



Lenvatinib versus sorafenib for unresectable hepatocellular carcinoma: a cost-effectiveness analysis

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Aim: To investigate the cost-effectiveness of lenvatinib and sorafenib in the treatment of patients with nonresected hepatocellular carcinoma in China. **Materials & methods:** Markov model was used to simulate the direct medical cost and quality-adjusted life years (QALY) of patients with hepatocellular carcinoma. Clinical data were derived from the Phase 3 randomized clinical trial in a Chinese population. **Results:** Sorafenib treatment resulted in 1.794 QALYs at a cost of \$43,780.73. Lenvatinib treatment resulted in 2.916 QALYs for patients weighing <60 and ≥60 kg at a cost of \$57,049.43 and \$75,900.36. The incremental cost-effectiveness ratio to the sorafenib treatment group was \$11,825.94/QALY and \$28,627.12/QALY, respectively. **Conclusion:** According to WHO's triple GDP per capita, the use of lenvatinib by providing drugs is a cost-effective strategy.

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Keywords: cost-effectiveness • hepatocellular carcinoma • lenvatinib • sorafenib

In 2018, hepatocellular carcinoma (HCC) is expected to be the sixth most common cancer type and the fourth major cause of cancer death in the world with 841,000 new cases and 782,000 deaths each year [1]. Nearly 50% of the world's HCC patients are from China, which has the highest number of new cases and deaths of HCC in the world [2]. Latest statistics show that primary HCC has jumped to the secondary cause of death in China, which is a serious threat to people's lives and health [3–5]. The pathological type of primary carcinoma of the liver is mainly HCC, accounting for 85–95% [6]. The most important influencing factors of HCC in China are chronic hepatitis B virus (HBV) infection and eating of food contaminated with aflatoxin [1]. The incidence of HCC is hidden, most patients are no longer able to receive radical surgical treatment at the time of diagnosis, and drug therapy has become one of the important methods of HCC treatment.

Lenvatinib was approved for listing in China in September 2018, which provides new options for the first-line treatment of HCC patients. Only sorafenib and lenvatinib have been approved for the first-line treatment of advanced HCC molecular targeted drugs. REFLECT is a global multicenter, randomized, open and noninferior Phase III clinical trial [7]. Lenvatinib's overall survival (OS) improvement is not inferior to sorafenib, progression-free survival (PFS), time to progress and objective response rate values were significantly better for lenvatinib than for sorafenib. The China subgroup data [8,9] showed lenvatinib's OS was significantly better by 4.8 months (15.0 vs 10.2 months) compared with that of sorafenib. In addition, lenvatinib was significantly better than sorafenib at the three secondary end points of PFS (9.2 vs 3.6 months), time to progress (11.0 vs 3.7 months) and objective response rate (21.5 vs 8.3%). For patients with HBV infection, lenvatinib has a more significant advantage than sorafenib (OS: 14.9 vs 9.9 months). Lenvatinib has shown better effectiveness in the Chinese population, it may be due to Chinese patients mostly in combination with HBV, cirrhosis and other basic liver diseases.

In 2017, China's National Healthcare Security Administration included sorafenib into the scope of healthcare payments based on medical insurance/drug catalog access negotiations [10]. Sorafenib prices fell sharply, thus greatly reducing the financial burden of patients. Even so, the high prices of sorafenib and lenvatinib still limit

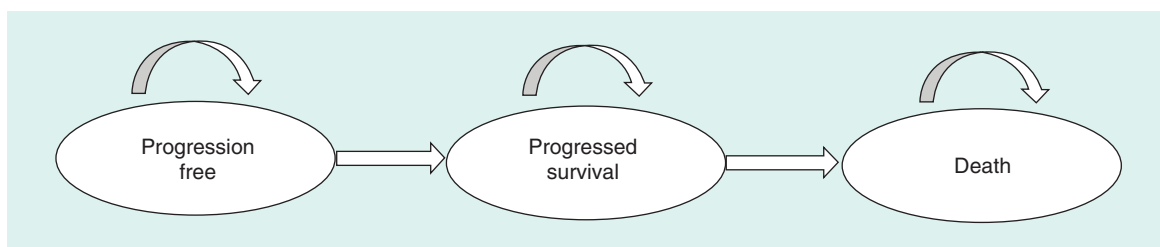


Figure 1. The Markov state transition model.

their widespread use, especially in areas with limited health resources. Several studies focused on the cost effects of sorafenib and chemotherapy programs, lenvatinib and sorafenib still do not have an economic evaluation [11–13]. Therefore, medical decision-makers, patients and doctors are very interested in the selection of first-line targeted treatment options for advanced HCC.

This study aimed to evaluate the cost–effectiveness of lenvatinib compared with sorafenib for the first-line treatment of Chinese nonresected HCC patients, to build models based on the recommendations of the latest clinical guidelines, and to explore the cost effects of lenvatinib by using the latest clinical efficacy data. Subsequently, we aimed to provide reference for dynamic adjustment, patent drug negotiation and clinical decision-making of medical insurance catalog.

Materials & methods

Model structure

Based on the perspective of China's health service system, this study analyzed the clinical and economic output of the two treatment options of lenvatinib and sorafenib by constructing a dynamic Markov model. The included population was previously untreated, nonresected patients with advanced HCC, liver function with Child–Pugh score graded as A or better B (≤ 7). The Markov model structure consisted of three states, PFS, progressed survival (PS) and death (Figure 1) [14]. Patients were in PFS at the initial stage of the model, and each cycle was left in PFS or converted to PS according to the transfer probability. Entering PS can only be in PS or into a state of death. Patients received treatment until the disease progressed. After progress, the patients entered the best support treatment. According to clinical research and treatment options, the cycle of the model was set to 1 month. After 10 years of model operation, all patients were in a state of death, and the study duration is set to 10 years to fully present the benefits of the two treatment options. All cost units were converted to USD with an average RMB exchange rate of \$1–6.6174 Yuan for the full year of 2018 [15]. TreeAge2015 software was used to build the Markov model to calculate the incremental cost–effectiveness ratio (ICER) of all parameters after substituting all parameters. The ICER is the cost per additional quality-adjusted life year (QALY) gained. This study used the following formula to calculate the ICER: [16]

$$\text{ICER} = \frac{(\text{cost}[\text{strategy A}] - \text{cost}[\text{strategy B}])}{(\text{effectiveness}[\text{strategy A}] - \text{effectiveness}[\text{strategy B}])}$$

Clinical data

Clinical efficacy data were obtained from a multicenter, open-label, randomized Phase III clinical trial (REFLECT study of Chinese population subgroup) [8,9]. This study was a head-to-head study on lenvatinib and sorafenib for HCC. The individual level data of all Kaplan–Meier curves were reconstructed using the GetData Graph Digitizer software (version 2.26). Survival analysis was also adopted to fit the data. Weibull distribution can fit the survival data well. Therefore, through Kaplan–Meier curve fitting and extrapolation, the nonprogress probability and survival probability of the patient's lifespan at every time point t were estimated. According to Weibull distribution, the survival probability at t was $S(t) = \exp(-\lambda t^\gamma)$, and the transition probability was $P(t) = 1 - \exp[\lambda(t - 1)^\gamma - \lambda t^\gamma]$ given that the model cycle was t [17–20]. The final survival models chosen were based on the goodness of fit measured using the r^2 statistic [21]. Weibull distribution parameter scale parameter λ and shape parameter γ were shown in Table 1.

Table 1. Key model input parameters.			
Input parameter	Value		[Ref.]
	Lenvatinib	Sorafenib	
Weibull survival model			
– PFS	Scale = 0.040493; shape = 1.200305; r ² = 0.9878513	Scale = 0.125796; Shape = 0.979883; r ² = 0.9115187	[8,9]
– OS	Scale = 0.0146642; shape = 1.3568686; r ² = 0.9882742	Scale = 0.039869; Shape = 1.119715; r ² = 0.9671524	[8,9]
Quality of life			
– Utility of PFS	0.832	0.837	[22]
– Utility of PS	0.714	0.714	[22]
Incidence of SAE			
– Nausea + vomiting	6%	8%	[9]
– AST/ALT abnormal	20%	22%	
– Anorexia	3%	0%	
– Bilirubin abnormal	12%	10%	
– Fatigue	3%	2%	
– Diarrhea	2%	3%	
– HFSR	1%	7%	
– Rash	0%	1%	
– Hypertension	23%	15%	
– Bone marrow suppression	37	19%	
HFSR: Hand-foot skin reaction; OS: Overall survival; PFS: Progression-free survival; PS: Progressed survival; SAE: Serious adverse event (≥grade 3).			

Cost & utility

This study was based on the perspective of the health service system and considered only the cost of direct medical care. We assumed a 3% annual discount rate for both costs and outcomes [17]. The direct medical costs in the model included the following: drug costs, follow-up costs (including inspection and inspection fees), costs for severe adverse reaction treatment and costs for postprogression of the disease. The sorafenib fee used the Medicare payment standard established by the China National Healthcare Security Administration's Medicare drug catalog access negotiation, which was administered daily orally to 800 mg [6,10]. Lenvatinib costs were calculated based on the retail prices and the China primary healthcare foundation donation policy. For low-income population, the full self-funded continuous medication for 2 months can help them obtain 2 months of assistance drugs. Subsequent patients can obtain drug assistance until the progression of the disease after 2 months of continuous medication fully at their own expense, with assistance for no more than 10 months. For patients weighing <60 kg, lenvatinib was administered orally daily for 8 and 12 mg for patients weighing ≥ 60 kg [6]. The above programs were carried out until the progression of the disease or the emergence of intolerant toxicity. The model assumed no significant change in the weight of the patient during treatment. Serious adverse reactions only considered the adverse reactions of level 3 and above, and the incidence of adverse reactions were obtained from the REFLECT study of Chinese population subgroups. The formula for adverse reaction cost is as follows: cost of serious adverse events per cycle $\times$ probability of serious adverse events in related treatment program [23]. Other cost data were derived from relevant published literature.

The health utility values of three states were derived from the study of Kobayashi [22], and the utility values of lenvatinib and sorafenib PFS were 0.832 and 0.837, respectively. The utility value considered the effects of the two groups of adverse events. The utility value of both groups in the PS state was 0.714. Cost and utility model input data are shown in Tables 1 & 2.

Basic & sensitivity analysis

A Markov queue model was established to evaluate the QALYs and lifetime costs of HCC patients. By calculating the ICER, cost utility analysis was carried out by comparing it with the threshold value. The cost utility threshold for HCC patients in China has not yet been determined. According to the WHO triple GDP per capita [24,25],

Table 2. Base-case costs estimates.

Input parameter	Value	PSA distribution	[Ref.]
Cost of sorafenib per day (US \$)	122.71	Gamma	Negotiated price
Cost of lenvatinib per day(<60 kg)	169.25 (11.55, 28.88)	Gamma	Local charge
Cost of lenvatinib per day (≥60 kg)	253.88 (13.97, 34.92)	Gamma	Local charge
Cost of the PF state	345.58	Gamma	[11]
Cost of follow-up per cycle (US \$)	481.81	Gamma	[11]
Cost of SAEs for lenvatinib per cycle	96.49	Gamma	
Cost of SAEs for sorafenib per cycle	74.44	Gamma	
– Cost of nausea + vomiting	65		[12]
– Cost of AST/ALT abnormal	59		[12]
– Cost of anorexia	26		[12]
– Cost of bilirubin abnormal	349		[12]
– Cost of fatigue	3		[12]
– Cost of diarrhea	13		[12]
– Cost of HFSR	4		[12]
– Cost of rash	7		[12]
– Cost of hypertension	37		[12]
– Cost of bone marrow suppression	79		[12]

HFSR: Hand-foot skin reaction; PF: Progression free; PS: Progressed survival; PSA: Probabilistic sensitivity analysis; SAE: Serious adverse event (≥grade 3).

Table 3. Base-case analysis.

Strategy	Costs (\$)	QALYs	Δ Costs (\$)	Δ QALYs	ICER (\$/QALY)
Sorafenib	43780.73	1.794	†	†	†
Lenvatinib (<60 kg)	57049.43	2.916	13268.70‡	1.122‡	11825.94‡
Lenvatinib (≥60 kg)	75900.36	2.916	32119.63‡	1.122‡	28627.12‡

†No comparison.

‡Compared with sorafenib.

ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life years.

when the ICER is less than the triple GDP per capita, the increased cost is acceptable. Otherwise, the increased cost is not worth it. This study will take 2018 China's triple GDP per capita of (\$29,306.37) as the threshold value.

In order to test the influence of the variables on the results of cost–effectiveness analysis, one-way sensitivity analysis was carried out for all the parameters of input Markov model. The results are presented using a tornado diagram. The range of drug price changes is limited by decreasing trend of 20%. When the range of other parameters was unattainable, the variation range was $\pm 20\%$. In addition, probabilistic sensitivity analysis was carried out using second order Monte Carlo simulation. Based on the different distribution assumptions of each parameter, 1000-times of sampling were repeated, and the two treatment schemes were calculated based on the ICER value of each sample, which were presented using a scatter plot. The results of the probabilistic sensitivity analysis are presented by the cost–effectiveness acceptable curve.

Results

Basic analysis

Basic analysis results in Table 3 shows that the QALY of lenvatinib (2.916 QALYs) is 1.122 QALYs higher than that of sorafenib (1.794 QALYs). For patients weighing <60 kg, lenvatinib lifetime medical expenses (\$57,049.43) was \$13,267.70 higher than that of sorafenib (\$43,780.73) and the ICER value is \$11,825.94/QALY. For patients weighing ≥60 kg, lenvatinib lifetime medical expenses (\$75,900.36) was \$32,119.63 higher than that of sorafenib (\$43,780.73) and ICER value is \$28,627.12/QALY. The ICER values are lower than China's triple GDP per capita threshold in 2018 (\$29,306.37).

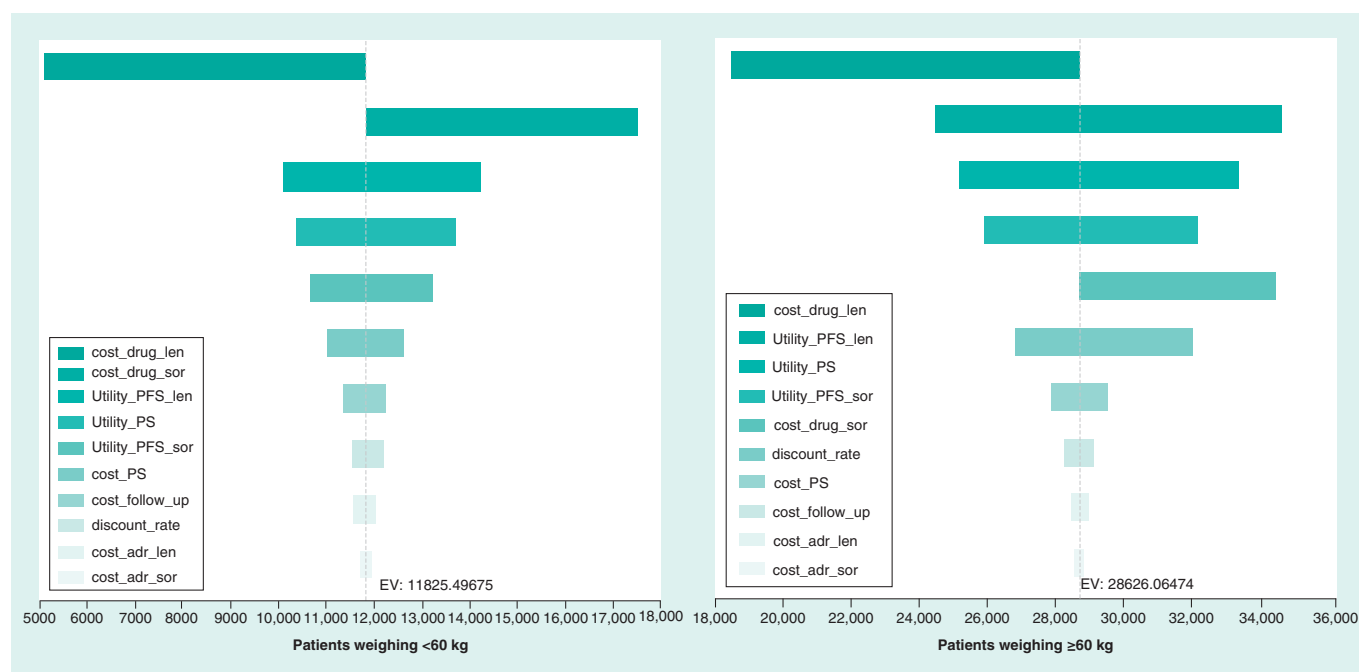


Figure 2. One-way sensitivity analysis.

EV: Expected value; PFS: Progression-free survival; PS: Progressed survival.

Sensitivity analysis

One-way sensitivity analyses found that for patients weighing <60 kg, the lenvatinib and sorafenib price, the utility of PFS and PS and the cost of postprogression treatment were the main influencing factors. For patients weighing ≥60 kg, lenvatinib price has the greatest effect on the result followed by utility and sorafenib price. The tornado diagram of one-way sensitivity analyses is shown in Figure 2.

The results of probabilistic sensitivity analysis are shown in Figure 3. For patients weighing <60 and ≥60 kg, lenvatinib had 96.7 and 55.6% scatter points above the willingness payment curve compared with sorafenib, and the probability of lenvatinib with cost effect was 96.7 and 55.6%, respectively. The cost-effective acceptable curve shows that the higher the social average willingness to pay, the higher the probability that lenvatinib has a cost effect (Figure 4). For patients weighing ≥60 kg, when the willingness to pay was \$586, 12.73, the probability of lenvatinib with cost effect was significantly higher than that of sorafenib (94.5%).

Discussion

Based on the latest data from the Chinese population in existing clinical studies, this study was the first to analyze the cost-effectiveness of the first-line treatment with lenvatinib and sorafenib for unresectable HCC patients. The dosage of lenvatinib in patients with different weights was not consistent. We studied the economics of the use of two schemes in patients with weights of <60 and ≥60 kg. In comparison with sorafenib, lenvatinib had an improved QALY. The lifetime cost has also increased, but the ICER value was lower than the threshold of China's triple GDP per capita. Uncertainty factors may exist at all stages of the evaluation of the model. One-way sensitivity analysis shows that drug price and utility were the two most sensitive parameters. To sum up, for patients weighing ≥60 kg, the ICER is close to the acceptability threshold, the probability of lenvatinib being economical is slightly higher than sorafenib. For patients weighing <60 kg, lenvatinib scheme had a comparative advantage of cost effect.

Some economic studies of sorafenib treatment of HCC are available, but they mainly provide comparison with chemotherapy regimens. Zhang [13] and Qin [11] established Markov models to study the cost effects of FOLFOX4 or sorafenib for the first-line treatment of advanced HCC in China. The use of FOLFOX4 may be the most cost effective, given the tripled GDP per capita threshold value. A study on the economy of lenvatinib in the

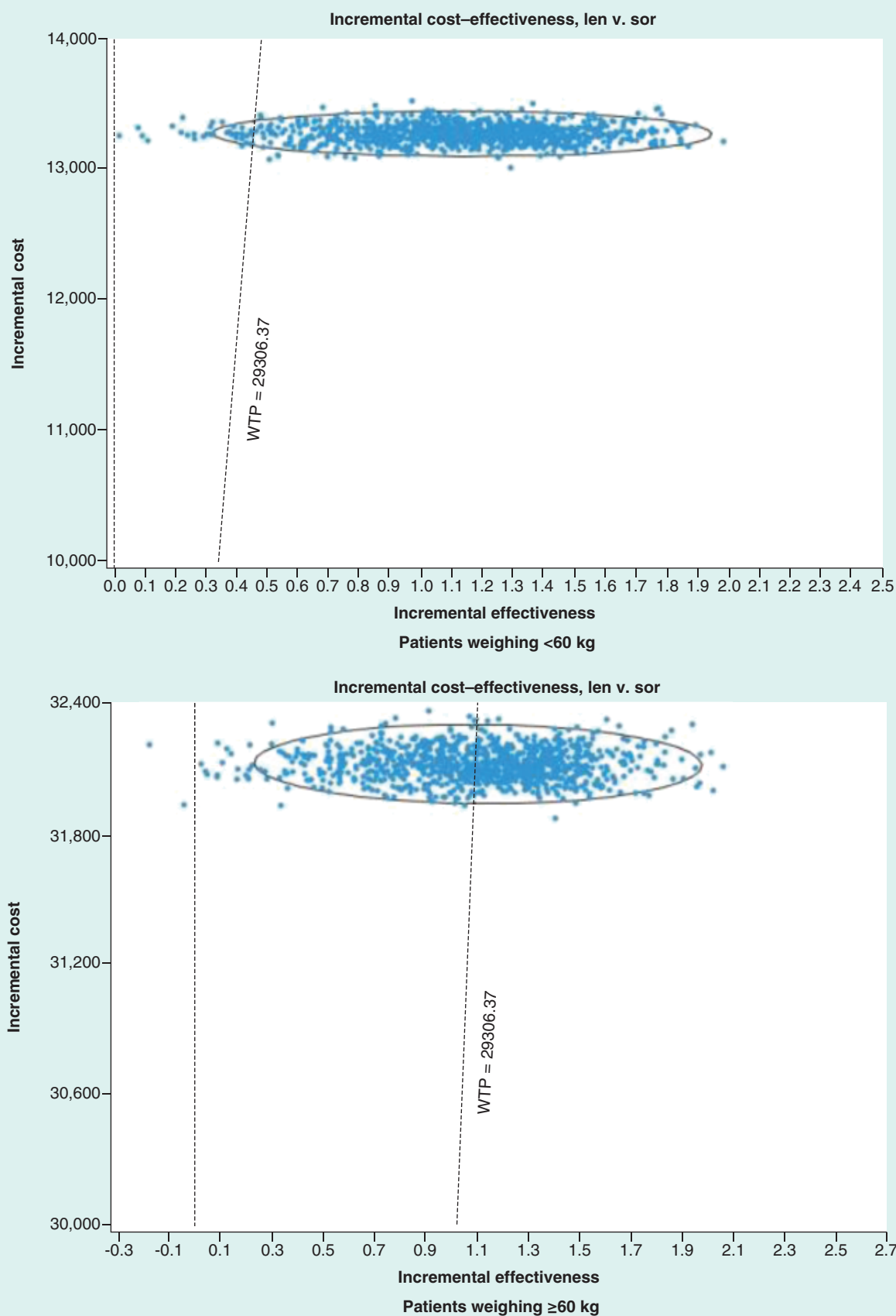


Figure 3. Probabilistic sensitivity analyses of lenvatinib versus sorafenib.
Len: Lenvatinib; Sor: Sorafenib; WTP: Willingness-to-pay.

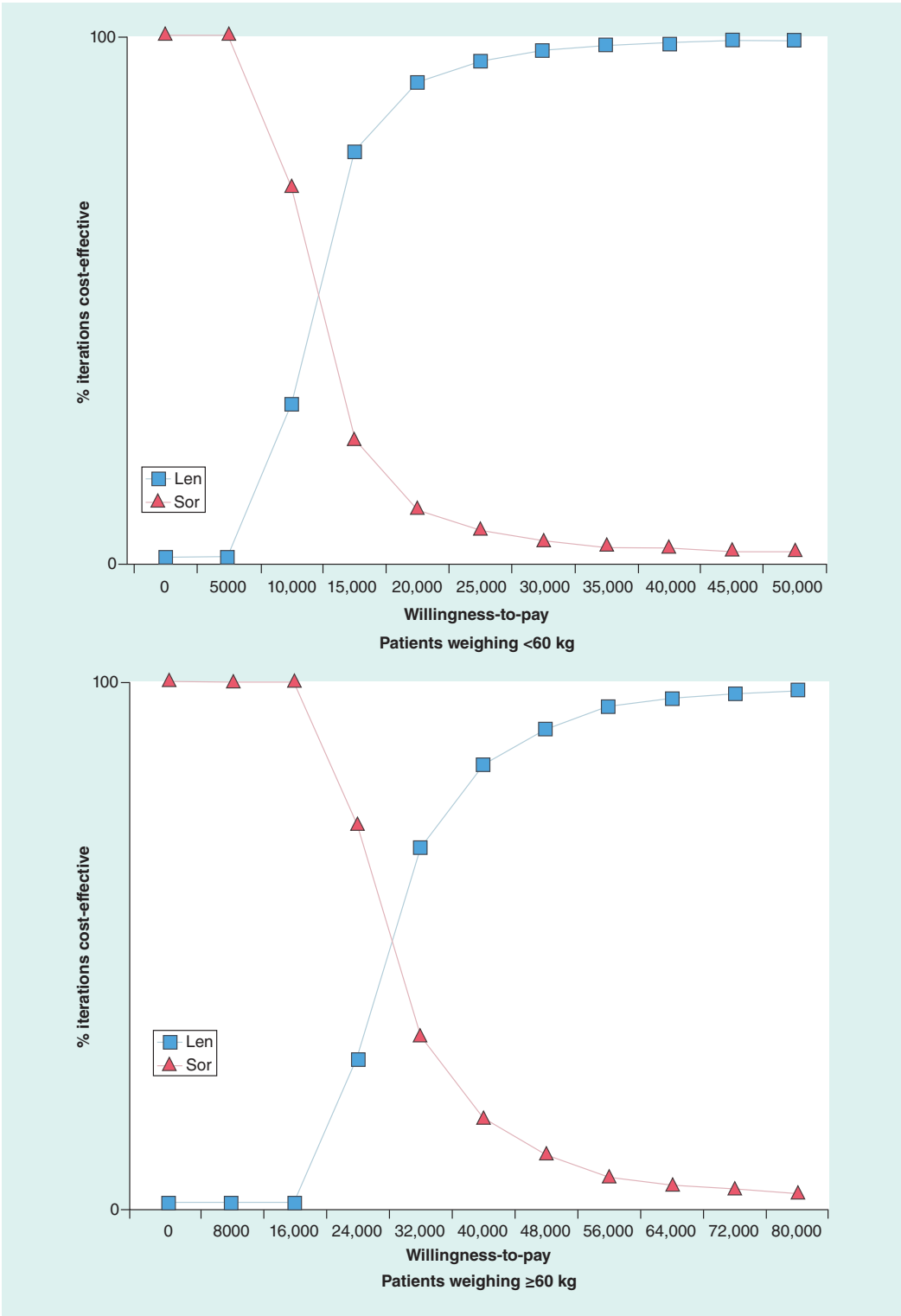


Figure 4. Cost-effectiveness acceptability curves.
Len: Lenvatinib; Sor: Sorafenib.

treatment of advanced HCC has been published in Japan, which indicate that the results of the study are more cost effective for lenvatinib than those from the Japan's study [22]. Another study showed that lenvatinib offered a similar clinical effectiveness at a lower cost than sorafenib, lenvatinib would be a cost-saving alternative in treating unresectable HCC in Canada [26]. However, different countries have different costs and effects, and economic research results cannot be universal. In our study, the QALY of lenvatinib was 2.916, which was significantly higher than that of the Japan study at 1.88, mainly because the clinical data of the Japan's study were based from an international multicenter study. The results of the International Multicenter study were slightly inferior to the effect of sorafenib on the end point OS. In the Phase III clinical study, lenvatinib was significantly more effective than sorafenib in Chinese liver cancer patients and HBV-related liver cancer, which was also not consistent with Canada. For Chinese HCC patients and HBV-related HCC patients, the OS of lenvatinib was significantly better than that of sorafenib. In addition, considering that half of the world's HCC patients are from China, the study is significantly necessary to evaluate the economic nature of lenvatinib and sorafenib treatment of HCC based on Chinese population.

In order to reduce the burden of patient's medical treatment, the Chinese medical insurance department will make dynamic adjustments to the medical insurance catalog. Innovative-targeted drugs will be negotiated nationally to determine whether they are reimbursed, and to determine payment criteria. Through equal negotiation and consultation between medical insurance and pharmaceutical enterprises, a relatively reasonable payment standard will be formulated. The average decrease rate of drugs for cancer and diabetes is about 65% in 2019 Medical Insurance Catalog [27]. In order to improve the economics of sorafenib, the national medical insurance department could reduce the price through medical insurance negotiations. By combining the level of China's economic development and the average social willingness to pay, exploring the reasonable medical payment standard of sorafenib will help to further improve the accessibility and compliance of targeted drugs, prolong the survival time of HCC patients, improve the quality of life and ensure that patients can bear the expenses for medical insurance fund.

The study has some limitations. First, the utility value of patients with advanced HCC in China has not been retrieved from the published literature. Hence, the utility value of PFS state and PS state was not derived from patients with advanced HCC in China. Each country or region has differences in ethnic and cultural backgrounds and preferences. China and Japan are Asian countries, and the utility value deviation may be relatively small. Second, the dose of lenvatinib may change as the weight of patients changes during treatment. The study assumes no significant change in the weight of the patient during treatment to simplify the model calculation. Third, the gamma distribution of cost parameters may result in deviation of the model output. Fourth, we have simplified the model and made several hypotheses to reduce the impact of parameter uncertainty. Different treatment options may be available after the progression of the disease, but we do not consider more individualized treatment decisions. Optional drugs after the advanced first-line treatment progression of advanced HCC are very limited. Hence, the study did not discuss the drug selection after the progression of the disease. The adverse reactions were similar in the two groups. Accordingly, the effects of death due to such reactions have not been considered. Hence, the state from PFS to death is not considered in the model. Fifth, the currently published REFLECT study only provides data on the global population. The Chinese population data are only partially described in the aforementioned study, and the PFS and OS curves are not presented. The clinical data of the Chinese subgroup are introduced in detail in the product package insert, including the PFS and OS curves and the adverse reaction data. The package insert is legally valid in China, and the conference paper results are consistent with the labeling. Therefore, we believe that the data are credible. In addition, compared with the results of global population studies, lenvatinib is significantly better than sorafenib for the Chinese HBV-related HCC. Hence, the cost-effectiveness of the first-line treatment of HBV related HCC should be evaluated. However, at present, we cannot obtain the Kaplan-Meier curve of HBV-related HCC in the Chinese subgroup.

Despite some limitations, for patients weighing <60 kg, the variables in the model did not affect the final result. One-way sensitivity analysis showed that the probability, utility and cost data were unlikely to affect the result.

Conclusion

From the perspective of the Chinese health service system, lenvatinib is a cost-effective drug for the targeted treatment of unresectable HCC patients. The results can be used to provide evidence and reference for healthcare policy makers, doctors and patients.

Summary points

- This study tested the cost-effectiveness of lenvatinib and sorafenib for unresectable hepatocellular carcinoma in China.
- The cost-effectiveness analysis suggested that lenvatinib is likely to be cost effective from the perspective of the Chinese medical system.

Author contributions

H Cai assisted in methodology, software, formal analysis, visualization, writing-original draft preparation, writing-review and editing. L Zhang assisted in conceptualization, methodology, supervision, project administration, formal analysis. N Li assisted in writing-original draft preparation, writing-review and editing. B Zheng assisted in formal analysis, visualization. M Liu assisted in methodology, supervision, project administration, resources.

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