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RESEARCH

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Cost-utility analysis of olaparib assisted targeted therapy for BRCA mutation HER2-negative early breast cancer in China and in the United States

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Abstract

Background Olaparib, an inhibitor of poly (ADP-ribose) polymerase (PARP), has demonstrated promising outcomes in treating HER2-negative early-stage breast cancer with BRCA mutations. However, a comprehensive evaluation of its cost-effectiveness in the context of the United States and China has yet to be undertaken. This study seeks to fill this research void by performing a thorough cost-utility analysis.

Methods This investigation takes as its foundation the findings from the OlympiA trial. We obtained survival curves from this trial and used the Weibull distribution function to calculate transition probabilities. Relevant literature provided the necessary data on costs, utility values, and discount rates applicable to both the United States and China. We utilized TreeAge software to construct Markov models for each country, simulating the progression of early-stage breast cancer. These models underwent extensive examination through multi-way analysis, cost-utility analysis, Monte Carlo simulations, one-way and two-way sensitivity analyses, as well as probabilistic sensitivity analysis.

Results The cost-utility analysis of the Chinese Markov model revealed that the total expenditure for the Olaparib cohort amounted to 384,274.75 RMB, generating 6.41 QALYs. Conversely, the placebo group incurred a total cost of 60,264.10 RMB, resulting in 6.34 QALYs. The Incremental Cost-Utility Ratio (ICUR) between the two cohorts stood at 5,007,332.36 RMB/QALY, which is significantly higher than thrice the Gross Domestic Product (GDP) per capita of China in 2022, set at 257,094 RMB. As for the U.S. model, the Olaparib group had a total expenditure of 245,604.01 USD, yielding 7.53 QALYs, while the placebo cohort had a total cost of 93,019.92 USD, generating 7.45 QALYs. The ICUR for the two groups was calculated at 1,891,974.19 USD/QALY, substantially surpassing the U.S. Willingness-To-Pay (WTP) threshold of 150,000 USD/QALY.

Conclusions When evaluated in the context of healthcare economics in both China and the United States, the implementation of an Olaparib-based treatment strategy for early-stage HER2-negative breast cancer with BRCA mutations does not present a cost-effective solution in either nation.

Keywords Olaparib, Early breast cancer, BRCA1/2 gene, Markov model, Cost-utility analysis

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Introduction

The findings of a comprehensive survey by the International Agency for Research on Cancer (IARC) in 2018 showed that breast cancer has emerged as the dominant type of cancer afflicting women across the globe, contributing to a remarkable 24.2% of all instances. A significant portion of these cases, approximately 52.9%, emerge from developing countries. An important change was observed by 2020, with breast cancer overtaking lung cancer as the primary cause of cancer worldwide [1].

Triple-negative breast cancer (TNBC), which lacks the presence of estrogen receptors, progesterone receptors, and HER2 receptors, has long posed a unique challenge in oncology. This subtype lacks defined hormonal and HER2 therapeutic targets, thus creating a dearth of standardized treatment strategies (Fig. 1).

In the fight against BRCA1/2 mutation-associated, HER2-negative breast cancer, PARP inhibitors and BRCA gene mutation screening have emerged as a formidable therapeutic duo. PARP inhibitors work by disrupting the DNA single-strand damage repair pathway, while BRCA-mutated patients are unable to repair DNA double-strand damage due to homologous recombination deficiency (HRD) [2]. When these two DNA damage repair pathways are simultaneously inhibited, a phenomenon known as "synthetic lethality" occurs, eventually leading to tumor cell apoptosis [3]. Olaparib, the world's first PARP inhibitor approved for patients with BRCA-mutated breast cancer [4], has been a game-changer in this field. Olaparib has received FDA endorsement for use in the management of advanced ovarian, pancreatic, and breast cancers, specifically those with BRCA gene mutations. In addition, the guidelines provided by the National Comprehensive Cancer Network (NCCN) support the use of olaparib for patients with HER2-negative breast cancer who carry germline BRCA1/2 gene mutations. In China, the medical authorities have given the go-ahead for the application of olaparib in the treatment of ovarian and advanced prostate cancers, and active investigations into its safety and effectiveness for breast cancer treatment are currently in progress.

PARP inhibitors have opened new horizons for cancer treatment, their prohibitive cost remains a deterrent for many individuals. A 2019 Japanese study found olaparib, used for treating BRCA1/2 mutation-related breast cancer, to be cost-ineffective. It pointed out the necessity to lower the costs of BRCA1/2 testing and olaparib treatment [5]. This conclusion offers valuable insights for healthcare authorities.

Even though per capita healthcare resources in China are considerably lower than in developed countries, the demand for quality of life and healthcare standards is equally high. The application of pharmacoeconomics to guide the optimal allocation of limited resources

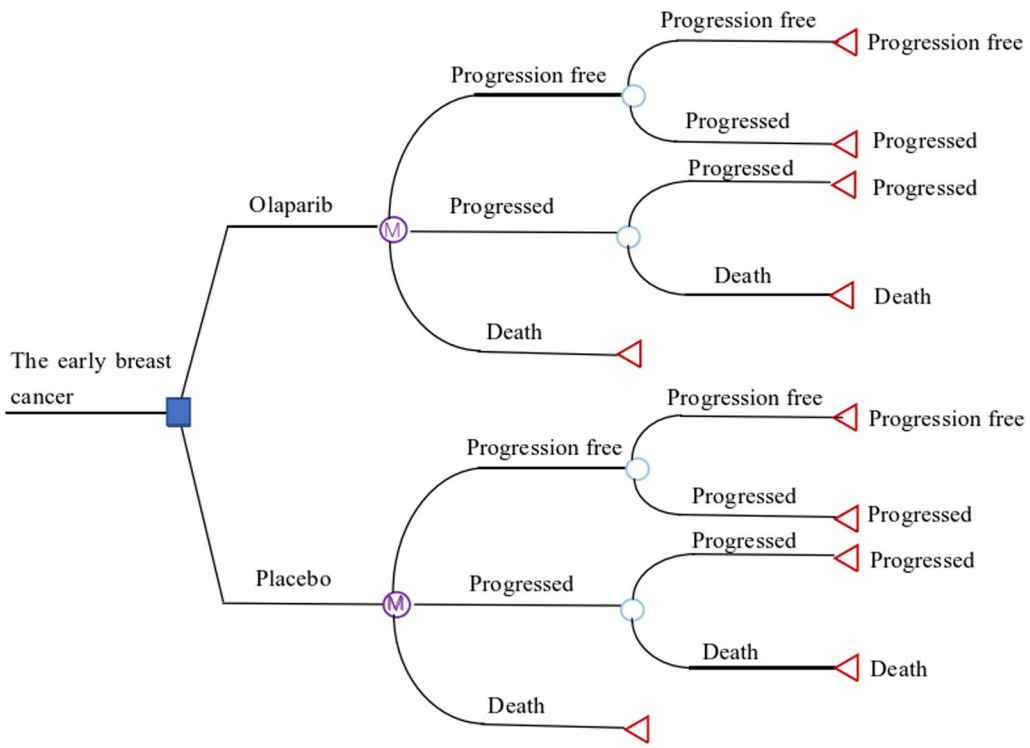

Fig. 1 Markov model structure diagram

has become a pressing need. In light of this, our study, based on the most recent data from the OlympiA clinical trial, aims to design and conduct a cost-utility analysis of olaparib adjuvant therapy in patients with early-stage breast cancer harboring BRCA1/2 mutations from the healthcare perspectives of both China and the United States [6].

Our research will provide a reliable reference for healthcare institutions in China and the United States in setting treatment strategies, informing health policy decisions at the national level, and ensuring the economic feasibility of treatment plans for patients. Moreover, it may serve as a reference for future pharmacoeconomic research involving olaparib-targeted cancer therapy, offering insights into methodological design and data handling. This research could also provide economic evidence to inform future decisions by China's health authorities regarding the approval of olaparib adjuvant therapy for early-stage breast cancer patients with BRCA1/2 mutations. It may also contribute to the consideration of incorporating new indications into the national health insurance program.

Methods

Subjects and methods

This study, based on the OlympiA trial an international, double-blind, phase III clinical study, conducts a cost-utility analysis of olaparib-assisted therapy for BRCA gene mutation early-stage breast cancer from healthcare perspectives in the United States and China. The trial enrolled 1836 patients with germline BRCA1/2 pathogenic or likely pathogenic variants at high risk for HER2-negative primary breast cancer after completing standard adjuvant or neoadjuvant chemotherapy and local treatment [7]. The included patient characteristics are as follows: Patients aged 36 to 50, with either a breast cancer susceptibility gene or BRCA1 or BRCA2 mutations. Around 80% of the participants had triple-negative breast cancer, while the remaining 20% had hormone receptor-positive, HER2-negative breast cancer. The cohort comprised 60% premenopausal and 40% postmenopausal women, 75% of whom had undergone a mastectomy, while 25% had only conservative surgery. About 26.5% of patients had received platinum drugs as neoadjuvant therapy, and almost 93.7% had previously received anthracyclines or taxanes, or both, as neoadjuvant or adjuvant chemotherapy. The patients were randomly allocated to receive either olaparib (300 mg) or placebo tablets, taken orally twice daily, for a treatment period of 52 weeks. The medication regimen during disease progression was based on the "Chinese Clinical Oncology Association Breast Cancer Diagnosis and Treatment Guidelines" 2022 edition. Both groups received single-use paclitaxel at a dosage of 100 mg/m^2 on days 1, 8, and 15, with each cycle lasting 28 days. In this study, an eight-cycle treatment period for disease progression was assumed due to the absence of clinical data. In the safety analysis, only grade 3 or above adverse reactions with an incidence rate of $\geq 1\%$ were included, such as anemia, neutropenia, and fatigue, with no such reactions in the placebo group exceeding a 1% incidence rate.

Model establishment

In this study, we devised Markov models for China and the U.S., with uniform states and transition probabilities derived from the OlympiA trial, but with country-specific cost and utility parameters due to variations in economics, healthcare systems, and demographics. The classification of early-stage breast cancer in this study involved three states: progression-free (PFS), disease progression (PD), and death. Transition probabilities, which represent the likelihood of a patient transitioning from one state to another, were determined using data from the OlympiA trial. To estimate these probabilities, we fitted Weibull functions to the disease-free survival (DDFS) and overall survival (OS) curves for both the olaparib and placebo groups. The resulting shape and scale parameters of the Weibull distribution function were used.

To calculate the transition probabilities (Tp), we employed TreeAge software, which allows for dynamic changes in probabilities across different stages and over time. In the formula, the variables "t" and "u" represent the running time and period of the Markov model, respectively. The Markov models in this study simulated a cycle length of 30 days and an economic evaluation horizon of 10 years to model the progression of early-stage breast cancer over that specific time frame.

Transition probabilities

Transition probabilities represent the likelihood of a patient moving from one state to another in a given period. In this study, we calculated the transition probabilities by extracting data from the DDFS and OS curves of the OlympiA clinical trial for both the olaparib group and the placebo group. We fitted the data from each group with the Weibull function, which allowed us to obtain the shape and scale parameters of the Weibull distribution function. These parameters are summarized in Table 1.

In terms of the Markov model, by replacing the scale and shape parameters for both the Olaparib group and the placebo group in the formula provided, we can derive the transition probabilities for each cycle in both groups. This includes the transition from the PFS state to the PD state (P1), as well as the transition from

Table 1 parameters of Weibull function

Parameters name	Average Scale (SD)	Average Shape(SD)
PFS		
Olaparib	0.0083250(0.0005174)	0.7488611(0.0173989)
Placebo	0.0213860(0.0009352)	0.6347360(0.0129636)
OS		
Olaparib	0. 005654(0.000355)	0.785309(0.017634)
Placebo	0.0079351(0.0003468)	0.7768977(0.0121948)

SD standardized deviation; *PFS* progression-free survival; *OS* overall survival

the OS state to the PD state (P2). Subsequently, the transition probability from the PD state to the state of Death is then calculated as P1—P2.

$$Tp = 1 - \exp\left(-scale \times (t+u)^{shape} - scale \times t^{shape}\right)$$

Statistical analysis

Costs and utilities

In this study, we approached pharmacoeconomic evaluations from both China and U.S. healthcare perspectives, focusing on direct medical costs due to data availability, excluding indirect costs like transportation and care giving expenses. We discounted all costs to 2023. Future cost-utility values in the Markov models were similarly discounted, with annual rates of 5% for China and 3% for the U.S., and sensitivity analysis ranges of 0–8% and 0–7%, respectively. The cost parameters in the Markov models were determined based on the OlympiA trial interventions and the actual clinical treatment process of breast cancer patients in both countries. The cost of progression-phase drugs in the China model was calculated based on a 1.6 m^2 average body surface area [8], while in the US. model it was referenced from literature [9]. The cost for adverse reaction treatment is derived by multiplying single treatment cost with an incidence rate.

Cost-effectiveness analysis

This study thoroughly analyzes costs, quality-adjusted life years (QALYs) and the ICUR. Each ICUR is evaluated against a set willingness-to-pay (WTP) threshold. If the ICUR is lower than the WTP, the intervention is deemed more cost-effective than the control; if higher, it is less cost-effective. We use the WTP threshold from the Chinese Pharmacoeconomic Evaluations Guidelines, generally three times the GDP. Given the per capita GDP of China for 2020 stood at ¥72,447, as per data from the National Bureau of Statistics, the resultant annual WTP value is ¥217,341. For the U.S. model, we have followed relevant literature to establish the WTP at $150,000.

Sensitivity analysis

This study assesses the stability of model parameters through one-way deterministic sensitivity analysis, two-way sensitivity analysis, and probabilistic sensitivity analysis. The one-way sensitivity analysis outcomes are portrayed in a tornado diagram. Following this, a two-way analysis of the health utility values of PFS and PD statuses is performed based on the one-way sensitivity analysis. Concurrently, the probabilistic sensitivity analysis involves extracting values for various variables from their specific distributions and conducting a Monte Carlo simulation for comparison between groups, which is repeated 1,000 times. The results from this analysis are exhibited in an ICUR scatter plot and a cost-utility acceptability curve.

Results

Basic results

Validation of survival curve fitting

The operation and outcomes of the entire Markov model are significantly influenced by the transition probability, which is a key parameter in such models. However, there are inherent errors and uncertainties in the process of obtaining transition probabilities, such as manually extracting raw survival curve data and using software for Weibull fitting. The reliability of the fitting results can be verified by comparing the fitted survival curve with the original survival curve and the goodness of fit (ADR) calculated by the software.

According to Figs. 2 and 3, the survival curves of the Olaparib and Placebo groups, as modeled by R software, do not show any significant deviations from the original PFS and OS curves. The ADR (Goodness of Fit) values for the fitted PFS curves are 0.982 (Olaparib) and 0.984 (Placebo), while the ADR values for the fitted OS curves are 0.987 (Olaparib) and 0.991 (Placebo). According to statistical principles, the closer the ADR value is to 1, the more accurate the fitting result, and the better the fit between the curves. Therefore, it can be seen that the Weibull scale parameter and shape parameter obtained after fitting by the software are accurate, indicating the reliability of the calculated transition probabilities in the model.

In our cost-utility analysis for the China model, as presented in Table 2, the olaparib group had a total cost of 384,274.75 RMB and achieved 6.41 QALYs. The placebo group had a total cost of 60,264.10 RMB, achieving 6.34 QALYs. The ICUR between the two groups was 5,007,332.36 RMB per QALY, which is substantially higher than three times the per capita GDP of ¥257,094 in

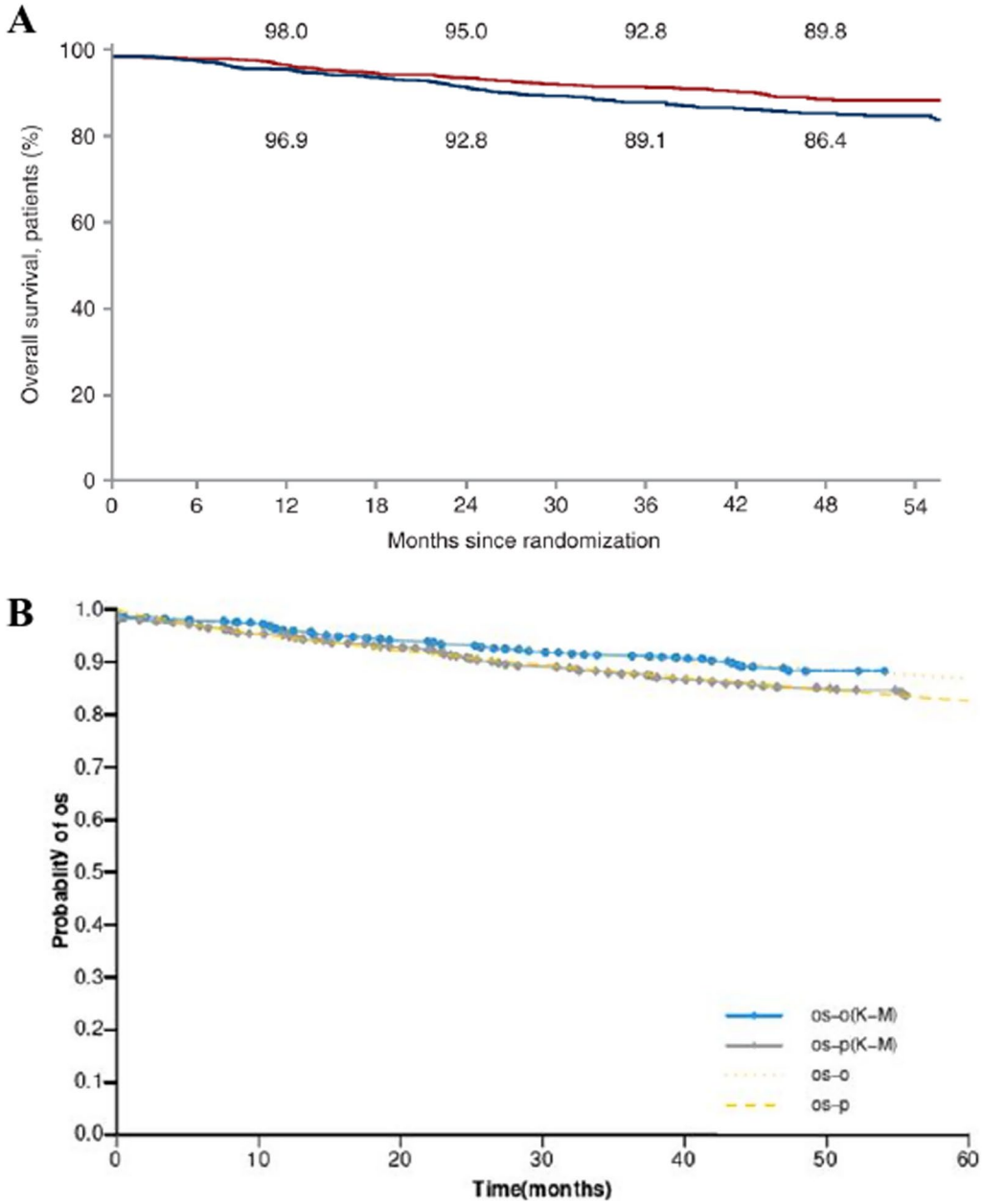

Fig. 2 Original OS curve (**A**) and refitted OS curve (**B**). OS, Overall Survival; OS-O(K-M), K-M curve of OS in olaparib group; OS-P (K-M), K-M curve of OS in placebo group;OS-O, OS in olaparib group; OS-P, OS in placebo group

2022. From this, we can conclude that while the Olaparib group gained an additional 0.065 QALYs compared to the placebo group, the cost associated with this treatment approach was significantly higher. Therefore, olaparib-assisted treatment for HER2-negative early breast cancer does not represent a cost-effective strategy in China as well.

In a parallel fashion, we conducted the cost-utility analysis for the model in the United States, as detailed in Table 3. Here, we found: The Olaparib group bore a total cost of $245,604.01, which led to 7.52 QALYs. In contrast, the Placebo group had a total cost of $93,019.92, yielding 7.45 QALYs. This means that the Olaparib group achieved an additional 0.081 QALYs when compared to the Placebo group. However, ICUR between the two groups was $1,891,974.19 per QALY. This is significantly greater than the WTP threshold of $150,000 in the United States.

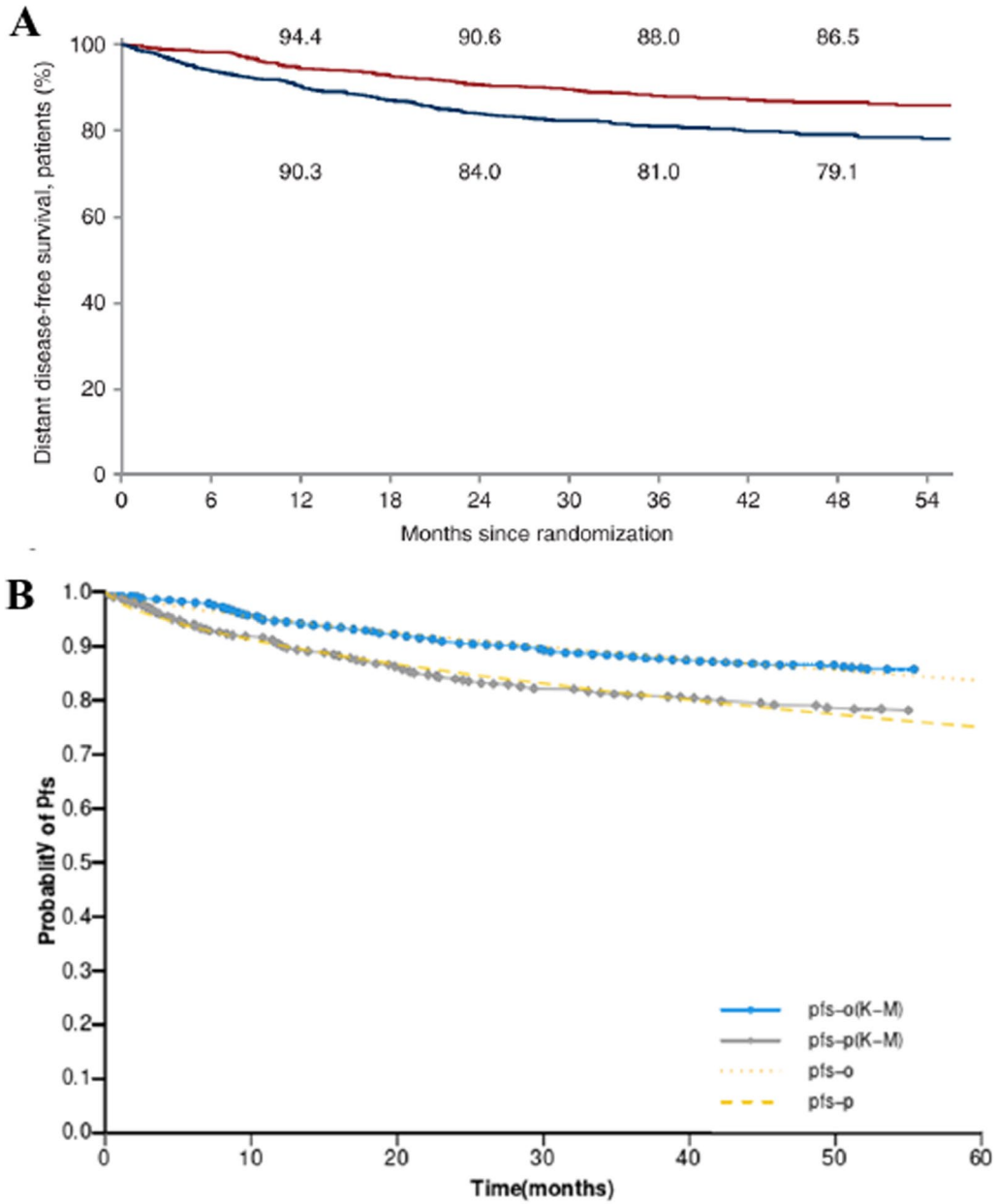

Fig. 3 Original DDFS curve (**A**)and refitted PFS curve (**B**). DDFS, Distant Disease-Free Survival; PFS, Progression-Free Survival: PFS-O (K-M), K-M curve of PFS in olaparib group; PFS-P(K-M), K-M curve of PFS in placebo group; PFS-O, PFS in olaparib group; PFS-P,PFS in placebo group

Therefore, it becomes clear that the use of Olaparib for treating HER2-negative early breast cancer does not provide a cost-effective solution in the United States (Tables 4, 5, 6, 7).

Sensitivity analysis

One-way deterministic sensitivity analysis

Figure 4A displays the tornado diagram derived from the one-way sensitivity analysis of the model used in China. This chart identifies the five most influential variables affecting the model's outcomes as the expenses related to docetaxel, olaparib, enzalutamide, abiraterone, and the Progression-Free Survival (PFS) utility score.

On the other hand, the United States model's tornado diagram is depicted in Fig. 4B. As per the diagram's arrangement, from the highest to the lowest impact, the factors are the utility score in the PFS state, the cost of olaparib, the utility score in the PD state, and the discount rate, with the other factors having a less profound impact. It's important to note that during

Table 2 Costs in China

Parameters name	Base (RMB)	Range (RMB)	Distribution	Source
Olaparib (150 mg)	102	89.76 ~ 442.68	–	www.yaozh.com
Olaparib (per cycle)	12,240	10,771.2 ~ 53,121.60	Triangle	www.yaozh.com
Placebo (per cycle)	–	–	–	–
Paclitaxel (100 mg)	802.7	602.0 ~ 1003.39	–	[1]
Paclitaxel (per cycle)	3082.37	2311.68 ~ 3853.02	Triangle	–
BRCA1/2 gene testing	532.61	426.09 ~ 639.14	Triangle	[2]
Laboratory testing (per cycle)	211.01	26.25 ~ 228.32	Triangle	[3]
Nursing fees (per cycle)	1350	900 ~ 2400	Triangle	Tertiary hospitals
Regular follow-up (per cycle)	260.49	208.37 ~ 312.63	Triangle	[10]
Imaging evaluation (per cycle)	89.57	57.49 ~ 119.7	Triangle	[11]
Injection fees (per cycle)	12	–	–	Tertiary hospitals
Bed charges (per cycle)	1950	30 ~ 150	Triangle	Tertiary hospitals
Cost of adverse reaction treatment				
Anemia	4087.7	3066.18 ~ 5110.04	Triangle	[4]
Fatigue	625.63	567.75 ~ 683.51	Triangle	[12]
Decrease in neutrophil count	4793.67	3834.94 ~ 5752.4	Triangle	[5]

RMB renminbi (Chinese currency)

Table 3 Costs in the United States

Parameters name	Base($)	Range ($)	Distribution	Source
Olaparib(150 mg)	115.72	61.13 ~ 125.78	–	Redbook,drug.com
Olaparib(per cycle)	13,886.4	7335.6 ~ 15,093.6	Triangle	–
Placebo (per cycle)	–	–	–	–
Paclitaxel(per cycle)	5328.14	4844.58 ~ 5860.43	Triangle	[9]
BRCA1/2 test	2759.03	1468.53 ~ 4405.6	Triangle	[7, 8]
Lab test(per cycle)	350.62	262.96 ~ 438.26	Triangle	[9]
Nursing(per cycle)	3458.74	2766.58 ~ 4149.87	Triangle	[13]
Routine follow-up(per cycle)	1252.27	920.08 ~ 1584.45	Triangle	[8]
CT(per cycle)	878.43	702.42 ~ 1054.11	Triangle	[10]
Mammography(per cycle)	171.01	85.51 ~ 256.52	Triangle	[7]
MRI(per cycle)	677.72	338.86 ~ 1016.58	Triangle	[7]
Adverse reaction				
Anemia	801.96	641.56 ~ 962.35	Triangle	[11]
Fatigue	147.47	117.97 ~ 176.96	Triangle	[10]
Neutropenia	920.84	736.67 ~ 1105.01	Triangle	[11]

CT Computed Tomography; *MRI* Magnetic Resonance Imaging

Table 4 Health utility value

Parameters name	Base	Range	Mean	SD	Distribution	Source
PFS						
China	0.81	±5%	0.81	0.23	Beta	[12]
The United States	0.868	±5%	0.868	0.135	Beta	[14]
PD						
China	0.74	±5%	0.74	0.27	Beta	[12]
The United States	0.786	±5%	0.786	0.0393	Beta	[9]

SD Standardized Deviation; *PFS* Progression-Free survival; *PD* Disease Progression

Table 5 Disutility

Parameters name	Base	Range	Source
China			
Fatigue	−0.029	−0.036 to −0.022	[1]
Anemia	−0.074	−0.11 to −0.037	[15]
Neutropenia	−0.09	−0.12 to −0.059	[15]
The US			
Fatigue	−0.29	−0.348 to −0.232	[13]
Anemia	−0.12	−0.144 to −0.096	[13]
Neutropenia	−0.09	−0.108 to −0.072	[13]

a one-way sensitivity analysis, when all parameters vary within a certain limit, the incremental cost-effectiveness ratio never falls below 1,000,000 US dollars. This is substantially higher than the WTP value.

Two-way deterministic sensitivity analysis

The two-way sensitivity analysis serves as a supplementary validation to the one-way sensitivity analysis. The goal is to compute and assess the impact level that the interplay of two sensitivity factors has on the net benefits of an intervention strategy, presuming that other factors of uncertainty remain constant. Consequently, in light of the one-way sensitivity analysis, this study conducted a two-way analysis on the health utility values in the PFS state and the PD

Table 6 The results of cost-effectiveness analysis (China)

Regimen	cost (RMB)	Utility (QALY)	Incremental cost (RMB)	The incremental utility (QALY gain)	Incremental cost-utility ratio (RMB/QALY gain)
Olaparib	384,274.75	6.41	324,010.64	0.06471	5,007,332.36
The control group	60,264.10	6.34	–	–	–

RMB renminbi(Chinese currency); *QALY* Quality-Adjusted Life Years

Table 7 The result of cost-effectiveness analysis(US)

Regimen	cost ($)	Utility (QALY)	Incremental cost ($)	The incremental utility (QALY gain)	cost-utility ratio ($/QALY gain)
Olaparib	245,604.01	7.52	152,584.09	0.08065	1,891,974.19
The control group	93,019.92	7.45	–	–	–

QALY Quality-Adjusted Life Years

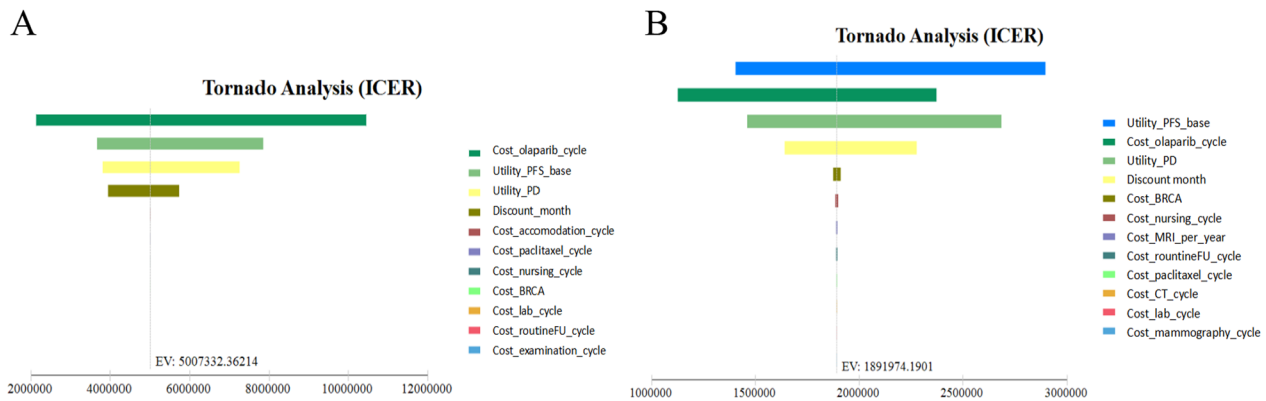

Fig. 4 Tornado diagram of single factor sensitivity analysis of the Markov model in China (**A**) and in the United States (**B**). *X-axis* Incremental cost-effectiveness ratio (ICER), measured in RMB/QALY for China and USD/QALY for the United States. *Y-axis* Parameters being analyzed (e.g., drug cost, utility values, transition probabilities). Bars: The length of each bar represents the range of ICER values when the parameter is varied. The longer the bar, the greater the impact of that parameter on the results

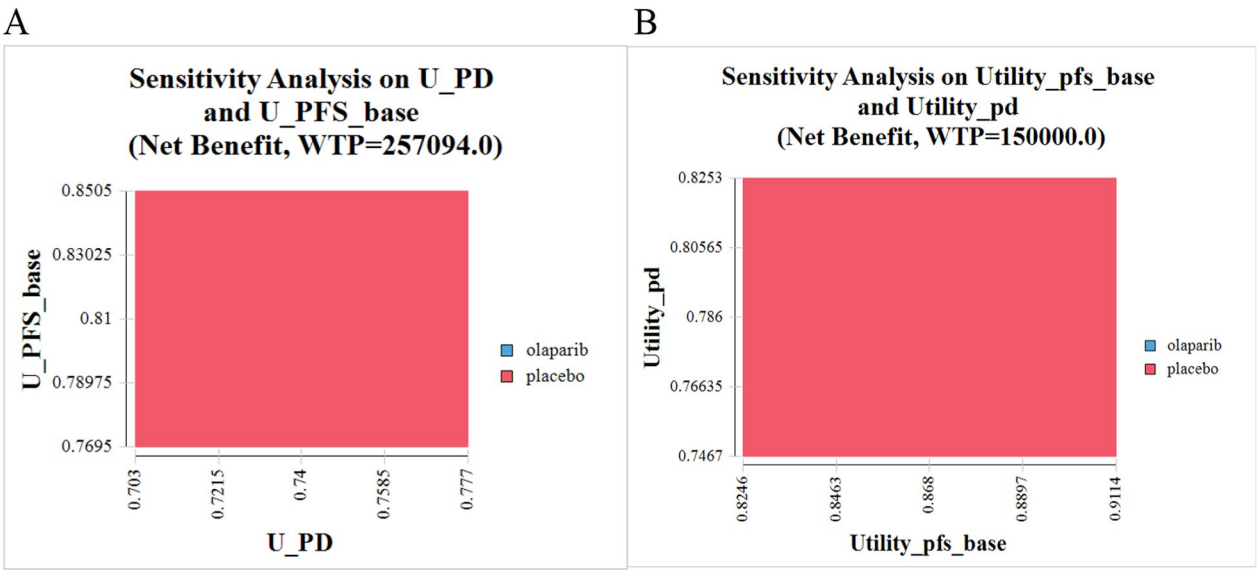

Fig. 5 two-way sensitivity analysis of American Markov model in China (**A**) and in the United States (**B**). X-axis: Variation in the first parameter (e.g., drug cost or effectiveness). Y-axis: Variation in the second parameter (e.g., utility values or transition probabilities). Color Gradient: Represents the resulting ICER values (The blue area signifies that the olaparib strategy is more cost-effective, while the red area suggests that the placebo strategy is more cost-effective).The blue area signifies that the olaparib strategy is more cost-effective, while the red area suggests that the placebo strategy is more cost-effective

state. These results are illustrated in Fig. 5. The blue area signifies that the olaparib strategy is more cost-effective, while the red area suggests that the placebo strategy is more cost-effective. Evidently, even when considering the interaction of these two parameters, in both China and the United States, the placebo strategy still holds a definitive advantage.

Probabilistic sensitivity analysis

Typically, Monte Carlo simulation results are depicted using an Incremental Cost-Utility scatter plot and a Cost-Utility Acceptability curve, as demonstrated in Figs. 6 and 7 respectively. In the Incremental Cost-Utility scatter plot, the diagonal line symbolizes the willingness-to-pay (WTP), and each dot signifies

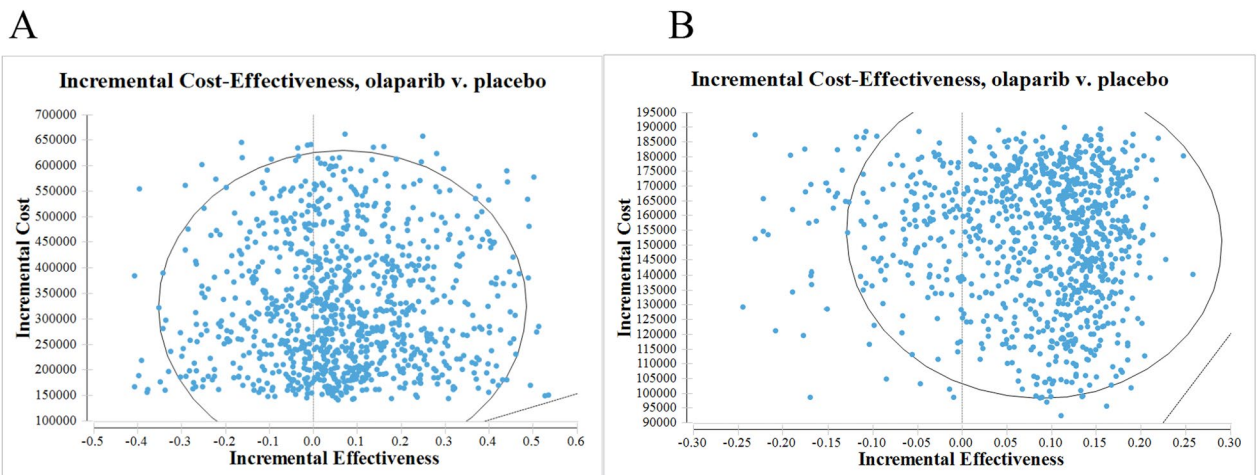

Fig. 6 The cost-effectiveness scatter plot of the Markov model in China (**A**) and in the United States (**B**). X-axis: Incremental effectiveness (measured in QALYs). Y-axis: Incremental cost (measured in RMB for China and USD for the United States). Points: Each point represents a simulation result, showing the combination of incremental cost and effectiveness. Ellipse: Represents the 95% confidence interval of the simulation results. Dashed Line: Represents the willingness-to-pay (WTP) threshold (e.g., 150,000 RMB/QALY for China and 150,000 USD/QALY for the United States)

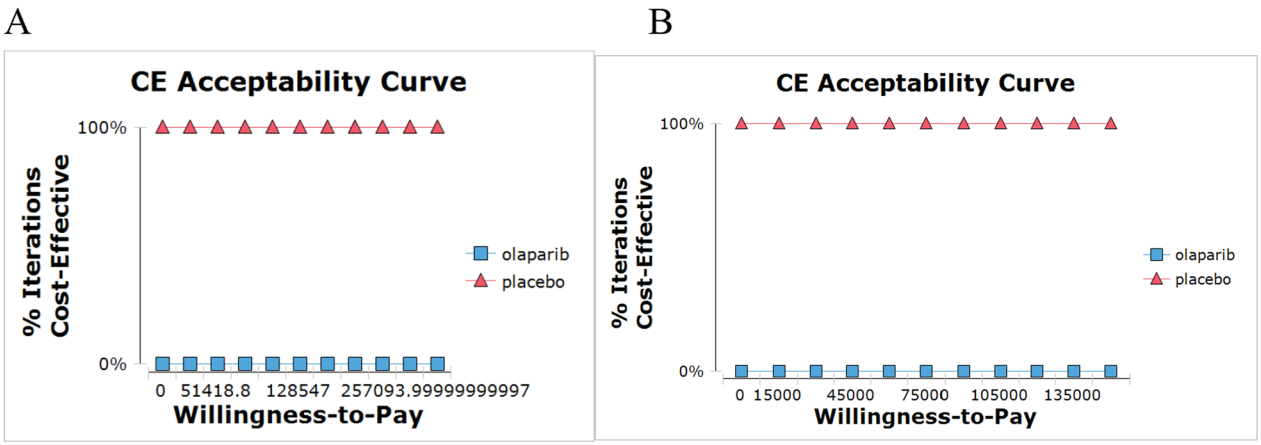

Fig. 7 The acceptability curve of the Markov model in China (**A**) and in the United States (**B**). CE, cost effectiveness. X-axis: Willingness-to-pay (WTP) threshold (measured in RMB/QALY for China and USD/QALY for the United States). Y-axis: Probability that the treatment is cost-effective (ranging from 0 to 100%). Curves: Each curve represents the probability that a specific treatment (e.g., Olaparib) is cost-effective at different WTP thresholds

a potential result from the Cost-Utility Analysis. A dot below the diagonal line indicates a cost-effective scenario, while a dot above the line represents a non-cost-effective situation. As seen in the scatter plot, almost 99.9% of the dots in the Chinese model are above the diagonal line, suggesting that the olaparib adjunctive therapy for early-stage breast cancer patients with BRCA gene mutation and HER2 negative is not cost-effective.

The acceptability curve exhibits a mild incline as the WTP increases, while the placebo group's curve shows a subtle decline. Should the WTP value continue to rise indefinitely, the two curves would intersect at some point. However, practically speaking, the economic performance of the olaparib group still significantly lags behind that of the placebo group, rendering the olaparib group not cost-effective.

In the American model, virtually 100.0% of the points are situated above the WTP diagonal line. This signifies that the placebo scheme maintains a substantial advantage, and the likelihood of the olaparib scheme being deemed cost-effective is exceedingly remote.

Discussion

This research carried out an evaluation on the cost-effectiveness of the supplementary treatment method of olaparib for early breast cancer that is BRCA-mutated and HER2-negative, from the vantage points of both China and the United States. The findings appear to be mostly in alignment. Practical application of the olaparib regimen proves to be economically challenging, with both the Chinese and American models heavily swayed by the cost of olaparib. The disparities between the two models come in two forms. Initially, the measured utility values for breast cancer in the PFS and PD states vary between the models. Therefore, at the end of the model run, the incremental utility value in the Chinese model is 0.065 and 0.081 in the U.S. model. There is a slight difference, but both imply that the benefits brought by olaparib compared to placebo are not significant. Secondly, the cost parameters included in the two models are different. The primary driving force behind this variance is the cost of Olaparib. In the United States, the cost of Olaparib has remained relatively consistent and has seen a considerable reduction. Conversely, in China, the market price disparity for Olaparib can reach up to four times. Although the price of olaparib has been reduced after it was included in the medical insurance for some indications, it is still unaffordable for many people. Thirdly, the amount people are willing to pay for a certain health utility differs. At present, there is no comprehensive study on the WTP value in the field of pharmacoeconomics in China. Therefore, in the cost-effectiveness analysis, the threshold is usually three times the per capita GDP recommended by WHO, while in the United States, experts in pharmacoeconomics have conducted studies on the threshold range and adopted a determined threshold for cost-effectiveness analysis after multiple measurements. Considering the combined impact of the country's economic level and the level of health and medical care, the actual WTP value in China may deviate from the value used in this study.

In summary, a country's level of economic development, the completeness of the pharmaceutical security system, the advancement of pharmaceutical research, etc., may all have a significant impact on whether an intervention plan is economical. Nevertheless, despite the significant divergence in parameters between China

and the United States, the end conclusion in both models is that the Olaparib regimen isn't cost-effective. This suggests that the survival advantages offered by the intervention plan itself to patients are of paramount importance.

In 2023, a pharmacoeconomic research conducted by Chinese scholars, including Wu H L, holds some pertinence to this study [16]. Their conclusion suggested that for all HER2-negative breast cancer patients, comprehensive gBRCA testing proves more cost-effective than selective gBRCA testing. Yet, our study's model contrasts a treatment plan of gBRCA testing combined with Olaparib to one of no gBRCA testing plus a placebo. Our findings indicate that the Olaparib approach does not provide cost-effectiveness compared to the placebo route. While the conclusions on the cost-effectiveness of the Olaparib scheme in the two studies do not align, under intricate real-world conditions, the two investigations could be viewed as reciprocal and can be factored into economic analyses. Analysts can delve into the unique details of each study based on their individual circumstances, unravel the commonalities and differences between the two investigations, and thereby make holistic decisions.

The 2024 study by Christina M. Zettler found olaparib to be cost-effective in the US [17]. But our results differ. Our study included costs like gBRCA testing, side effects, and nursing fees that were not in their study. Also, some other data were different. These differences may explain the contrasting results.

Limitations of our study should be acknowledged. Firstly, the cost parameters used in the cost-effectiveness analysis were derived from various sources and may have inherent uncertainties. While we employed rigorous data extraction and discounting techniques, the limitations of relying on published literature and inputting data into the Markov model cannot be ignored. Sensitivity and probability analyses were performed to address potential uncertainties; however, real-world complexities such as unaccounted indirect medical costs or variations in drug regimens pose additional limitations. Therefore, the cost parameters in this study should be considered as reference material for auxiliary decision-making rather than definitive values.

Secondly, the utility parameters utilized in the Markov model also have inherent uncertainties stemming from the data sources. Categorizing health utility values is a complex process involving factors such as ethnicity, age, gender, and economic factors within the research sample. Extrapolating research findings to broader populations is subject to conditional restrictions, particularly when the factors specific to the research sample are not adequately considered. Moreover, existing breast cancer health utility studies in China often have small sample sizes, limiting the generalizability of their conclusions to a national level [18]. Thus, while this study obtained health utility parameters for China and the United States, the limitations of these parameters still impact the extrapolation of research findings. The future development of pharmacoeconomics requires a solid and reliable foundation built through incremental efforts and contributions from researchers.

Thirdly, a significant constraint of this study pertains to the intricacies and limitations of the OlympiA trial itself. The trial included patients from various nations, with only a small fraction being Chinese patients, and primarily concentrated on triple-negative breast cancer [6]. The actual subtypes and conditions of breast cancer in China vary, which could lead to potential variances when applying the trial's conclusions to the Chinese scenario. The survival curve in the trial outcomes is based on transfer probability parameters in the Markov model, and the actual benefits of Olaparib adjuvant therapy for Chinese patients with BRCA gene mutation HER2-negative early-stage breast cancer remain unestablished. Nonetheless, the ongoing Chinese cohorts of the OlympiA clinical trial on Olaparib targeted therapy for breast cancer may yield additional insights, and the data and findings of this study can still be utilized as a benchmark for future research enhancements.

Fourthly, this investigation specifically scrutinized the cost-effectiveness of Olaparib adjuvant targeted therapy for early-stage breast cancer with BRCA gene mutation, considering the healthcare viewpoints of both China and the United States. The conclusions obtained can provide economic references for decision-making by health departments and treatment planning in both countries. However, differences in the field of pharmacoeconomics between these two contexts should be considered. Furthermore, this study can offer methodological and data processing references for future cost-effectiveness analyses related to olaparib treatment for breast cancer in different countries. The findings can contribute reliable economic evidence for the potential approval of olaparib treatment for HER2-negative early breast cancer with BRCA gene mutations by health departments and the inclusion of this indication in medical insurance catalogs in China and the United States.

Due to the constraints of the research scope, the applicability of this study also has certain limitations. Firstly, the research objective of this study is specifically focused on patients with BRCA gene mutation, HER2-negative, early-stage breast cancer, and the selection criteria for patient inclusion also have specific restrictions. The specific conclusions may be difficult to extrapolate to the treatment of different types of breast cancer; second, this study only conducted an analysis of China and the United States, and the conclusions are not sufficient to

extrapolate to other countries; third, since both China and the United States are countries with vast territories, the possible disparities in wealth, differences in medical service levels, and differences in medical security systems between different regions may result in actual situations that differ from the conclusions of this study. Therefore, it is necessary to consider the conclusions of this study from a comprehensive perspective and strive to maximize the use of reference literature with the spirit of inclusiveness.

Author contributions

X.X.W. and C.X.X. conceived and designed the study. All authors discussed, critically revised, and approved the study protocol. J.Z. and H.S. were responsible for the organization and conduct of the study and supervised it. J.R.S. was responsible for the data collection and analysis. J.R.S. and J.Q.C. contributed to the data collection and analysis. C.X.X. and X.X.W. drafted the first version of the manuscript. All authors elaborated, discussed, and approved the final version of the manuscript for publication.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The authors declare no competing interests.

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