Original Article

JHSMR Journal of Health Science and Medical Research

Cost-Effectiveness of Sorafenib, Lenvatinib, and FOLFOX4 for Advanced Hepatocellular Carcinoma in China

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Received 10 June 2024 ● Revised 19 July 2024 ● Accepted 28 July 2024 ● Published online 21 February 2025

Abstract:

Objective: Liver cancer is the third leading cause of cancer mortality in China. This study assesses the cost-effectiveness of sorafenib, lenvatinib, and FOLFOX4 in the treatment of advanced hepatocellular carcinoma (HCC) to inform clinical decision-making.

Material and Methods: We used a Markov model to simulate the progression of HCC and calculate Quality-Adjusted Life Years (QALYs) and Incremental Cost-Effectiveness Ratios (ICERs) under two scenarios. Costs were obtained from the Yaozhi Network, while transition probabilities and utilities were derived from the REFLECT, EACH, and CELESTIAL clinical trials. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to evaluate model robustness and parameter uncertainty.

Results: In Scenario A, using market-listed prices, sorafenib, and lenvatinib were found to be more cost-effective than FOLFOX4, with ICERs of $11,635.28 and $1,499.93 per QALY, respectively, both below the cost-effectiveness threshold. In Scenario B, with centralized procurement prices, sorafenib had a negative ICER of -$7,351.26 per QALY, indicating

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J Health Sci Med Res 2025;43(4):e20251153
doi: 10.31584/jhsmr.20251153
www.jhsmr.org

cost savings with improved outcomes, while lenvatinib had an ICER of $2,685.99 per QALY. Sensitivity analysis revealed that drug costs, utilities of disease progression, and discount rates were key determinants of ICER values.

Conclusion: Sorafenib and lenvatinib are significantly more cost-effective compared to FOLFOX4, particularly under centralized procurement pricing. These results support the inclusion of these treatments in public health policy to enhance healthcare outcomes and optimize resource allocation, thereby improving the economic and quality-of-life metrics for patients with HCC.

Keywords: centralized procurement policies, cost-effectiveness analysis, hepatocellular carcinoma, markov model, sensitivity analysis

Introduction

Hepatocellular carcinoma (HCC) remains one of the most formidable health challenges globally, with a particularly high burden in China, where it ranks among the leading causes of cancer-related mortality. Despite advances in treatment options, late-stage HCC presents unique challenges due to limited therapeutic interventions appropriate for advanced disease stages[1]. This study aims to analyze and compare the cost-effectiveness of three prevalent systemic treatment regimens for advanced HCC: Sorafenib, Lenvatinib, and FOLFOX4.

Sorafenib, a multi-targeted tyrosine kinase inhibitor, was the first systemic drug shown to provide survival benefits for patients with advanced HCC, receiving approval from the FDA in 2007 and subsequently in China in 2008[2]. It acts by inhibiting tumor cell proliferation and angiogenesis, extending patient survival significantly, as evidenced by various global clinical trials, including the SHARP trial, which showed a median overall survival (OS) of 10.7 months compared to 7.9 months for the placebo group[3]. However, studies conducted in Asian populations, including China, indicated a lower median OS. This suggests that drug efficacy can vary significantly across different geographical regions due to factors such as genetic differences, environmental influences, dietary habits and healthcare infrastructure. These variations highlight the need for region-specific clinical studies to better understand and optimize treatment outcomes for different populations.

Lenvatinib, another multi-receptor tyrosine kinase inhibitor approved for use in the US, EU, Japan, and China[4], demonstrated a median OS of 13.6 months in the REFLECT trial, surpassing that of Sorafenib's 12.3 months[5]. This establishes Lenvatinib as a potent first-line option for unresectable HCC.

On the other hand, FOLFOX4, a chemotherapeutic regimen consisting of Oxaliplatin, Fluorouracil (5-FU), and Leucovorin (LV), traditionally used in colorectal cancer, has been adapted for HCC treatment. The EACH study reported a median OS of 6.40 months for FOLFOX4 compared to 4.97 months for Doxorubicin in Asian populations, including China[6].

Given the complex nature of treatment costs, including direct costs (such as drug and healthcare service fees) and indirect costs (such as productivity losses due to illness), this study focuses on direct costs only. Indirect costs, although significant, are not included in this analysis to maintain clarity and precision in evaluating the economic and therapeutic impacts of these treatments under China's healthcare policy framework. Indirect costs typically include productivity losses, time, and other non-medical expenses, which are estimated by calculating their monetary value.

By employing quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) as primary metrics, we evaluate which regimen offers the best value for extending patient survival, especially within the constraints of China's centralized drug procurement policies. This assessment is crucial for optimizing resource allocation in China's healthcare system and enhancing patient outcomes in real-world settings.

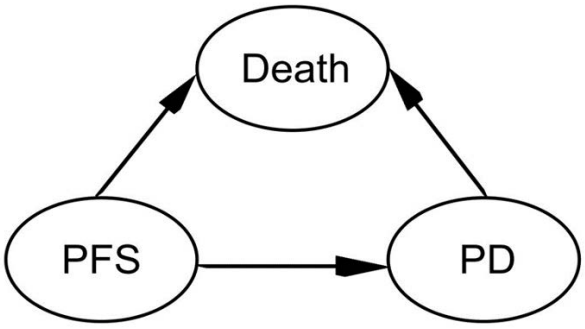
Material and Methods

Study perspective

This study evaluates the cost-effectiveness of Sorafenib, Lenvatinib, and FOLFOX4 for the treatment of advanced HCC from the healthcare system perspective in China, reflecting varying drug costs under two scenarios: (a) using market-listed prices for Sorafenib and Lenvatinib, and (b) using prices obtained through national centralized drug procurement.

Model structure

A Markov model was developed using TreeAge Pro (version 2023, TreeAge Software, Inc.) to simulate the disease process of advanced HCC and assess the cost-effectiveness of the treatment options. The model categorizes patients with advanced HCC undergoing first-line treatment into three health states: progression-free survival (PFS), disease progression (PD), and death. Each Markov cycle was set at one month, with a total simulation period of 120 months. The transitions between these states reflect changes in health over time, with cycle-specific survival curves derived from clinical trial data. A discount rate of 5% per annum, recommended by the "Chinese guidelines for pharmacoeconomic evaluations (2020)," was applied to costs and utilities to present the present value of future costs and health benefits[7].



PFS=progression-free survial, PD=disease progression

Figure 1 Markov model for advanced hepatocellular carcinoma treatment analysis

Model inputs

Efficacy and safety

Input data on the efficacy and safety profiles of the treatments were derived from various clinical trials. For Sorafenib and Lenvatinib, data were obtained from the REFLECT trial, a multicenter, randomized, open-label, non-inferiority Phase III study. The FOLFOX4 data came from the each trial, comparing FOLFOX4 against doxorubicin in patients across several Asian countries, including mainland China, Taiwan, Korea, and Thailand[8,9]. These trials provide the survival curves for calculating transition probabilities between health states (Table 1).

Cost inputs

From the perspective of the healthcare system, the costs inputted into the model include drug expenses, hospitalization fees, diagnostic testing fees, and the management costs of adverse reactions. As the data is derived from multiple international clinical trials and pharmacoeconomic literature on similar drugs, costs were originally calculated in USD. The costs are reported on June 30, 2023, the US Dollars (1 Dollar is equal to 7.2258 RMB)[10].

The treatment regimens used in the model adhere to the dosages and administrations provided in clinical trials. According to the latest statistical data report from China in 2023, the average height of a woman is 158 cm with a weight of 65.4 kg, while the average height for a man is 175.7 cm with a weight of 79.6 kg (National Health Commission of the People's Republic of China, 2023). Thus, the average adult height in China in 2023 is calculated to be 166.85 cm and the weight 71.8 kg. In the REFLECT trial, patients with advanced HCC recommended to undergo Sorafenib treatment are advised to take 400 mg twice daily. For Lenvatinib, according to the REFLECT trial, patients weighing under 60 kg should take 8 mg/day, while those over 60 kg are recommended a dose of 12 mg/day. Based on the average adult weight in China, the dose of Lenvatinib is calculated to be 12 mg/day. For the FOLFOX4 regimen, the EACH study recommends a treatment cycle of 48 hours every 14 days (approximately 2.14 cycles per month), and the dosage of FOLFOX4 is related to the patient's body surface area (BSA, cm^2), calculated as 0.0061×height (cm) +0.0128×weight (kg) −0.1529. The dosage and administration of the FOLFOX4 regimen are detailed in Table 2.

Table 1 Comparison of baseline characteristics

Characteristics	Sorafenib		Lenvatinib		FOLFOX4	
	n	%	n	%	n	%
Total patients	476	(100)	478	(100)	184	(100)
Age (years)	64	–	63	–	53	–
Gender						
Male	401	(84)	405	(85)	166	(90.2)
Female	75	(16)	73	(15)	18	(9.8)
HBV infection	228	(48)	251	(53)	171	(92.9)
HCV infection	126	(27)	91	(19)	9	(4.9)
Child-pugh stage						
A	357	(75)	368	(77)	163	(88.6)
B	119	(25)	110	(23)	21	(11.4)
BCLC stage						
B	92	(19)	104	(22)	39	(21.2)
C	384	(81)	374	(78)	145	(78.8)
HR (PFS)	1.08	–	1.01	–	1.10	–
HR (OS)	0.92	–	0.85	–	1.05	–
Median PFS (months)	6.5	–	7.3	–	5.9	–
Median OS (months)	14.7	–	13.8	–	12.5	–

HR (PFS)=hazard ratio for progression-free survival, HR (OS)=hazard ratio for overall survival, Median PFS=median progression-free survival in months, Median OS=median overall survival in months, HBV=hepatitis B virus, HCV= hepatitis C virus, BCLC=Barcelona clinic liver cancer Child-pugh stage is a liver function assessment system, BCLC stage is the clinical staging system for hepatocellular carcinoma (Barcelona clinic liver cancer)

Table 2 FOLFOX4 treatment regimen: dosage and administration

Drug	Dosage	Administration Method
Oxaliplatin	85 mg/m^2	Day 1, intravenous infusion over 2 hours
5-FU	400 mg/m^2	Intravenous on day 1 and day 2
	600 mg/m^2	Continuous infusion over 22 hours from day 1 to day 2
Leucovorin (LV)	200 mg/m^2	Day 1 and day 2, intravenous infusion over 2 hours

Given China's centralized procurement policies, the inclusion of Sorafenib and Lenvatinib in the procurement system has led to reduced drug prices and altered cost-effectiveness, making the pre- and post-procurement economics a worthy research focus[11]. This study includes the procurement and original research prices for the drugs, including the three medications in the FOLFOX4 regimen: Oxaliplatin, 5-FU, and LV. Prices for Sorafenib, Lenvatinib, Oxaliplatin, 5-FU, and LV were obtained from drug intelligence network, and the per-cycle costs were calculated based on the prescribed dosage and administration.

In addition to basic medication treatments, patients undergoing the three treatment regimens need to have their medical and hospitalization costs calculated (Table 3). Since adverse reactions occur throughout the treatment process, the incidence rates of these reactions are evenly distributed monthly. For each of the three treatment strategies, costs for grade 3 adverse reactions with an incidence rate higher than 10% are calculated, including hand-foot skin reaction and hypertension (Supplementary Table 1). These calculations are based on recommendations from Chinese clinical experts on advanced HCC and literature data.

Transition probabilities and utility

To assess the cost-effectiveness of treatments for advanced HCC, a model incorporating three health states—progression-free, progression, and death—was established. The model cycle was set to one month. Transition probabilities for HCC patients were derived from survival curves of the CELESTIAL clinical trial[12]. The monthly transition probabilities were calculated using the formula: P (1 month)=1−(0.5)$^{(1/\text{median PFS})}$ and P (1 month)=1−(0.5)$^{(1/\text{median OS})}$[13].

Utility values were assessed using the EQ-5D index, which measures health outcomes based on specific health states with QALYs. Different health states were assigned specific utility values: 0.76 for PFS, 0.68 for OS, and 0 for the death state[14].

Cost-effectiveness analysis

A Markov model was established to evaluate the cost and effectiveness of different treatment strategies for first-line treatment in HCC patients. The total costs, QALYs, and ICERs were calculated. Following the guidelines of the "Chinese Pharmacoeconomic Evaluations" (2020), the willingness-to-pay (WTP) threshold was set at 1.5 to 3 times the average GDP per capita of China. As of December 2023, following the final verification of the 2022 GDP data by the National Bureau of Statistics, based on the statistical yearbook, Ministry of Finance final accounts, and annual financial data from relevant departments, the study set the WTP at $35,569 (3 times the average GDP per capita of China)[15]. Considering the healthcare policy environment, this study established two scenarios to conduct cost-effectiveness analyses for the three treatment regimens: (a) drug costs based on the original research prices of Sorafenib and Lenvatinib; (b) drug costs based on the centralized procurement prices of Sorafenib and Lenvatinib.

Table 3 Model input parameters

Parameter	Baseline value	Range	Distribution	Source
Drug cost/month				
Sorafenib	$1,483.14	$1,186.52–$1,779.76	Gamma	Yaozhi network
Lenvatinib	$1,345.57	$1,076.45–$1,614.69	Gamma	Yaozhi network
FOLFOX4	$575.42	$459.96–$690.88	Gamma	Yaozhi network
Drug cost/month (Centralized procurement)				
Sorafenib	$220.14	$176.88–$263.40	Gamma	Yaozhi network
Lenvatinib	$602.31	$481.85–$722.77	Gamma	Yaozhi network
FOLFOX4	$575.42	$459.96–$690.88	Gamma	Yaozhi network
Monthly medical cost				
PFS	$81.87	$65.47–$98.27	Gamma	Calculated
PD	$163.72	$130.98–$196.46	Gamma	Calculated
AE cost/month (Sorafenib)	$7.71	$6.18–$9.24	Gamma	Calculated
AE cost/month (Lenvatinib)	$0.92	$0.74–$1.10	Gamma	Calculated
AE cost/month (FOLFOX4)	$153.66	$122.93–$184.39	Gamma	Calculated
Inpatient cost/month	$12.18	$9.74–$14.62	Gamma	Calculated
Sorafenib transition probability				
PFS to PD	0.0625	0.04375–0.08125	Generalized gamma	Weiting Liao et al.
PFS to Death	0.102	0.0714–0.1326	Generalized gamma	Weiting Liao et al.
PD to Death	0.1184	0.08288–0.15392	Generalized gamma	Weiting Liao et al.
Lenvatinib transition probability				
PFS to PD	0.0906	0.06342–0.1178	Generalized gamma	Calculate
PFS to Death	0.0497	0.03479–0.06461	Generalized gamma	Calculate
PD to Death	0.1042	0.07294–0.13546	Generalized gamma	Calculate
FOLFOX4 transition probability				
PFS to PD	0.2509	0.17563–0.32617	Generalized gamma	Calculate
PFS to Death	0.1145	0.08015–0.14885	Generalized gamma	Calculate
PD to Death	0.1145	0.08015–0.14885	Generalized gamma	Calculate
Utility values				
Utility PFS	0.76	0.61–0.91	Beta	Thompson et al.
Utility PD	0.68	0.54–0.82	Beta	Thompson et al.
Discount (%)	5	0–8	Beta	Guidelines for pharmacoeconomic evaluations in China (2020)

PFS=progression-free survival, PD=disease progression, AE=adverse event, PFS to PD=progression-free survival to disease progression
All costs have been converted to USD based on the exchange rate of 1 USD=7.2258 RMB

Uncertainty analysis

Sensitivity analysis

To test the robustness of the model outcomes, a one-way sensitivity analysis (OWSA) was performed on 21 parameters, including all costs, transition probabilities, and utility values. The study assumed that medical service costs could fluctuate by ±20%. Based on data from the drug intelligence network, drug price limits were set to allow for a fluctuation range of ±20%. Additionally, the costs for adverse reaction management, the utility values during PFS and PD, and the costs during the PD period were assumed to vary by ±20% from the mean. Transition probabilities were allowed to fluctuate within a range of ±30%.

Probabilistic sensitivity analysis (PSA)

A PSA was performed by simulating the model 1,000 times, allowing all parameters to vary simultaneously according to predefined distributions (Gamma for cost parameters and Beta for probabilities and utilities). This analysis helps in understanding the impact of parameter uncertainty on the study results, visualized through cost-effectiveness acceptability curves (CEACs) and scatter plots on the cost-effectiveness plane.

Ethics approval

This study used previously published, anonymized data, exempting it from ethical approval according to institutional and national guidelines. All procedures conformed to the Helsinki Declaration (1975, revised 2013) and complied with data protection and privacy laws.

Results

Cost-effectiveness analysis

This study followed the consolidated health economic evaluation reporting standards reporting guideline (Supplementary Table 2). The study evaluated the cost-effectiveness of Sorafenib, Lenvatinib, and FOLFOX4 under two different pricing scenarios: market-listed prices (Scenario A) and centralized procurement prices (Scenario B). The analysis incorporated total costs, QALYs, and ICERs to determine the economic value of each treatment (Table 4).

In Scenario A, which considers market-listed prices, monthly treatment costs were $1,483.14 for Sorafenib, $1,345.57 for Lenvatinib, and $575.42 for FOLFOX4. Throughout the study period, the total expenses accrued were $9,937.22 for Sorafenib, $12,099.95 for Lenvatinib, and $5,129.94 for FOLFOX4. The QALYs recorded were 4.58 for Sorafenib, 6.02 for Lenvatinib, and 4.16 for FOLFOX4. The ICERs showed that Sorafenib is cost-effective compared to FOLFOX4, with an ICER of $11,635.28 per QALY. Sorafenib was then compared to Lenvatinib, yielding an ICER of $1,499.93 per QALY.

In Scenario B, which explores the impact of centralized procurement prices, the monthly treatment costs were significantly reduced to $220.14 for Sorafenib, $602.31 for Lenvatinib, and $575.42 for FOLFOX4. Over the course of the study, this resulted in total costs of $2,094.15 for Sorafenib, $5,963.23 for Lenvatinib, and $5,129.88 for FOLFOX4. The ICERs demonstrated notable economic benefits, with Sorafenib showing a negative ICER of -$7,351.26 per QALY relative to FOLFOX4, indicating significant cost savings and enhanced cost-effectiveness. Sorafenib was then compared to Lenvatinib, yielding an ICER of $2,685.99 per QALY.

Table 4 Comprehensive cost-effectiveness analysis of cancer treatments under different pricing scenarios

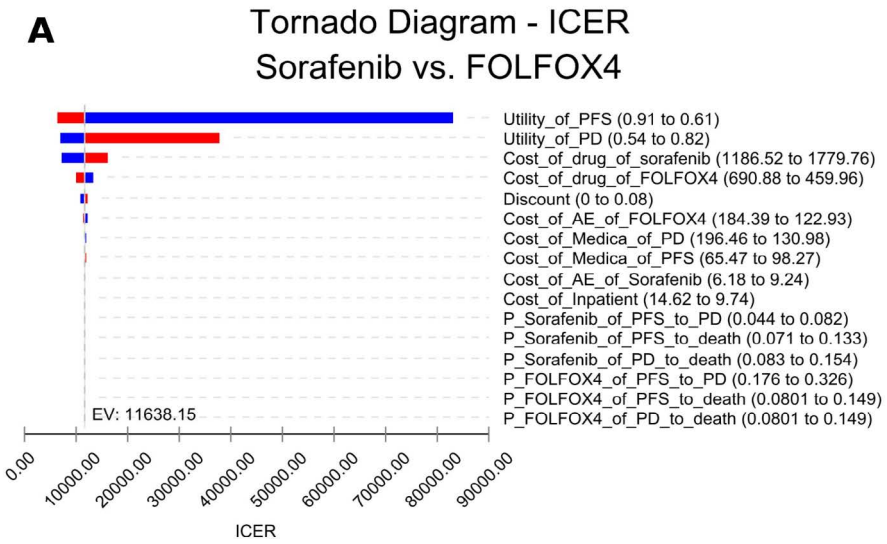
Scenario	Treatment	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	ICER ($/QALY)
A	FOLFOX4	$5,129.94	4.16	-	-	-
	Sorafenib	$9,937.22	4.58	$4,807.28	0.42	$11,635.28
	Lenvatinib	$12,099.95	6.02	$2,161.90	1.44	$1,499.93
B	FOLFOX4	$5,129.88	4.16	-	-	-
	Sorafenib	$2,094.15	4.58	-$3,035.73	0.42	-$7,351.26
	Lenvatinib	$5,963.23	6.02	$3,868.85	1.44	$2,685.99

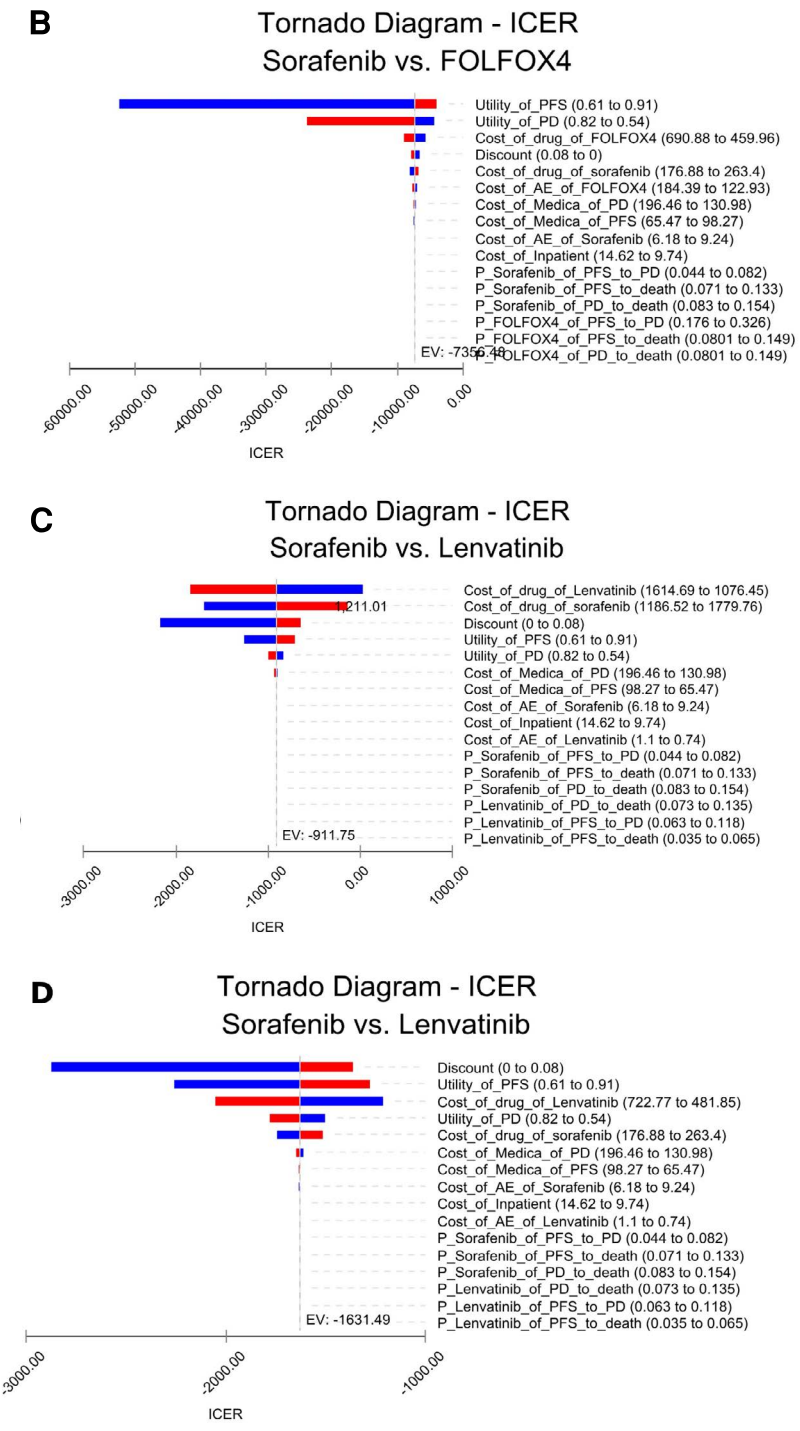
QALY (Quality-Adjusted Life Year) measures the value of health outcomes. ICER (Incremental Cost-Effectiveness Ratio) is the ratio of the change in costs to the change in effects (QALYs)

OWSA

The OWSA was conducted to determine the robustness of the model's outcomes to changes in individual parameters. Figures 2A and 2B illustrate the tornado diagrams from Scenario A and Scenario B, comparing Sorafenib with FOLFOX4. Figure 2A demonstrates that the utilities of PFS and PD are the most impactful variables affecting the ICER when comparing Sorafenib with FOLFOX4. Changes in these utilities have the greatest influence on the ICER, highlighting their importance in the analysis. In Figure 2B, which presents results under centralized procurement scenarios, the utilities of PFS and PD still play a significant role. Additionally, the cost of the drug Sorafenib and the discount rate also have considerable impacts, suggesting that both clinical and economic factors are crucial in determining cost-effectiveness in centralized procurement settings.

Figures 2C and 2D display the OWSA results for Sorafenib compared to Lenvatinib under Scenario A and Scenario B, respectively. Figure 2C indicates that the cost of the drugs and the discount rate had a greater impact on the model than the utilities of PFS and PD, underscoring the importance of drug pricing and economic parameters in the cost-effectiveness analysis. Figure 2D shows the results for centralized procurement scenarios, comparing Sorafenib with Lenvatinib. The discount rate and utilities of PFS again show significant influence, along with the cost of the drugs. The parameters with substantial impacts on the model include the cost of drugs, utilities of PFS and PD, discount rate, costs of managing adverse reactions, and medical costs. The transition probabilities among the different health states of the three treatment strategies had the least impact.





ICER=incremental cost-effectiveness

Figure 2 Figure 2 Tornado diagrams of ICER sensitivity analysis panel A compares branded Sorafenib vs. FOLFOX4 (Scenario A), Panel B compares centralized procurement Sorafenib vs. FOLFOX4 (Scenario B), panel C compares branded Sorafenib vs. branded Lenvatinib (Scenario A), and panel D compares centralized procurement Sorafenib vs. centralized procurement Lenvatinib (Scenario B).

PSA and cost-effectiveness acceptability curves

The PSA and CEACs were combined to illustrate the economic viability of each treatment strategy under different WTP thresholds. The CEACs (Figure 3 A and B) illustrate the probability that each treatment is cost-effective, ensuring that the summed probabilities of all comparison scenarios equal one. The scatter plots (Figure 4) further visualize the probabilistic distribution of the cost-effectiveness outcomes.

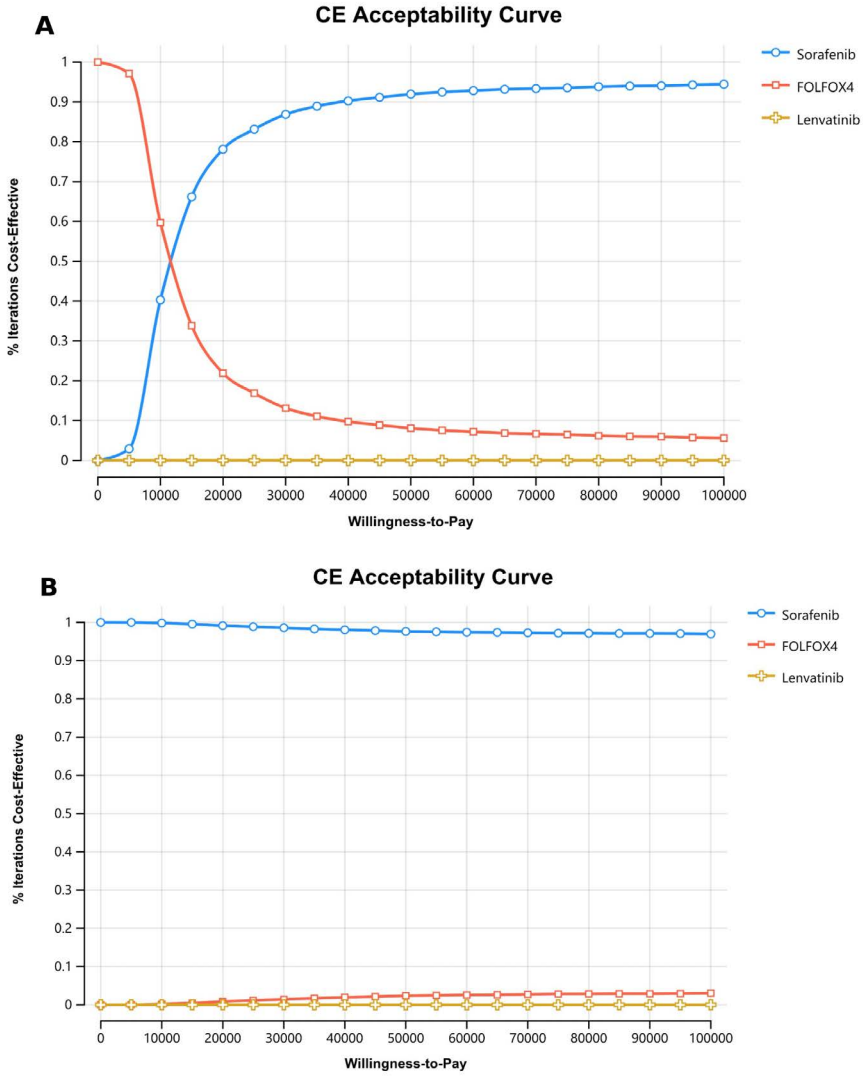
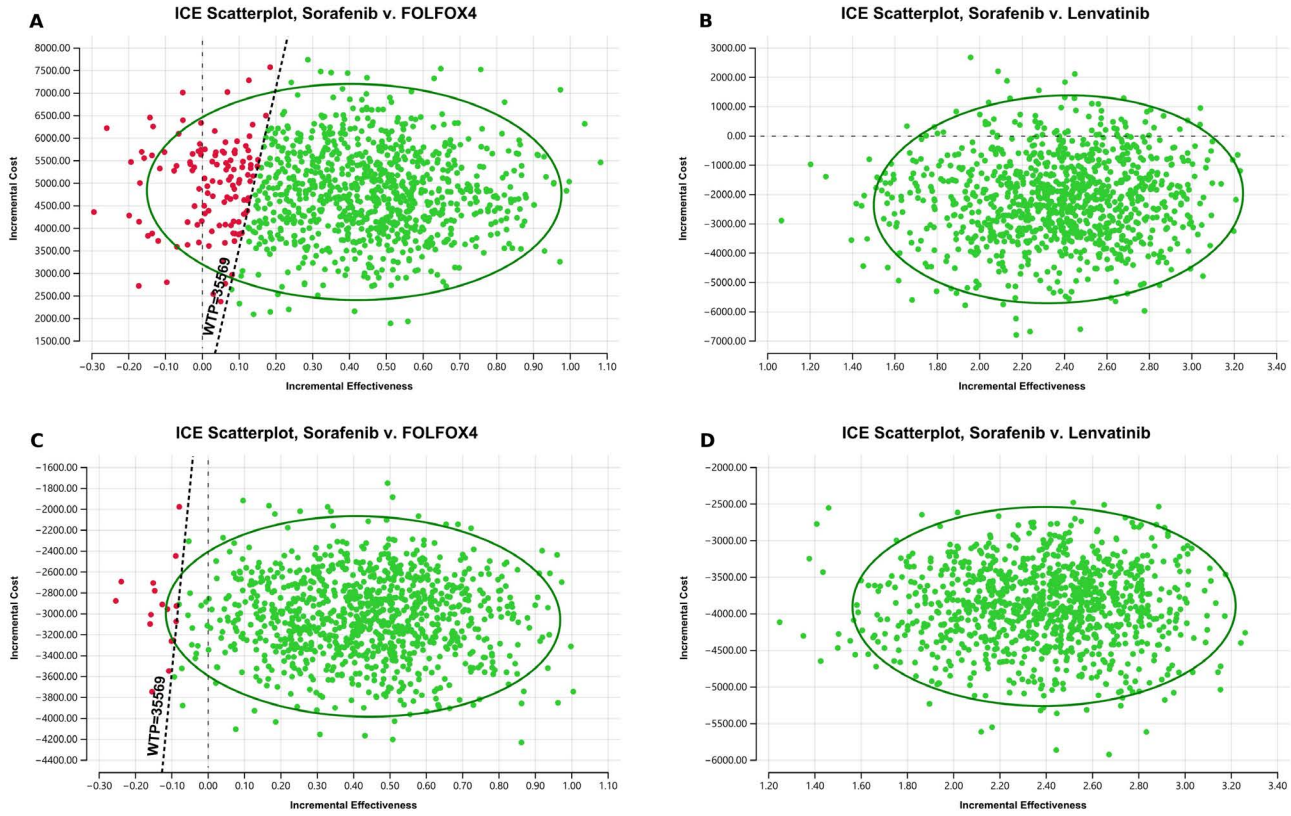


Figure 3 Cost-Effectiveness Acceptability Curves Based on Willingness-to-Pay Thresholds Panel A compares branded Sorafenib vs. FOLFOX4 vs. Lenvatinib, while Panel B compares centralized procurement Sorafenib vs. FOLFOX4 vs. Lenvatinib.

In Scenario A, the PSA and CEAC results showed that Sorafenib had a higher probability of cost-effectiveness compared to FOLFOX4 at a WTP threshold of $35,569 (three times the average GDP per capita of China). Sorafenib also demonstrated cost-effectiveness when compared to Lenvatinib. The scatter plot for branded Sorafenib vs. FOLFOX4 (Figure 4A) shows a concentration of green points indicating cost-effectiveness at higher WTP thresholds, while the scatter plot for branded Sorafenib vs. Lenvatinib (Figure 4B) shows a similar trend with Sorafenib being more cost-effective.

In Scenario B, the analysis indicated that Sorafenib was cost-effective compared to FOLFOX4, with a significant probability of cost savings. Sorafenib also maintained a high probability of cost-effectiveness when compared to Lenvatinib. The scatter plot for centralized procurement Sorafenib vs. FOLFOX4 (Figure 4C) and centralized procurement Sorafenib vs. Lenvatinib (Figure 4D) both highlight the cost-effectiveness of Sorafenib, especially at higher WTP thresholds.



Panel A compares branded Sorafenib vs. FOLFOX4, Panel B compares branded Sorafenib vs. branded Lenvatinib, Panel C compares centralized procurement Sorafenib vs. FOLFOX4, and Panel D compares centralized procurement Sorafenib vs. centralized procurement Lenvatinib.

Figure 4 Cost-effectiveness probabilistic scatter plots based on willingness-to-pay thresholds.

Discussion

The findings of this study indicate a significant impact of centralized procurement on the cost-effectiveness of treatments for advanced HCC. When using market-listed prices, Lenvatinib emerged as the most cost-effective treatment with an ICER of $1,499.93 per QALY. However, when centralized procurement prices were applied, Sorafenib demonstrated a substantial cost advantage with a negative ICER of -$7,351.26 per QALY, indicating cost savings with improved outcomes[16,17]. This shift highlights the critical role of pricing policies in determining the economic viability of cancer treatments. Centralized procurement not only reduces drug costs but also makes high-cost medications more economically justifiable and accessible[18]. Our study further illustrates the superior cost-effectiveness of Sorafenib and Lenvatinib over FOLFOX4 in treating advanced HCC. In both pricing scenarios, these two drugs offered better QALYs and lower ICERs compared to FOLFOX4. For instance, under market-listed prices, Sorafenib and Lenvatinib yielded ICERs of $11,635.28 and $1,499.93 per QALY, respectively[19]. These results are consistent with clinical trials showing better median PFS and OS for Sorafenib and Lenvatinib. The integration of these treatments into clinical practice, especially under centralized procurement policies, could significantly enhance patient outcomes and resource allocation efficiency in China's healthcare system[20].

The robustness of our economic evaluations was validated through OWSA and PSA. The OWSA results indicated that the utilities of PFS and PD were the most impactful variables affecting the ICER. The PSA further demonstrated the stability of our models, showing that variations in key clinical and economic parameters, such as drug costs and discount rates, significantly influence cost-effectiveness outcomes[21]. These analyses provide a comprehensive understanding of the potential variability in our findings and underscore the reliability of our economic models.

These results underscore the importance of pricing policies in healthcare economics. The significant reduction in drug costs through centralized procurement not only makes high-cost medications more accessible but also enhances their economic justification. This finding is crucial for policymakers and healthcare providers, as it illustrates the potential of policy-driven pricing strategies to improve cost-effectiveness and optimize resource allocation in the healthcare system[22].

While our study provides valuable insights into the cost-effectiveness of treatments for advanced HCC, it has limitations. The economic models rely on assumptions that may not universally apply across different healthcare settings or populations. Additionally, our study does not account for potential long-term side effects or the impacts on quality of life beyond the QALY measure. Future research should include more detailed cost calculations that consider the full spectrum of adverse reaction management costs and regional variations in health insurance policies. Moreover, incorporating international data could enhance the global applicability of our findings, considering the variability in medical cost structures and treatment strategies across different countries[23].

Conclusion

This study used a Markov model to evaluate the cost-effectiveness of Sorafenib, Lenvatinib, and FOLFOX4 in treating advanced HCC in China. The findings demonstrate that Lenvatinib is the most cost-effective option under market-listed prices, while Sorafenib shows a significant cost advantage under centralized procurement prices. Both drugs offer superior benefits over FOLFOX4. These results highlight the critical role of healthcare system reforms and policy adjustments in optimizing treatment strategies to ensure efficient resource utilization and improved patient outcomes.

Author contribution

M.Z. conceptualized the study and prepared the original draft. X.Z. and M.Y. were responsible for data curation and analysis. XL.Z. contributed to the research and assisted with manuscript preparation. J.Y. and F.L. supervised the project, secured funding, and provided final approval for publication. All authors have read and agreed to the published version of the manuscript.

Acknowledgement

We sincerely thank all individuals and organizations that significantly contributed to this manuscript. Their expertise and support were crucial to our research. Special thanks to our colleagues at Kunming Medical University for their valuable guidance and feedback.

Funding sources

This study was funded by (1) Yunnan Provincial Department of Education Science Research Fund (2025J0227); (2) Kunming Medical University Education and Teaching Research Project, 2023 (2023-JY-Y-090); (3) Undergraduate Teaching Quality and Reform Project, Kunming Medical University, 2024 (Clinical Pharmacokinetics, 2024KCSZSFXM022); (4) First-Class Discipline Team of Kunming Medical University (Pharmaceutical Policy Research and Practice), 2024 (2024XKTDPY21); (5) "Establishing a Model Modern Biomedical Industry College" Project (JG2023001). The funding bodies had no role in the design, data collection, analysis, interpretation, or manuscript preparation of this study.

Conflict of interest

The authors declare no conflicts of interest.

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Supplementary Table 1: Incidence and costs of adverse reactions

Intervention	Adverse reaction	Incidence per cycle (30 days) (%)	Cost per treatment
Sorafenib	HFSR (Hand-foot skin reaction)	12.00	$4.00
	Hypertension	18.80	$38.50
Lenvatinib	HFSR (Hand-foot skin reaction)	23.00	$4.00
FOLFOX4	AST/ALT elevation	31.70	$59.00
	Anorexia	26.80	$26.00
	Bilirubin elevation	20.20	$349.00
	Fatigue	17.50	$3.00
	Diarrhea	15.90	$13.00
	Sensory neuropathy	15.30	$3.00
	Myelosuppression	68.90	$79.00

HFSR=hand-foot skin reaction, often caused by multi-targeted tyrosine kinase inhibitors (MTKI) affecting the hands or feet.

Supplementary Table 2: CHEERS 2022 Checklist

Item	Guidance for Reporting	Reported in Section
Title	1. Identify the study as an economic evaluation and specify the interventions being compared.	Page 1
Abstract	2. Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 1
Background and objectives	3. Give the context for the study, the study question, and its practical relevance for decision-making in policy or practice.	Page 2
Health economic analysis plan	4. Indicate whether a health economic analysis plan was developed and where available.	Page 3
Study population	5. Describe characteristics of the study population (such as age range, demographics, socioeconomic or clinical characteristics).	Page 4, Table 1
Setting and location	6. Provide relevant contextual information that may influence findings.	Page 4
Comparators	7. Describe the interventions or strategies being compared and why chosen.	Page 3
Perspective	8. State the perspective(s) adopted by the study and why chosen.	Page 5
Time horizon	9. State the time horizon for the study and why appropriate.	Page 5
Discount rate	10. Report the discount rate(s) and reason chosen.	Page 5
Selection of outcomes	11. Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 6
Measurement of outcomes	12. Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 6
Valuation of outcomes	13. Describe the population and methods used to measure and value outcomes.	Page 6

Supplementary Table 2: (continued)

Item	Guidance for Reporting	Reported in Section
Measurement and valuation of resources and costs	14. Describe how costs were valued.	Page 6
Currency, price date, and conversion	15. Report the dates of the estimated resource quantities and unit costs plus the currency and year of conversion.	Page 6
Rationale and description of model	16. If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Page 7, Figure 1
Analytics and assumptions	17. Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 7
Characterizing heterogeneity	18. Describe any methods used for estimating how the results of the study vary for sub-groups.	Page 8
Characterizing distributional effects	19. Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Page 8
Characterizing uncertainty	20. Describe methods to characterize any sources of uncertainty in the analysis.	Page 8
Approach to engagement with patients and others affected by the study	21. Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	Page 9
Results		
Study parameters	22. Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Page 9, Table 3
Summary of main results	23. Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	Page 10, Table 4
Effect of uncertainty	24. Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon if applicable.	Page 11, Figures 2A-2D
Effect of engagement with patients and others affected by the study	25. Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study.	N/A
Discussion		
Study findings, limitations, generalizability, and current knowledge	26. Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	Page 12

Supplementary Table 2: (continued)

Item	Guidance for Reporting	Reported in Section
Other relevant information		
Source of funding	27. Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis.	Page 13
Conflicts of interest	28. Report authors' conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Page 13

This checklist is based on the revised manuscript provided, ensuring that each section corresponds accurately to the manuscript's content.