more than half of Chinese households with cancer patients, particularly those from better-off households. Public health insurance failed to reduce the financial risks posed to cancer patients' families. Individualized and targeted guidelines for cancer management, strategic purchasing models in cancer care, and social health insurance with expanded benefit packages are crucial to easing the burden of cancer care in China.

Data availability statement

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

Author contributions

PD led the study including the interpretation of the results and manuscript drafting. LS and MC conceived and supervised the study. YF contributed to data analysis and drafting of the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.943271/full#supplementary-material

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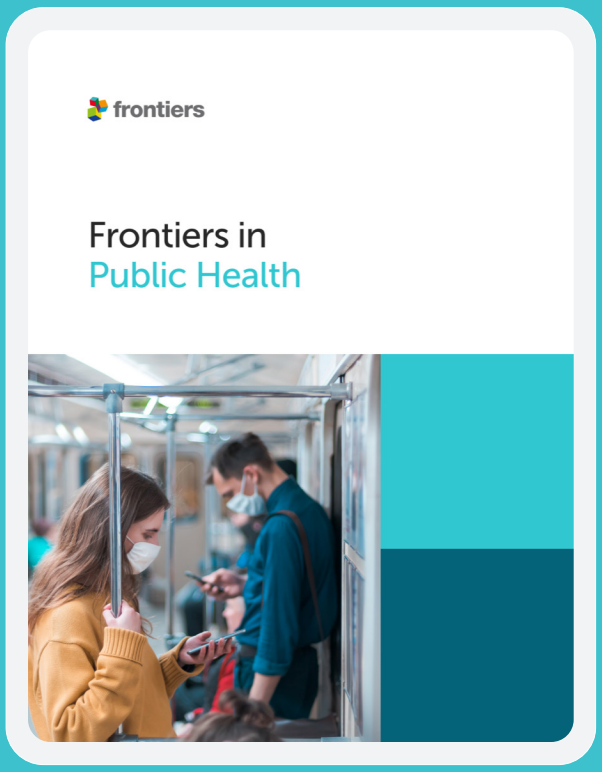

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