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Interventional Arterial Chemotherapy versus Sorafenib for Advanced Hepatocellular Carcinoma in China: A Health Economic Evaluation of Open-Label, Randomized, Phase 3 Study

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Abstract

Objective: As demonstrated by the FOHAIC-1 trial, hepatic artery infusion chemotherapy (HAIC-FO) using fluorouracil, leucovorin, and oxaliplatin can improve survival in patients developing advanced hepatocellular carcinoma (HCC) compared to sorafenib. The present work focused on evaluating cost-effectiveness of HAIC-FO for managing advanced HCC based on Chinese payers.

***Methods*:** This study employed a Markov model for comparing cost-effectiveness of HAIC-FO compared with sorafenib in advanced HCC, utilizing patient information in the FOHAIC-1 phase 3 trial conducted from 2017 to 2020. Health outcome and cost data were obtained in previous studies. The incremental cost-effectiveness ratio (ICER), representing the additional cost per quality-adjusted life year (QALY), served as our primary outcome. We also conducted sensitivity analyses (including one-way and probabilistic) for assessing our result robustness.

***Results*:** Sorafenib yielded 0.66 QALY at a cost of $15,011.73, while HAIC-FO produced 1.00 QALY at $18,470.98. ICER of HAIC-FO versus sorafenib was $12,242.56 per QALY, well below willingness-to-pay (WTP) threshold at $30,492.00 per QALY. HAIC-FO was cost-effective across various subgroups. Sensitivity analyses confirmed that ICER was still under WTP threshold regardless of variable fluctuations, and probabilistic sensitivity results indicated the cost-effectiveness probability of 99.9% upon the WTP threshold. Subgroup analysis revealed that the economic benefits were more pronounced in patients with Vp 4 portal vein tumor thrombus (PVTT, $7,003.33 per QALY) and high tumor burden ($7,382.86 per QALY).

***Conclusion*:** HAIC-FO is cost-effective compared with sorafenib in treating advanced HCC based on the Chinese payer, especially for patients with Vp 4 PVTT and/or a high tumor burden.

Keywords: Cost-effectiveness; Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; China

What is already known on this topic: The IMbrave 150 trial established atezolizumab and bevacizumab (T+A) as the preferred treatment for unresectable hepatocellular carcinoma (HCC), though T+A was not deemed cost-effective. Previous research has established that hepatic artery infusion chemotherapy (HAIC) with fluorouracil, leucovorin, and oxaliplatin (HAIC-FO) enhances survival rates in advanced HCC compared to sorafenib. However, there has been limited assessment of the cost-effectiveness of HAIC-FO, particularly from the perspective of Chinese healthcare payers.

What this study adds: This study demonstrates that HAIC-FO not only improves survival outcomes but also remains highly (99.9%) cost-effective compared to sorafenib, with an incremental cost-effectiveness ratio (ICER) of $12,242.56 per quality-adjusted life year (QALY), well below the willingness-to-pay threshold in China. The economic benefits are more pronounced in patients with Vp 4 portal vein tumor thrombus (PVTT), with a cost of $7,003.33 per QALY, and those with a high tumor burden, with a cost of $7,382.86 per QALY.

How this study might affect research, practice, or policy: The findings indicate that HAIC-FO is a cost-effective treatment option for advanced HCC. This could inform clinical decision-making and influence healthcare policies in China, potentially leading to broader adoption of HAIC-FO in patients with Vp 4 PVTT and/or high tumor burden.

Introduction

Hepatocellular carcinoma (HCC) takes the fourth place among factors inducing cancer-associated mortality worldwide [1]. In developing nations, particularly in China, a majority of patients develop advanced HCC [2]. Sorafenib was recommended as the first-line systemic therapy for HCC prior to 2017, and lenvatinib has also become a first-line treatment option since 2018 [3]. Following IMbrave 150 trial results in 2020 [4], international guidelines, including those from China and Western countries, have recommended atezolizumab and bevacizumab (T+A) as the preferred treatment regimens for unresectable HCC patients without previous systemic treatment [5-8]. However, T+A may not be the cost-effective treatment at present in comparison with sorafenib [9-11].

While hepatic artery infusion chemotherapy (HAIC) may not be universally recognized as a well-established treatment regimen, it is effective and commonly used to treat advanced HCC among East Asian countries [5]. The recent FOHAIC-1 trial showed that HAIC of fluorouracil, leucovorin, and oxaliplatin (HAIC−FO) enhanced clinical outcomes relative to sorafenib for advanced HCC [12]. Median overall survivals were 13.9 and 8.2 months for HAIC−FO and sorafenib, separately (hazard ratio [HR] 0.408; P <0.001), while the median progression-free survivals were 7.8 and 4.3 months, respectively (HR 0.451; P<0.001). Despite the reported clinical effects brought by HAIC−FO for advanced HCC, its health economic evaluation remains largely unknown.

Concerns on health economic value of T+A regimen persist, prompting exploration into alternative therapies with improved cost-effectiveness. The present work focused on comparing the health economic evaluation between HAIC−FO and sorafenib for the Chinese patients with advanced HCC.

Materials and Methods

FOHAIC-1 trial

The institutional review board approved the study (IRB No.SB5010-2017-015). Every participant provided informed consent. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. The trial, carried out at a medical institution in China, was a phase III randomized study comparing the therapeutic effect between HAIC−FO and sorafenib on advanced HCC [12]. Its major inclusion criterion included a dominant liver mass, with additional criteria outlined in the clinicaltrials.gov with a registration ID of 03164382. From 2017 to 2020, altogether 262 qualified cases were randomized into 2 groups, among them, 130 received HAIC−FO regimen, whereas 132 underwent sorafenib therapy at the ratio of 1:1 (**Figure 1**). Of them, 89.3% of individuals were found to have hepatitis B virus (HBV) infection, while 82.8% exhibited macrovascular invasion. In the HAIC−FO arm, the regimen was consisted of sequential infusion of oxaliplatin 130 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 400 mg/m^2, and fluorouracil 2,400 mg/m^2 through the catheter every 3 weeks. The HAIC−FO procedure and adverse events (AEs) associated with treatment have been previously described in studies [12-14]. Patients in the sorafenib control group orally consumed totally 800 mg of sorafenib per day, divided into two doses, with the dosage adjusted as needed.

Economic evaluation using Markov model

TreeAge 2011 software was adopted in this study conducted following CHEERS reporting guidelines in constructing a Markov model for cost-effectiveness analysis [15]. In this model, health state was categorized as 3 types: stable disease, progressive disease, or death. Patients underwent HAIC−FO or sorafenib therapy in stable disease stage, while during disease progression, they received second-line therapy till death. This study deemed HAIC−FO to be

economically viable if incremental cost-effectiveness ratio (ICER) was under a certain willingness-to-pay (WTP) threshold. To be specific, WTP thresholds refer to WTP per quality-adjusted life-years (QALYs). We set WTP thresholds in China based on previous research as $30492/QALY [16]. **Table 1** provides details of model parameters as well as the corresponding sources. When patients received HAIC−FO treatment, hospitalization was necessary, and they were responsible for covering the hospitalization cost. However, if the patient received sorafenib treatment, hospitalization was not required, and this cost did not arise. Furthermore, when patients received HAIC−FO treatment, they needed to pay another fee apart from the hospitalization cost. The present work assigned a value to the QALY below: 0.76 in the absence of disease progression, 0.68 if there was disease progression, and 0 if the patient died [16]. This research considered AEs ≥3 (including elevated total bilirubin, hypertension, fatigue, neutropenia, thrombocytopenia, higher aspartate aminotransferase [AST]/alanine transaminase [ALT]) with an incidence exceeding 1% as documented in Lyu's study [12].

Statistical analysis

During cost-effectiveness analysis, we carried out sensitivity analysis for assessing how uncertainties of treatment effectiveness, cost and utility affected ultimate ICER outcome. We acquired model parameters in pertinent literature, which varied in 20% of baseline for establishing parameter ranges. Concurrently, discount rate was 0%-5%. During Monte Carlo simulations, 1,000 tests were repeated, and every key parameter was assigned according to a suitable distribution, like costs that follow the Gamma distribution or utilities that followed the Beta distribution.

Results

Base case results

In our analysis of the base case, the HAIC−FO arm paid $18,470.98 on the whole, yielding the QALY of 1.00. Conversely, the total cost in sorafenib group was $15,011.73, with the QALY being 0.66. **Table 2** shows discounted costs and QALYs. When HAIC−FO was compared to sorafenib, an ICER of $10,235.56/QALY could be calculated. This ICER decreased compared with the Chinese referential WTP threshold, as shown in **Figure 2A**.

The subgroup analyses revealed that the ICERs of HAIC−FO versus sorafenib were lower relative to WTP threshold in all analyzed subgroups. These subgroups included tumor size (>10/<=10 cm), tumor number (1-3/>3), tumor burden (>=50%/<50%), portal vein tumor thrombosis (Vp4/Vp1-3), macrovascular invasion (yes/no), gender (male/female), etiology (hepatitis B virus [HBV]/non-HBV), extrahepatic spread (yes/no), Child-Pugh score (B/A), age (>55/<=55 years), and alpha-fetoprotein level (>400/<=400 ng/ml) (**Figure 2B**). Subgroup analysis revealed that the ICER was $7,003.33 per QALY for patients with Vp 4 portal vein tumor thrombus and $7,382.86 per QALY for those with a high tumor burden.

One-way sensitivity analysis

This study conducted one-way sensitivity analysis for identifying key model parameters for comparing HAIC−FO with sorafenib. From **Figure 3A**, we utilized the tornado diagram for representing fluctuations of cost-effectiveness of HAIC−FO versus sorafenib according to modeled variables. Based on tornado diagram, HAIC−FO still had a lower ICER than $30,492 per QALY (WTP threshold for reference) among all modeled parameters in comparison with sorafenib.

To be specific, parameters related to AEs exhibited the least influence on eventual ICER variation, with fluctuations of less than $11.50 per QALY. Consequently, **Figure 3A** does not show AE parameters.

Probabilistic sensitivity analysis

Based on Monte Carlo analysis, the HAIC−FO strategy proved to be a cost-effective approach with a rate of up to 99.9% in China (**Figure 3B**). From **Figure 3C**, with the increasing WTP per incremental QALY, proportion of modeled samples favoring HAIC−FO as the highly cost-effective strategy elevated corresponding in the probabilistic sensitivity analysis, whereas the proportion favoring sorafenib decreased. HAIC−FO was the preferred strategy in 48.9% of patients, with the WTP threshold being $10,000. This percentage rapidly increased to 97.2% with the WTP threshold being $20,000, and reached 99.9% upon the WTP threshold being $30,000. Additionally, it was predicted with 100.0% at a WTP threshold of $40,000.

Discussion

The HCC treatment cost constitutes a substantial part in cancer healthcare expenditure, making it essential to evaluate health economics for determining practical significance of HAIC−FO. Utilizing the Markov model, the present work was performed for comparing cost-effectiveness between HAIC−FO and sorafenib in advanced HCC patients. Our results indicated that, according to Chinese payers, HAIC−FO was the cost-effective therapeutic choice. The present work can shed precious lights on evaluating evaluate HAIC−FO in the management of HCC from a health economics standpoint for policymakers, physicians, and patients.

Recently, clinical benefits brought by HAIC−FO have garnered wide attention of physicians and patients [17]. However, there is limited cost-effectiveness studies comparing HAIC−FO or HAIC-FO based therapy with sorafenib for advanced HCC being published, resulting in uncertainty in health decision-making [18-20]. Based on our research findings, HAIC−FO has been demonstrated as the cost-effective therapy alternative for advanced HCC patients relative to sorafenib, which was supported by the results across a wide range of parameters.

Previously, as suggested by Li et al., adding HAIC−FO to sorafenib showed no cost-effectiveness in comparison with sorafenib monotherapy for the treatment of HCC invading the portal vein [16], but the conclusion must be explained with caution because it was assumed that patients might not stop HAIC−FO till disease progression. The authors set the HAIC−FO duration as 8 years in Markov model, which remarkably surpasses the real duration of HAIC−FO treatment in clinical practice. In real world, HAIC−FO therapy is typically administered every three weeks, and the overall duration is approximately 6-8 months for 8 sessions. Therefore, it is reasonable to assume that when Li et al. employed the Markov model for simulating cost-effectiveness of HAIC−FO versus sorafenib, there may be a deviation in the HAIC−FO treatment cycle from the actual clinical treatment scenario. In survivors at 8 months after receiving HAIC−FO, Markov model will considerably increase treatment expenses related to HAIC−FO. Conversely, our study limited HAIC−FO treatment to a maximum of 6–8 cycles, consistent with the trials and clinical practice.

HAIC was determined as the cost-effective strategy relative to sorafenib when AEs, such as neutropenia, elevated AST, and thrombocytopenia, were included into Markov model for calculating the ICER. Furthermore, one-way sensitivity analysis indicated that AEs had minimal influence on the outcomes (not shown in the tornado plot). Despite the potential limited influence on cost-effectiveness caused by AEs, the clinical value persists since they affect patients' healthcare experience and impact treatment adherence of patients. As reported by Kudo et al. [21], AEs ≥ grade 3 occurred at a higher frequency in HAIC based therapy; however, they could be managed through treatment interruption or dose reduction. HAIC combination treatment is the research focus, and more research is necessary for evaluating treatment effectiveness and safety, and for considering the possible economic benefits.

While our research findings indicated HAIC−FO as the more cost-effective option than sorafenib, it is vital to note that sorafenib is an orally administered medication that offers the advantage of convenience and independence from factors like medical facilities and professional medical personnel. Therefore, considering the current disparities in healthcare conditions across regions in China [22], the feasibility of interventional procedure may not have been optimal in areas with inadequate equipment or insufficient training of medical personnel, as opposed to oral or intravenous therapy. Additionally, the health administration department in China has actively contributed to reducing drug costs through mechanisms such as multilateral negotiations and volume-based discounts [23]. Therefore, we have also considered the potential impact of drug price fluctuations and have determined that HAIC−FO outperforms sorafenib.

Certain limitations should be noted in this work. Firstly, this research found that most patients displayed a high burden of liver tumors at the time of initial diagnosis, which was a common feature in the Chinese advanced HCC patients, typically associated with HBV infection. Notably, sorafenib has limited efficacy in patients with HBV infection, yet it can significantly improve survival of patients developing hepatitis C virus (HCV) infection [24]. Consequently, the health economics evaluation between HAIC−FO and sorafenib remains uncertain in cases from other areas in which HCC may be induced by factors such as HCV infection or alcohol drinking. Second, chemotherapeutic regimens are heterogeneous [12, 25-27]. Consequently, further research is warranted for precisely assessing whether diverse HAIC strategies are cost-effective and safe among different populations. Finally, Markov modeling is associated with limitations on the basis of assumptions and input data quality. Nonetheless, the results were sound among various model inputs, suggesting that other inputs might not markedly affect our findings.

Taken together, the HAIC−FO strategy is more cost-effective than sorafenib for advanced HCC among the Chinese patients, particularly for patients with Vp 4 portal vein tumor thrombus and/or high tumor burden.

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Figure Legends

Figure 1. Study flow diagram.

Figure 2. The base case findings. (A) When comparing HAIC−FO to sorafenib, the incremental cost-effectiveness ratio (ICER) was calculated to be $10,235.56 per quality-adjusted life year (QALY). (B) Subgroup analysis results. AFP, alpha fetoprotein; EHS, extrahepatic spread; HBV, hepatitis B virus; ICER: incremental cost-effectiveness ratio; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; QALYs: quality-adjusted life-years.

Figure 3. Sensitivity analysis. (A) A tornado diagram was adopted for performing a one-way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) for hepatic artery infusion chemotherapy of fluorouracil, leucovorin, and oxaliplatin (HAIC−FO) and sorafenib, with the parameters sorted based on their magnitude. (B) In the probabilistic sensitivity analysis, HAIC−FO was shown to be a cost-effective treatment option. To evaluate the influence of parameter uncertainty on the results of the cost-effectiveness analysis, 1,000 Monte Carlo simulations were performed using the input parameters and their respective distributions listed in Table 1. The dots below the lines represent simulations where the cost per quality-adjusted life year (QALY) gained was below the willingness-to-pay (WTP) threshold. (C) The curves display the probabilities of cost-effectiveness for HAIC−FO and sorafenib.

Tables

Table 1. Markov inputs in cost-effectiveness analysis.

Variable	Baseline	Range low	Range high	Distribution	Reference
Survival input					
HR of HAIC−FO vs sorafenib for OS	0.408	0.301	0.553	Normal	[1]
HR of HAIC−FO vs sorafenib for PFS	0.451	0.340	0.598	Normal	[1]
Weibull OS survival model with HAIC−FO	λ 0.0170272, γ 1.3635872				[1]
Weibull PFS survival model with HAIC−FO	λ 0.071169, γ 1.037127				[1]
Weibull OS survival model with sorafenib	λ 0.0151598, γ 1.8083652				[1]
Weibull PFS survival model with sorafenib	λ 0.0888648, γ 1.3537234				[1]
Utility input					
utility of PFS	0.760	0.610	0.910	Beta	[2]
utility of PD	0.680	0.540	0.820	Beta	[2]
disutility due to neutropenia	0.090	0.006	0.120	Beta	[3]

disutility due to fatigue	0.073	0.037	0.110	Beta	[3]
Cost input					
sorafenib (per month)	3077.760	2462.208	3693.312	Gamma	[2]
oxaliplatin (per month)	364.413	291.531	437.296	Gamma	[2]
cisplatin (per month)	14.310	11.448	17.172	Gamma	[4]
fluorouracil (per month)	686.200	548.960	823.440	Gamma	[2]
leucovorin (per month)	31.653	25.323	37.984	Gamma	[2]
HAIC procedure (per month)	2422.707	1938.165	2907.248	Gamma	[2]
hospitalization (per month)	502.560	402.048	603.072	Gamma	[2]
test (per month)	469.587	375.669	563.504	Gamma	[2]
second_line (per month)	959.160	767.328	1150.992	Gamma	[5]
hypertension	1.350	1.080	1.620	Gamma	[5]
elevated total bilirubin	113.530	90.824	136.236	Gamma	[5]
neutropenia	82.390	65.912	98.868	Gamma	[2]
fatigue	64.120	51.296	76.944	Gamma	[6]
elevated AST	42.540	34.032	51.048	Gamma	[2]
thrombocytopenia	1054.220	843.376	1265.064	Gamma	[6]
Incidence of adverse events					
hypertension with sorafenib	0.101	0.081	0.121	Beta	[1]

elevated total bilirubin with sorafenib	0.070	0.056	0.084	Beta	[1]
neutropenia with sorafenib	0.062	0.050	0.074	Beta	[1]
fatigue with sorafenib	0.062	0.050	0.074	Beta	[1]
elevated AST with sorafenib	0.031	0.025	0.037	Beta	[1]
thrombocytopenia with sorafenib	0.023	0.018	0.028	Beta	[1]
hypertension with HAIC	0.000	0.000	0.050	Beta	[1]
elevated total bilirubin with HAIC	0.055	0.044	0.066	Beta	[1]
neutropenia with HAIC	0.078	0.062	0.094	Beta	[1]
fatigue with HAIC	0.000	0.000	0.050	Beta	[1]
elevated AST with HAIC	0.109	0.087	0.131	Beta	[1]
thrombocytopenia with HAIC	0.109	0.087	0.131	Beta	[1]
Body surface area	1.720	1.380	2.060	Normal	[2]
Discount rate	0.030	0.000	0.050	Fixed	[2]

HR, hazard ratio. HAIC, hepatic arterial infusion chemotherapy. FO, oxaliplatin+fluorouracil. OS, overall survival. PFS, progression free survival. PD, progression disease. AST, aspartate aminotransferase.

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Table 2. Cost-effectiveness results.

	QALYs	Total cost ($)	ICER ($/QALY)
Sorafenib	0.66	15011.73	/
HAIC−FO	1.00	18470.98	10235.56

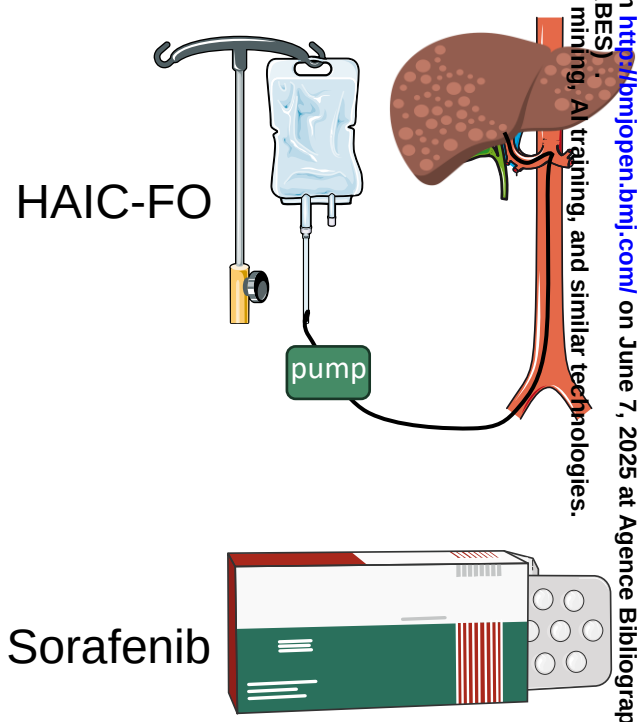
HAIC−FO: hepatic artery infusion chemotherapy of fluorouracil, leucovorin, and oxaliplatin; QALYs: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio.

Cost-effectiveness of HAIC-FO versus Sorafenib for Advanced HCC

Study Population

Eligibility Criteria	Details
Age	≤18 years
Condition	Locally advanced or unresectable HCC confirmed histologically or with cirrhosis diagnosed clinically
Dominant Mass	Present in the liver with or without extrahepatic oligometastasis
Suitability for Other Treatments	Unsuitable for surgery, ablation, or transarterial chemoembolization, or progressive disease after such therapies
Prior Systemic Treatment	No
Child-Pugh Grade	≤7
ECOG Performance Status	0-2

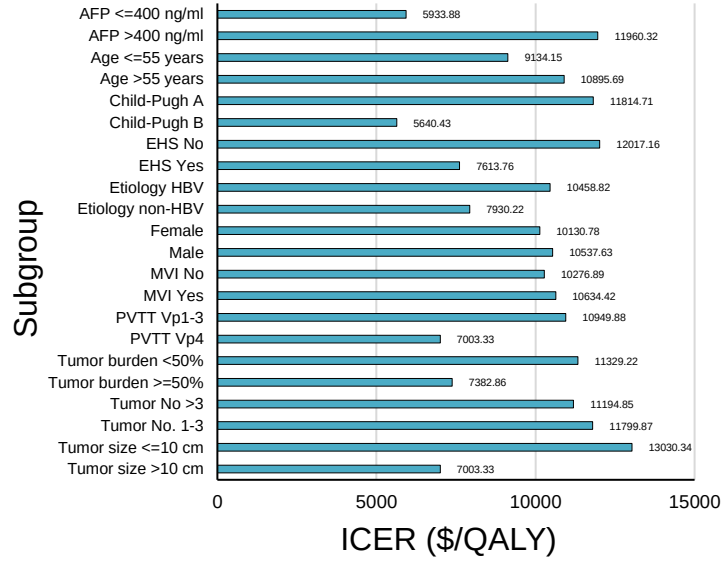
Intervention



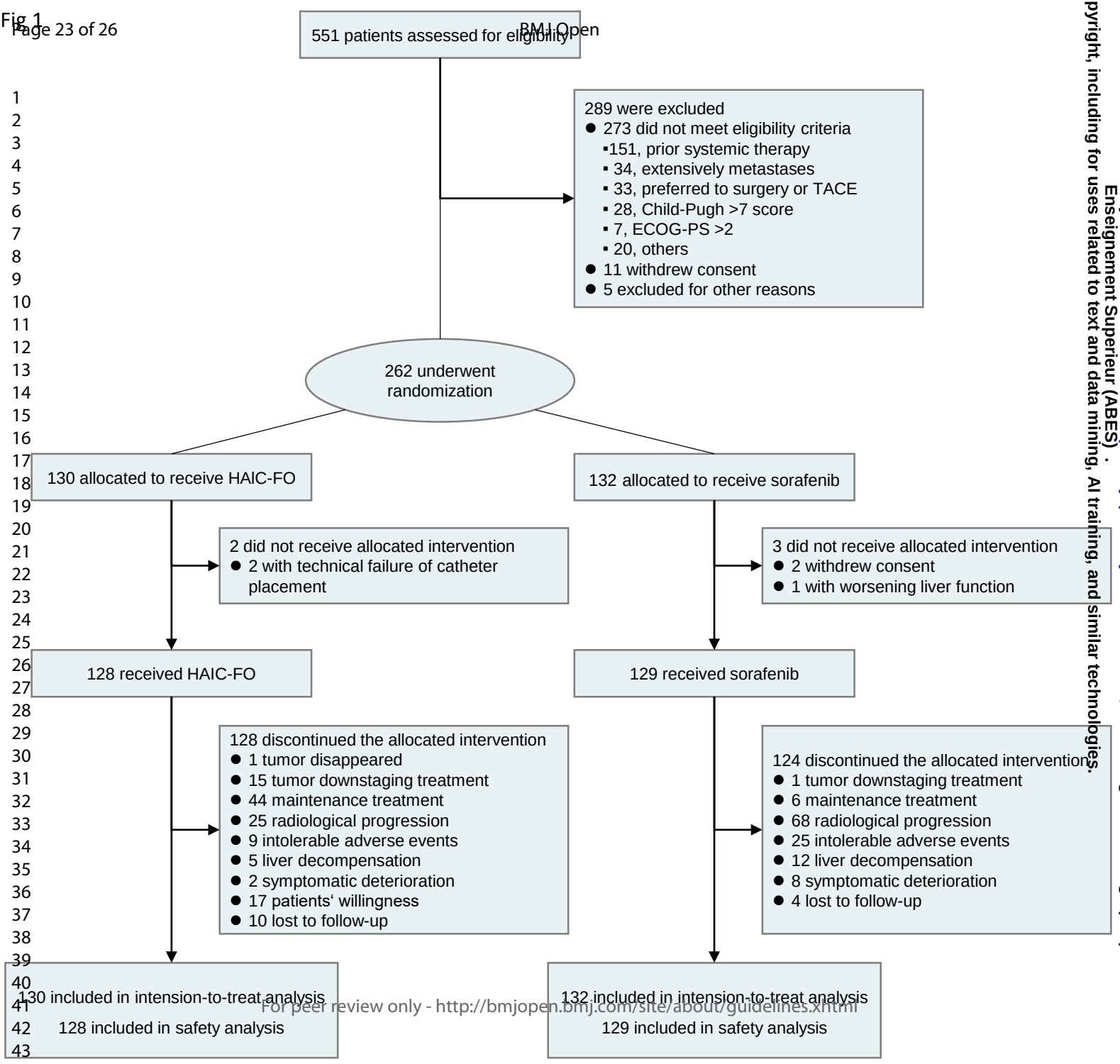
Outcome

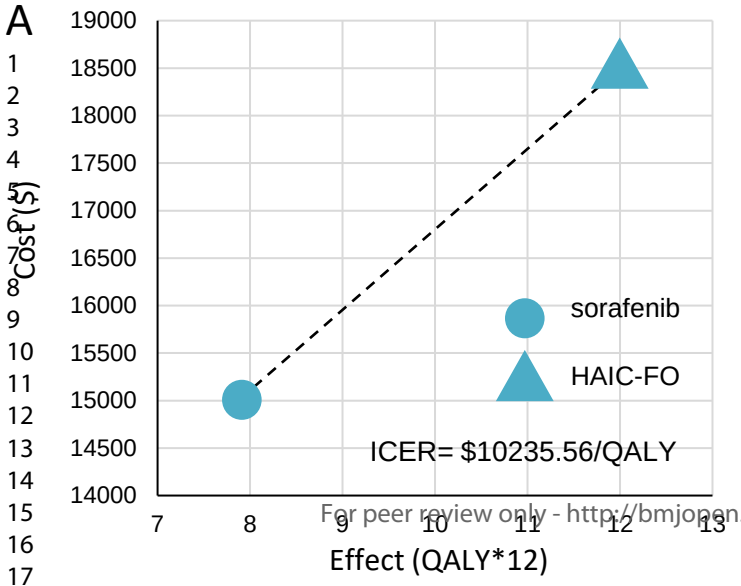
HAIC-FO is cost-effective compared to sorafenib

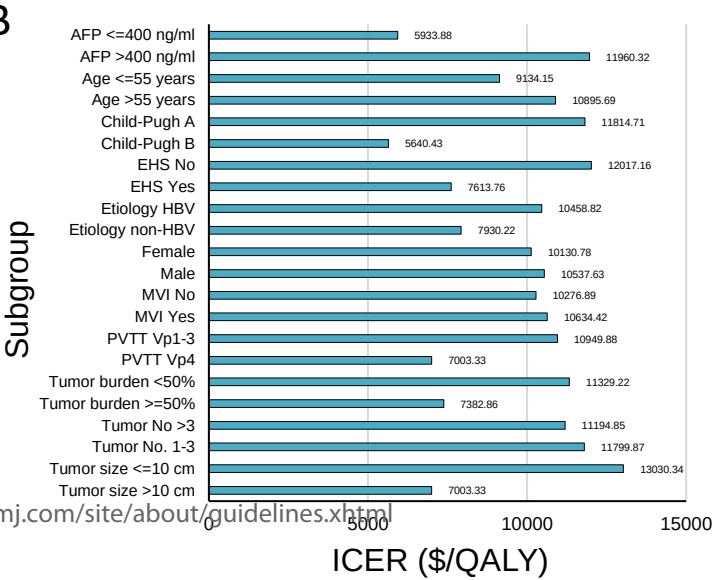
	QALYs	Cost ($)	ICER ($/QALY)
Sorafenib	0.66	15011.73	/
HAIC−FO	1.00	18470.98	10235.56



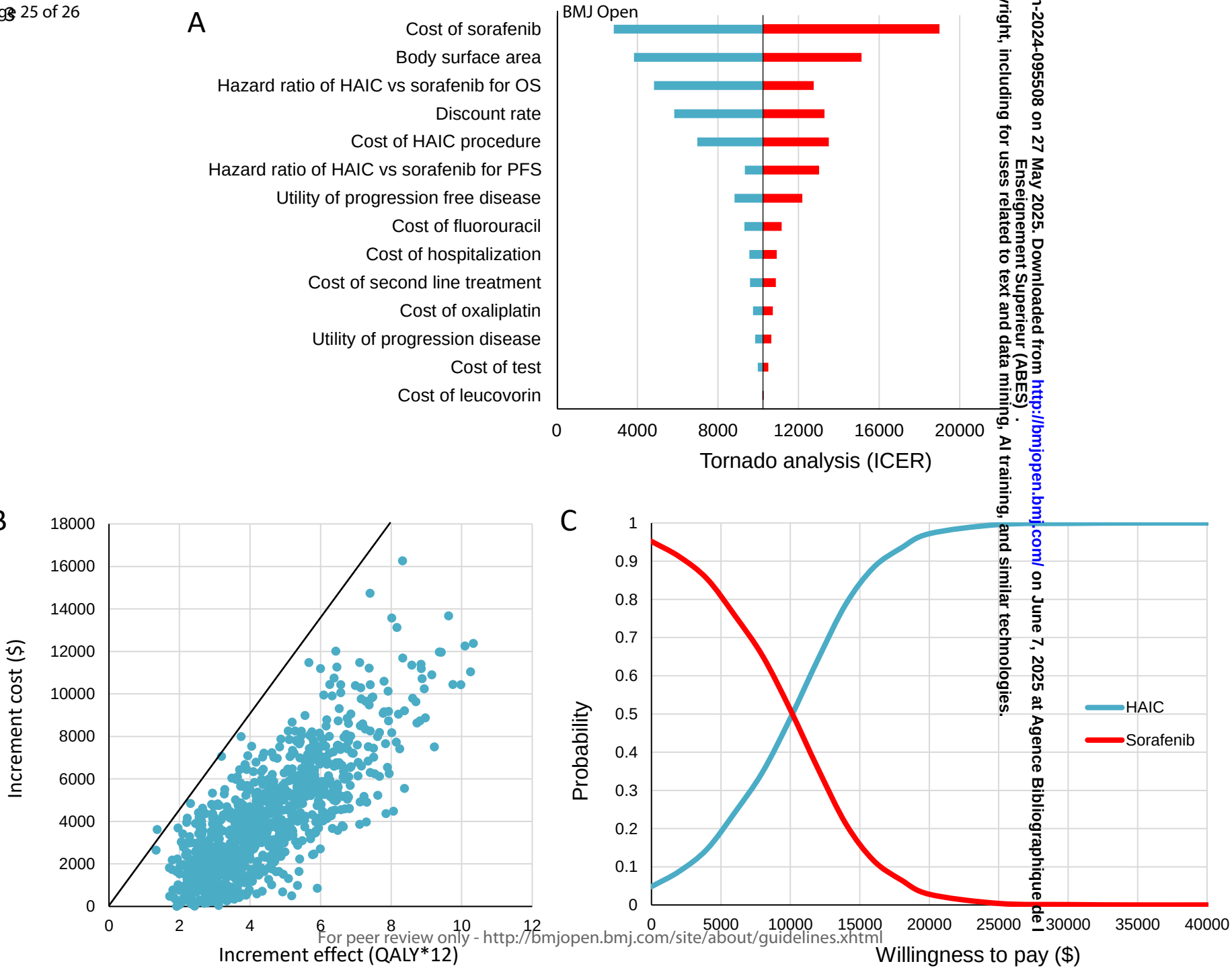
clinicaltrials.gov, NCT03164382







Figs



中山大学肿瘤防治中心伦理委员会

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审批号：5010-2018-01-01　　审批日期：2018 年 12 月 05 日

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试验研究题目：肝动脉灌注 FOLFOX 化疗对比索拉菲尼（Sorafenib）治疗 BCLC-C 期肝癌的随机、平行对照、单中心、III期临床研究

试验方案版本号及日期： 1.0　2018 年 06 月 29 日

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试验研究单位及研究人员： 中山大学肿瘤防治中心

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申办单位/研制单位： 中山大学肿瘤防治中心

审查频率： □3 个月，□6 个月，☑12 个月，□其他

审批意见：

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中山大学肿瘤防治中心伦理委员会

主任（签名）：

2018 年 12 月 05 日

4

项目名称：肝动脉灌注 FOLFOX 化疗对比索拉菲尼（Sorafenib）治疗 BCLC-C 期肝癌的随机、平行对照、单中心、III期临床研究

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日期：2018年12月5日

BMJ Open

Interventional Arterial Chemotherapy versus Sorafenib for Advanced Hepatocellular Carcinoma in China: A Health Economic Evaluation of Open-Label, Randomized, Phase 3 Study

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Interventional Arterial Chemotherapy versus Sorafenib for Advanced Hepatocellular Carcinoma in China: A Health Economic Evaluation of Open-Label, Randomized, Phase 3 Study

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Abstract

Objectives: This post hoc study aimed to evaluate the cost-effectiveness of hepatic artery infusion chemotherapy (HAIC-FO) with fluorouracil, leucovorin, and oxaliplatin compared to sorafenib in patients with advanced hepatocellular carcinoma (HCC) from the perspective of Chinese payers.

Design: A cost-effectiveness analysis using a Markov model based on data from a phase 3 randomized controlled trial (FOHAIC-1) conducted between 2017 and 2020.

Setting: Tertiary care settings in China.

Participants: Patients with advanced HCC who participated in the FOHAIC-1 trial. Inclusion criteria followed trial protocols, and patients were stratified by disease severity, including the presence of Vp 4 portal vein tumor thrombus (PVTT) and high tumor burden.

Interventions: HAIC-FO, consisting of fluorouracil, leucovorin, and oxaliplatin, was compared with sorafenib in terms of cost and health outcomes.

Primary outcome measure: The primary outcome was the incremental cost-effectiveness ratio (ICER), defined as the additional cost per quality-adjusted life year (QALY) gained.

Results: Sorafenib resulted in 0.66 QALYs at a cost of $15,011.73, while HAIC-FO achieved 1.00 QALY at a cost of $18,470.98. The ICER of HAIC-FO versus sorafenib was $12,242.56 per QALY, significantly below the willingness-to-pay (WTP) threshold of $30,492.00 per QALY. Sensitivity analyses confirmed that HAIC-FO remained cost-effective under variable assumptions, with probabilistic sensitivity analysis indicating a 99.9% probability of cost-effectiveness at the WTP threshold. Subgroup analyses showed more favorable ICERs for patients with Vp 4 PVTT ($7,003.33 per QALY) and those with high tumor burden ($7,382.86 per QALY).

Conclusions: HAIC-FO is a cost-effective treatment for advanced HCC compared to sorafenib from the Chinese payer's perspective, particularly in patients with Vp 4 PVTT and/or high tumor burden. Further research should explore long-term economic implications and real-world effectiveness.

Keywords: Cost-effectiveness; Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; China

Strengths and limitations of this study:

1. The study uses a Markov model based on data from the FOHAIC-1 phase 3 trial, providing a robust comparison between HAIC-FO and sorafenib.
2. The incremental cost-effectiveness ratio (ICER) for HAIC-FO was well below the willingness-to-pay threshold, demonstrating its cost-effectiveness.
3. Subgroup analysis highlighted the economic benefits of HAIC-FO in patients with Vp 4 PVTT and high tumor burden.
4. Sensitivity analyses confirmed the robustness of the results, with a 99.9% probability of cost-effectiveness.
5. The study focuses on the Chinese healthcare payer perspective, which may limit generalizability to other regions with different economic conditions.

Introduction

Hepatocellular carcinoma (HCC) takes the fourth place among factors inducing cancer-associated mortality worldwide [1]. In developing nations, particularly in China, a majority of patients develop advanced HCC [2]. Sorafenib was recommended as the first-line systemic therapy for HCC prior to 2017, and lenvatinib has also become a first-line treatment option since 2018 [3]. Following IMbrave 150 trial results in 2020 [4], international guidelines, including those from China and Western countries, have recommended atezolizumab and bevacizumab (T+A) as the preferred treatment regimens for unresectable HCC patients without previous systemic treatment [5-8]. However, T+A may not be the cost-effective treatment at present in comparison with sorafenib [9-12].

While hepatic artery infusion chemotherapy (HAIC) may not be universally recognized as a well-established treatment regimen, it is effective and commonly used to treat advanced HCC among East Asian countries [5]. The recent FOHAIC-1 trial showed that HAIC of fluorouracil, leucovorin, and oxaliplatin (HAIC−FO) enhanced clinical outcomes relative to sorafenib for advanced HCC [13]. Median overall survivals were 13.9 and 8.2 months for HAIC−FO and sorafenib, separately (hazard ratio [HR] 0.408; P <0.001), while the median progression-free survivals were 7.8 and 4.3 months, respectively (HR 0.451; P<0.001). Despite the reported clinical effects brought by HAIC−FO for advanced HCC, its health economic evaluation remains largely unknown.

Concerns on health economic value of T+A regimen persist, prompting exploration into alternative therapies with improved cost-effectiveness. The present work focused on comparing the health economic evaluation between HAIC−FO and sorafenib for the Chinese patients with advanced HCC.

Materials and Methods

FOHAIC-1 trial

The institutional review board approved the study (IRB No.SB5010-2017-015). Every participant provided informed consent. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. The trial, carried out at a medical institution in China, was a phase III randomized study comparing the therapeutic effect between HAIC−FO and sorafenib on advanced HCC [13]. Its major inclusion criterion included a dominant liver mass, with additional criteria outlined in the clinicaltrials.gov with a registration ID of 03164382. From 2017 to 2020, altogether 262 qualified cases were randomized into 2 groups, among them, 130 received HAIC−FO regimen, whereas 132 underwent sorafenib therapy at the ratio of 1:1 (**Figure 1**). Of them, 89.3% of individuals were found to have hepatitis B virus (HBV) infection, while 82.8% exhibited macrovascular invasion. In the HAIC−FO arm, the regimen was consisted of sequential infusion of oxaliplatin 130 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 400 mg/m^2, and fluorouracil 2,400 mg/m^2 through the catheter every 3 weeks. The HAIC−FO procedure and adverse events (AEs) associated with treatment have been previously described in studies [13-15]. Patients in the sorafenib control group orally consumed totally 800 mg of sorafenib per day, divided into two doses, with the dosage adjusted as needed. **Table S1** showed detailed information on subsequent treatments.

Economic evaluation using Markov model

TreeAge 2011 software was adopted in this study conducted following CHEERS reporting guidelines in constructing a Markov model for cost-effectiveness analysis [16]. In this model, health state was categorized as 3 types: stable disease, progressive disease, or death. Patients underwent HAIC−FO or sorafenib therapy in stable disease stage, while during disease

progression, they received second-line therapy till death. The time horizon of this model was 42 months. This study deemed HAIC−FO to be economically viable if incremental cost-effectiveness ratio (ICER) was under a certain willingness-to-pay (WTP) threshold. To be specific, WTP thresholds refer to WTP per quality-adjusted life-years (QALYs). We set WTP thresholds in China based on previous research as $30492/QALY [17]. **Table 1 and Table S2** provides details of model parameters as well as the corresponding sources. When patients received HAIC−FO treatment, hospitalization was necessary, and they were responsible for covering the hospitalization cost. However, if the patient received sorafenib treatment, hospitalization was not required, and this cost did not arise. Furthermore, when patients received HAIC−FO treatment, they needed to pay another fee apart from the hospitalization cost. The present work assigned a value to the QALY below: 0.76 in the absence of disease progression, 0.68 if there was disease progression, and 0 if the patient died [17]. This research considered AEs ≥3 (including elevated total bilirubin, hypertension, fatigue, neutropenia, thrombocytopenia, higher aspartate aminotransferase [AST]/alanine transaminase [ALT]) with an incidence exceeding 1% as documented in Lyu's study [13]. To simplify modeling, we assumed that all AEs occurred during the first treatment cycle, and subjects could experience more than one AE at a time.

Statistical analysis

During cost-effectiveness analysis, we carried out sensitivity analysis for assessing how uncertainties of treatment effectiveness, cost and utility affected ultimate ICER outcome. We acquired model parameters in pertinent literature, which varied in 20% of baseline for establishing parameter ranges. Concurrently, discount rate was 0%-5%. During Monte Carlo simulations, 1,000 tests were repeated, and every key parameter was assigned according to a suitable distribution, like costs that follow the Gamma distribution or utilities that followed the Beta distribution.

Patient and public involvement statement

Patients and the public were not involved in the design and conception of this study.

Results

Base case results

In our analysis of the base case, the HAIC−FO arm paid $18,470.98 on the whole, yielding the QALY of 1.00. Conversely, the total cost in sorafenib group was $15,011.73, with the QALY being 0.66. **Table 2** shows discounted costs and QALYs. When HAIC−FO was compared to sorafenib, an ICER of $10,235.56/QALY could be calculated. This ICER decreased compared with the Chinese referential WTP threshold, as shown in **Figure 2A**.

The subgroup analyses revealed that the ICERs of HAIC−FO versus sorafenib were lower relative to WTP threshold in all analyzed subgroups. These subgroups included tumor size (>10/<=10 cm), tumor number (1-3/>3), tumor burden (>=50%/<50%), portal vein tumor thrombosis (Vp4/Vp1-3), macrovascular invasion (yes/no), gender (male/female), etiology (hepatitis B virus [HBV]/non-HBV), extrahepatic spread (yes/no), Child-Pugh score (B/A), age (>55/<=55 years), and alpha-fetoprotein level (>400/<=400 ng/ml) (**Figure 2B**). Subgroup analysis revealed that the ICER was $7,003.33 per QALY for patients with Vp 4 portal vein tumor thrombus and $7,382.86 per QALY for those with a high tumor burden.

One-way sensitivity analysis

This study conducted one-way sensitivity analysis for identifying key model parameters for comparing HAIC−FO with sorafenib. From **Figure 3A**, we utilized the tornado diagram for representing fluctuations of cost-effectiveness of HAIC−FO versus sorafenib according to modeled variables. Based on tornado diagram, HAIC−FO still had a lower ICER than $30,492 per QALY (WTP threshold for reference) among all modeled parameters in comparison with sorafenib.

To be specific, parameters related to AEs exhibited the least influence on eventual ICER variation, with fluctuations of less than $11.50 per QALY. Consequently, **Figure 3A** does not show AE parameters.

Probabilistic sensitivity analysis

Based on Monte Carlo analysis, the HAIC−FO strategy proved to be a cost-effective approach with a rate of up to 99.9% in China (**Figure 3B**). From **Figure 3C**, with the increasing WTP per incremental QALY, proportion of modeled samples favoring HAIC−FO as the highly cost-effective strategy elevated corresponding in the probabilistic sensitivity analysis, whereas the proportion favoring sorafenib decreased. HAIC−FO was the preferred strategy in 48.9% of patients, with the WTP threshold being $10,000. This percentage rapidly increased to 97.2% with the WTP threshold being $20,000, and reached 99.9% upon the WTP threshold being $30,000. Additionally, it was predicted with 100.0% at a WTP threshold of $40,000.

Discussion

The HCC treatment cost constitutes a substantial part in cancer healthcare expenditure, making it essential to evaluate health economics for determining practical significance of HAIC−FO. Utilizing the Markov model, the present work was performed for comparing cost-effectiveness between HAIC−FO and sorafenib in advanced HCC patients. Our results indicated that, according to Chinese payers, HAIC−FO was the cost-effective therapeutic choice. The present work can shed precious lights on evaluating evaluate HAIC−FO in the management of HCC from a health economics standpoint for policymakers, physicians, and patients (Figure 4).

Recently, clinical benefits brought by HAIC−FO have garnered wide attention of physicians and patients [18]. However, there is limited cost-effectiveness studies comparing HAIC−FO

or HAIC-FO based therapy with sorafenib for advanced HCC being published, resulting in uncertainty in health decision-making [19-21]. Based on our research findings, HAIC−FO has been demonstrated as the cost-effective therapy alternative for advanced HCC patients relative to sorafenib, which was supported by the results across a wide range of parameters. Previously, as suggested by Li et al., adding HAIC−FO to sorafenib showed no cost-effectiveness in comparison with sorafenib monotherapy for the treatment of HCC invading the portal vein [17], but the conclusion must be explained with caution because it was assumed that patients might not stop HAIC−FO till disease progression. The authors set the HAIC−FO duration as 8 years in Markov model, which remarkably surpasses the real duration of HAIC−FO treatment in clinical practice. In real world, HAIC−FO therapy is typically administered every three weeks, and the overall duration is approximately 6-8 months for 8 sessions. Therefore, it is reasonable to assume that when Li et al. employed the Markov model for simulating cost-effectiveness of HAIC−FO versus sorafenib, there may be a deviation in the HAIC−FO treatment cycle from the actual clinical treatment scenario. In survivors at 8 months after receiving HAIC−FO, Markov model will considerably increase treatment expenses related to HAIC−FO. Conversely, our study limited HAIC−FO treatment to a maximum of 6–8 cycles, consistent with the trials and clinical practice.

HAIC was determined as the cost-effective strategy relative to sorafenib when AEs, such as neutropenia, elevated AST, and thrombocytopenia, were included into Markov model for calculating the ICER. Furthermore, one-way sensitivity analysis indicated that AEs had minimal influence on the outcomes (not shown in the tornado plot). Despite the potential limited influence on cost-effectiveness caused by AEs, the clinical value persists since they affect patients' healthcare experience and impact treatment adherence of patients. As reported by Kudo et al. [22], AEs ≥ grade 3 occurred at a higher frequency in HAIC based therapy; however, they could be managed through treatment interruption or dose reduction. HAIC

combination treatment is the research focus, and more research is necessary for evaluating treatment effectiveness and safety, and for considering the possible economic benefits.

While our research findings indicated HAIC−FO as the more cost-effective option than sorafenib, it is vital to note that sorafenib is an orally administered medication that offers the advantage of convenience and independence from factors like medical facilities and professional medical personnel. Therefore, considering the current disparities in healthcare conditions across regions in China [23], the feasibility of interventional procedure may not have been optimal in areas with inadequate equipment or insufficient training of medical personnel, as opposed to oral or intravenous therapy. Additionally, the health administration department in China has actively contributed to reducing drug costs through mechanisms such as multilateral negotiations and volume-based discounts [24]. Therefore, we have also considered the potential impact of drug price fluctuations and have determined that HAIC−FO outperforms sorafenib.

Certain limitations should be noted in this work. Firstly, this research found that most patients displayed a high burden of liver tumors at the time of initial diagnosis, which was a common feature in the Chinese advanced HCC patients, typically associated with HBV infection. Notably, sorafenib has limited efficacy in patients with HBV infection, yet it can significantly improve survival of patients developing hepatitis C virus (HCV) infection [25]. Consequently, the health economics evaluation between HAIC−FO and sorafenib remains uncertain in cases from other areas in which HCC may be induced by factors such as HCV infection or alcohol drinking. The trial was conducted at a single medical institution in China, which may limit the generalizability of our findings to other regions with different healthcare systems, treatment practices, and economic conditions [26]. Second, chemotherapeutic regimens are heterogeneous [13, 27-29]. Consequently, further research is warranted for precisely assessing whether diverse HAIC strategies are cost-effective and safe among

different populations. Third, Markov modeling is associated with limitations on the basis of assumptions and input data quality. Nonetheless, the results were sound among various model inputs, suggesting that other inputs might not markedly affect our findings. Finally, future research should compare the cost-effectiveness of HAIC-FO with other treatment modalities for advanced HCC, including emerging systemic therapies, to provide a more comprehensive economic evaluation.

Taken together, the HAIC−FO strategy is more cost-effective than sorafenib for advanced HCC among the Chinese patients, particularly for patients with Vp 4 portal vein tumor thrombus and/or high tumor burden.

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Author contribution:

- Conceptualization: Qi-Feng Chen and Ming Zhao
- Data curation: Qi-Feng Chen and Xiong-Ying Jiang
- Formal analysis: Qi-Feng Chen, Xiong-Ying Jiang, Yue Hu, and Song Chen
- Funding acquisition: Qi-Feng Chen, Ning Lyu and Ming Zhao
- Investigation: Qi-Feng Chen, Xiong-Ying Jiang, Yue Hu, and Song Chen
- Methodology: Qi-Feng Chen and Xiong-Ying Jiang
- Project administration: Ming Zhao
- Resources: Ming Zhao
- Software: Ming Zhao
- Supervision: Ming Zhao
- Validation: Qi-Feng Chen, Xiong-Ying Jiang, Yue Hu, and Song Chen
- Visualization: Qi-Feng Chen and Xiong-Ying Jiang
- Writing-original draft: Qi-Feng Chen and Xiong-Ying Jiang
- Writing-review & editing: Ming Zhao
- Ming Zhao is the guarantor

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Competing interests: None declared.

Patient consent for publication: Not applicable.

Data availability statement: [dataset] The datasets generated or analyzed during the study are available in the [Research Data Deposit] repository, [https://www.researchdata.org.cn/Search.aspx?k=RDDA2021002021].

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Figure Legends

Figure 1. Study flow diagram.

Figure 2. The base case findings. (A) When comparing HAIC−FO to sorafenib, the incremental cost-effectiveness ratio (ICER) was calculated to be $10,235.56 per quality-adjusted life year (QALY). (B) Subgroup analysis results. AFP, alpha fetoprotein; EHS, extrahepatic spread; HBV, hepatitis B virus; ICER: incremental cost-effectiveness ratio; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; QALYs: quality-adjusted life-years.

Figure 3. Sensitivity analysis. (A) A tornado diagram was adopted for performing a one-way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) for hepatic artery infusion chemotherapy of fluorouracil, leucovorin, and oxaliplatin (HAIC−FO) and sorafenib, with the parameters sorted based on their magnitude. (B) In the probabilistic sensitivity analysis, HAIC−FO was shown to be a cost-effective treatment option. To evaluate the influence of parameter uncertainty on the results of the cost-effectiveness analysis, 1,000 Monte Carlo simulations were performed using the input parameters and their respective distributions listed in Table 1. The dots below the lines represent simulations where the cost per quality-adjusted life year (QALY) gained was below the willingness-to-pay (WTP) threshold. (C) The curves display the probabilities of cost-effectiveness for HAIC−FO and sorafenib.

Figure 4. Schematic diagram of the study.

Tables

Table 1. Markov inputs in cost-effectiveness analysis.

Variable	Baseline	Range low	Range high	Distribution	Reference
Survival input					
HR of HAIC−FO vs sorafenib for OS	0.408	0.301	0.553	Normal	[13]
HR of HAIC−FO vs sorafenib for PFS	0.451	0.340	0.598	Normal	[13]
Weibull OS survival model with HAIC−FO	λ 0.0170272, γ 1.3635872				[13]
Weibull PFS survival model with HAIC−FO	λ 0.071169, γ 1.037127				[13]
Weibull OS survival model with sorafenib	λ 0.0151598, γ 1.8083652				[13]
Weibull PFS survival model with sorafenib	λ 0.0888648, γ 1.3537234				[13]
Utility input					
utility of PFS	0.760	0.610	0.910	Beta	[17]
utility of PD	0.680	0.540	0.820	Beta	[17]
disutility due to neutropenia	0.090	0.006	0.120	Beta	[30]
disutility due to fatigue	0.073	0.037	0.110	Beta	[30]
Cost input					

sorafenib (per month)	3077.760	2462.208	3693.312	Gamma	[17]
oxaliplatin (per month)	364.413	291.531	437.296	Gamma	[17]
cisplatin (per month)	14.310	11.448	17.172	Gamma	[31]
fluorouracil (per month)	686.200	548.960	823.440	Gamma	[17]
leucovorin (per month)	31.653	25.323	37.984	Gamma	[17]
HAIC procedure (per month)	2422.707	1938.165	2907.248	Gamma	[17]
hospitalization (per month)	502.560	402.048	603.072	Gamma	[17]
test (per month)	469.587	375.669	563.504	Gamma	[17]
second_line (per month)	959.160	767.328	1150.992	Gamma	[9]
Body surface area	1.720	1.380	2.060	Normal	[17]
Discount rate	0.030	0.000	0.050	Fixed	[17]

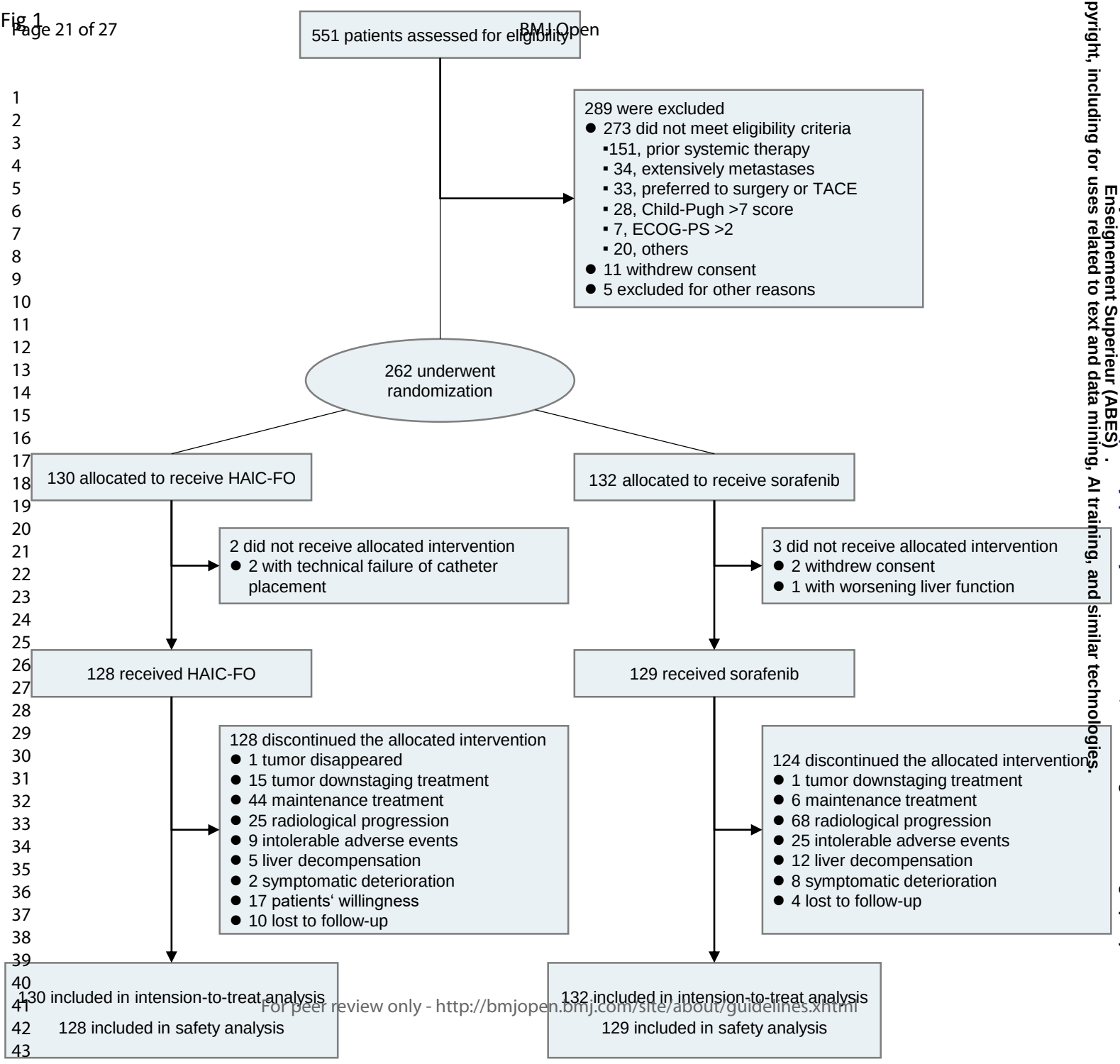
Note: Regarding the choice of survival distribution, we evaluated multiple potential distributions, including Weibull, log-logistic, log-normal, gamma, Gompertz, and exponential distributions. We selected the Weibull distribution based on the principle of minimum Akaike Information Criterion (AIC) and Bayesian Information Criterion values, as smaller AIC and BIC values indicate a better model fit.

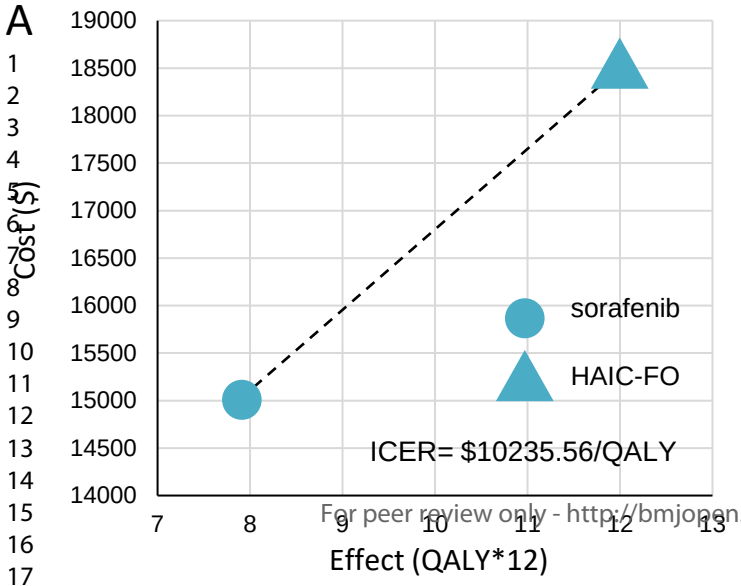
HR, hazard ratio. HAIC, hepatic arterial infusion chemotherapy. FO, oxaliplatin+fluorouracil. OS, overall survival. PFS, progression free survival. PD, progression disease. AST, aspartate aminotransferase.

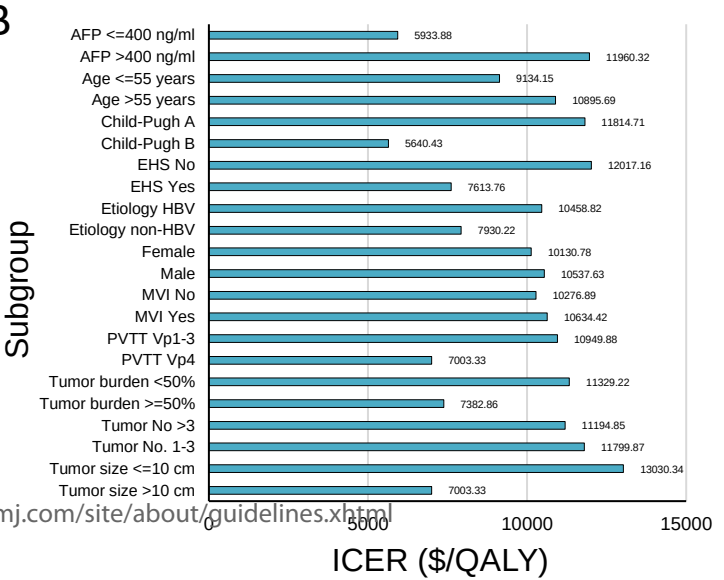
Table 2. Cost-effectiveness results.

	QALYs	Total cost ($)	ICER ($/QALY)
Sorafenib	0.66	15011.73	/
HAIC−FO	1.00	18470.98	10235.56

HAIC−FO: hepatic artery infusion chemotherapy of fluorouracil, leucovorin, and oxaliplatin; QALYs: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio.







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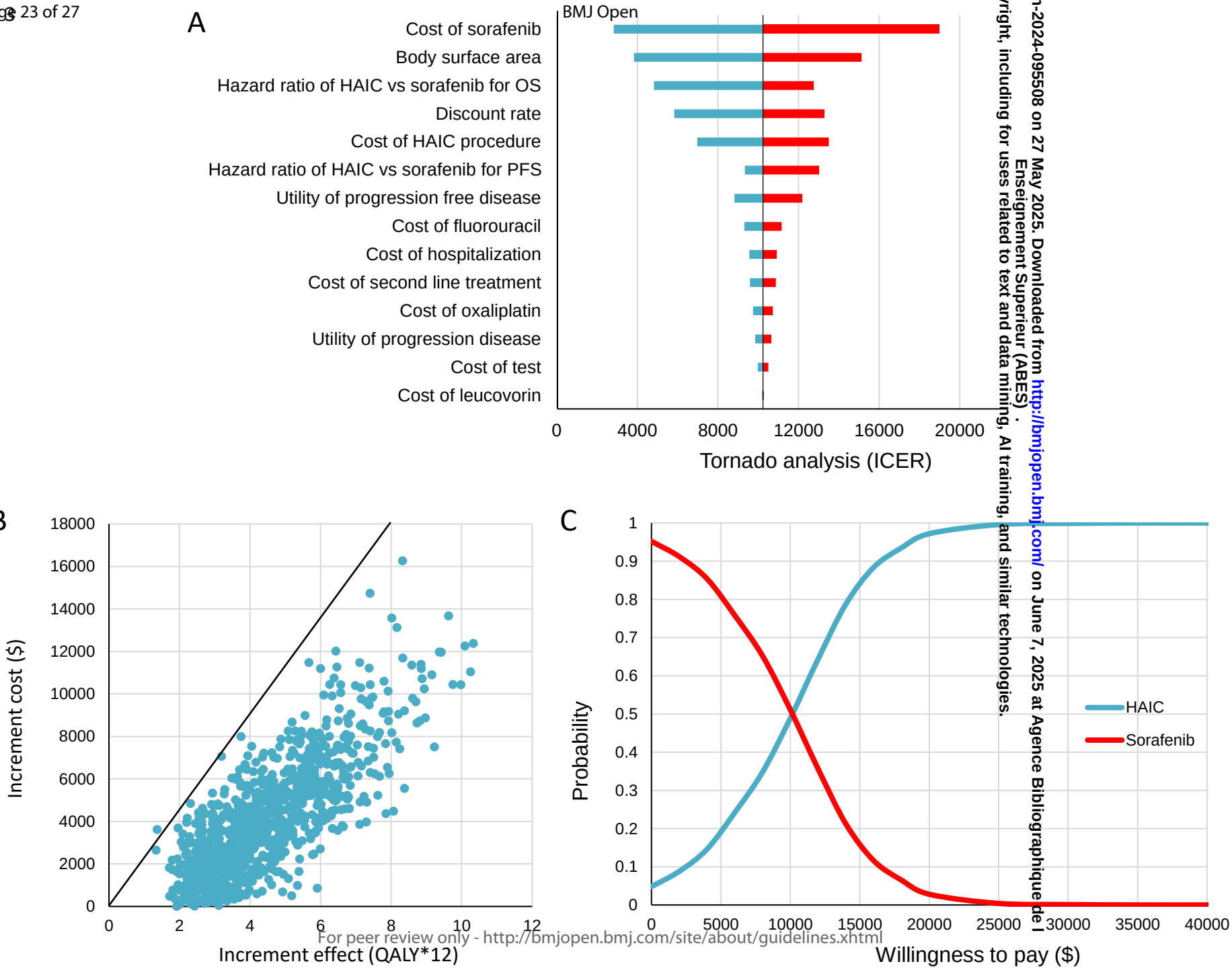
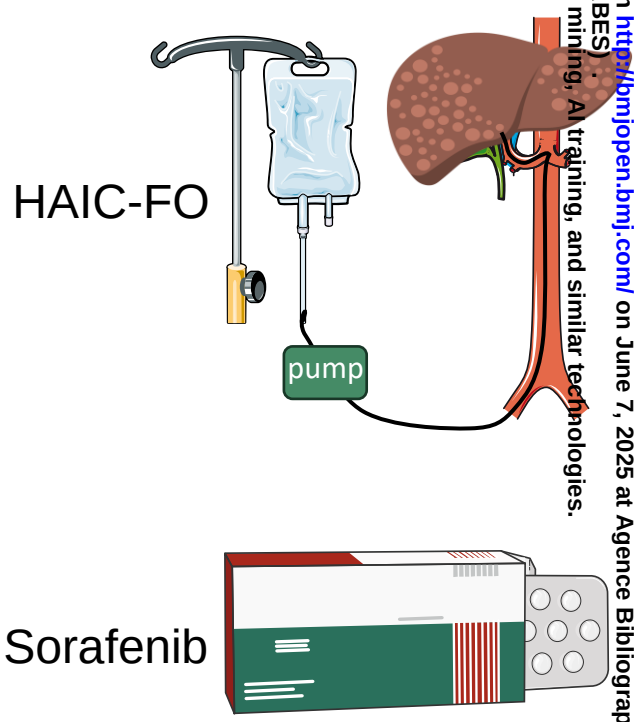


Cost-effectiveness of HAIC-FO versus Sorafenib for Advanced HCC

Study Population

Eligibility Criteria	Details
Age	≤18 years
Condition	Locally advanced or unresectable HCC confirmed histologically or with cirrhosis diagnosed clinically
Dominant Mass	Present in the liver with or without extrahepatic oligometastasis
Suitability for Other Treatments	Unsuitable for surgery, ablation, or transarterial chemoembolization, or progressive disease after such therapies
Prior Systemic Treatment	No
Child-Pugh Grade	≤7
ECOG Performance Status	0-2

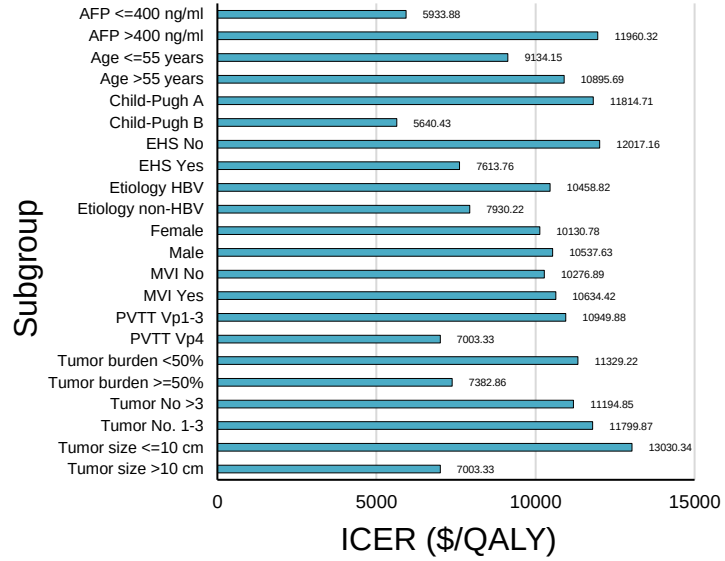
Intervention



Outcome

HAIC-FO is cost-effective compared to sorafenib

	QALYs	Cost ($)	ICER ($/QALY)
Sorafenib	0.66	15011.73	/
HAIC−FO	1.00	18470.98	10235.56



clinicaltrials.gov, NCT03164382

Supplementary tables

Table S1. Subsequent treatment regimens.		
	HAIC-FO group (n = 130)	**Sorafenib group (n = 132)**
	No. (%)	**No. (%)**
Number of patients with at least one 2-line treatment after disease progression	25 (19.2)	41 (31.1)
Percutaneous thermal ablation	1 (0.8)	0 (0)
Surgical resection	0 (0)	0 (0)
Transarterial chemoembolization	2 (1.5)	5 (3.8)
HAIC-FO	0 (0)	6 (4.5)
Radiotherapy for vascular invasion	0 (0)	2 (1.5)
Tyrosine kinase inhibitor	14 (10.8)	20 (15.2)
Anti-PD-1 immune checkpoint inhibitor	5 (3.8)	5 (3.8)
Tyrosine kinase inhibitor + Anti-PD-1 immune check point inhibitor	1 (0.8)	2 (1.5)
Tislelizumab + Bevacizumab	1 (0.8)	1 (0.8)
Number of patients with at least one 3-line treatment after	4 (3.1)	9 (6.8)

disease progression		
Percutaneous thermal ablation	0 (0)	0 (0)
Surgical resection	0 (0)	0 (0)
Transarterial chemoembolization	1 (0.8)	0 (0)
HAIC-FO	1 (0.8)	0 (0)
Radiotherapy for vascular invasion	0 (0)	0 (0)
Tyrosine kinase inhibitor	2 (1.5)	5 (3.8)
Anti-PD-1 immune check point inhibitor	0 (0)	3 (2.3)
Tyrosine kinase inhibitor + Anti-PD-1 immune check point inhibitor	0 (0)	0 (0)
Tislelizumab + Bevacizumab	0 (0)	1 (0.8)
Note: Percentage in the parenthesis was calculated as the accrual number of patients receiving such treatment divided by the total number of patients receiving treatment. Abbreviations: HAIC-FO, hepatic arterial infusion chemotherapy of FOLFOX regimens; PD-1, programmed cell death protein-ligand 1;		

Table S2. Markov inputs in cost-effectiveness analysis.

Variable	Baseline	Range low	Range high	Distribution	Reference
Cost input					
hypertension	1.350	1.080	1.620	Gamma	[9]
elevated total bilirubin	113.530	90.824	136.236	Gamma	[9]
neutropenia	82.390	65.912	98.868	Gamma	[17]
fatigue	64.120	51.296	76.944	Gamma	[32]
elevated AST	42.540	34.032	51.048	Gamma	[17]
thrombocytopenia	1054.220	843.376	1265.064	Gamma	[32]
Incidence of adverse events					
hypertension with sorafenib	0.101	0.081	0.121	Beta	[13]
elevated total bilirubin with sorafenib	0.070	0.056	0.084	Beta	[13]
neutropenia with sorafenib	0.062	0.050	0.074	Beta	[13]

fatigue with sorafenib	0.062	0.050	0.074	Beta	[13]
elevated AST with sorafenib	0.031	0.025	0.037	Beta	[13]
thrombocytopenia with sorafenib	0.023	0.018	0.028	Beta	[13]
hypertension with HAIC	0.000	0.000	0.050	Beta	[13]
elevated total bilirubin with HAIC	0.055	0.044	0.066	Beta	[13]
neutropenia with HAIC	0.078	0.062	0.094	Beta	[13]
fatigue with HAIC	0.000	0.000	0.050	Beta	[13]
elevated AST with HAIC	0.109	0.087	0.131	Beta	[13]
thrombocytopenia with HAIC	0.109	0.087	0.131	Beta	[13]
HAIC, hepatic arterial infusion chemotherapy. AST, aspartate aminotransferase.					

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Interventional Arterial Chemotherapy versus Sorafenib for Advanced Hepatocellular Carcinoma in China: A Health Economic Evaluation of Open-Label, Randomized, Phase 3 Study

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Interventional Arterial Chemotherapy versus Sorafenib for Advanced Hepatocellular Carcinoma in China: A Health Economic Evaluation of Open-Label, Randomized, Phase 3 Study

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Abstract

Objectives: This post hoc study aimed to evaluate the cost-effectiveness of hepatic artery infusion chemotherapy (HAIC) with fluorouracil, leucovorin, and oxaliplatin (HAIC-FO) compared to sorafenib in patients with advanced hepatocellular carcinoma (HCC). The analysis was conducted from the perspective of Chinese payers.

Design: A cost-effectiveness analysis was performed using a Markov model derived from data obtained in the FOHAIC-1 trial (phase 3 randomized controlled trial; conducted 2017–2020).

Setting: The study was conducted in tertiary-care centers in China.

Participants: The study included advanced HCC patients enrolled in the FOHAIC-1 trial. Inclusion criteria followed the trial protocols, with patients stratified by disease severity (including the presence of Vp4 portal vein tumor thrombus (PVTT) and high tumor burden).

Interventions: HAIC-FO (fluorouracil, leucovorin, and oxaliplatin) was compared with sorafenib for cost and health outcomes.

Primary outcome measure: The primary outcome was the incremental cost-effectiveness ratio (ICER), calculated as the additional cost per quality-adjusted life-year (QALY) gained.

Results: Sorafenib yielded 0.66 QALYs at a cost of $15,011.73, whereas HAIC-FO yielded 1.00 QALY at a cost of $18,470.98. The ICER of HAIC-FO compared with sorafenib was $10,235.56 per QALY, which was below the willingness-to-pay (WTP) threshold of $30,492.00 per QALY. Sensitivity analyses confirmed that HAIC-FO remained cost-effective across variable assumptions, with probabilistic sensitivity analysis showing a 99.9% probability of cost-effectiveness at the WTP threshold. Subgroup analyses demonstrated

more favorable ICERs for patients with Vp4 PVTT ($7,003.33 per QALY) and those with high tumor burden ($7,382.86 per QALY).

Conclusions: HAIC-FO is a more cost-effective treatment for advanced HCC than sorafenib from the Chinese payer's perspective, particularly in patients with Vp4 PVTT and/or high tumor burden. Further research is needed to explore long-term economic implications and real-world effectiveness data.

Keywords: Cost-effectiveness; Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; China

Strengths and limitations of this study:

1. The study utilized a Markov model based on data from the FOHAIC-1 Phase 3 trial, providing robust comparative data between HAIC-FO and sorafenib.
2. The incremental cost-effectiveness ratio (ICER) for HAIC-FO was well below the willingness-to-pay threshold, confirming its cost-effectiveness.
3. Subgroup analysis identified specific economic benefits of HAIC-FO in patients with Vp4 PVTT and high tumor burden.
4. Sensitivity analyses confirmed the robustness of the results with a 99.9% probability of cost-effectiveness.
5. This study focused on the Chinese healthcare payer perspective, which may limit generalizability to regions with differing economic conditions.

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related mortality worldwide [1]. In developing nations, particularly in China, most patients develop advanced HCC [2]. Prior to 2017, sorafenib was the recommended first-line systemic therapy for HCC; lenvatinib was approved as a first-line treatment option in 2018 [3]. Following IMbrave 150 trial results published in 2020 [4], Chinese and international guidelines have endorsed atezolizumab plus bevacizumab (T+A) as the preferred first-line regimen for patients with unresectable HCC and no prior systemic treatment [5-8]. However, current evidence suggests T+A may not be cost-effective compared with sorafenib [9-12].

Although hepatic artery infusion chemotherapy (HAIC) is not universally recognized as a well-established treatment regimen, it is effective and commonly used in treating advanced HCC in East Asian countries [5]. The recent FOHAIC-1 trial demonstrated that HAIC with fluorouracil, leucovorin, and oxaliplatin (HAIC-FO) improved clinical outcomes compared with sorafenib in advanced HCC [13]. Median overall survival was 13.9 months for HAIC-FO versus 8.2 months for sorafenib (hazard ratio [HR], 0.408; P <0.001), and median progression-free survival was 7.8 months versus 4.3 months, respectively (HR, 0.451; P<0.001). Despite these reported clinical benefits of HAIC-FO in advanced HCC, its cost-effectiveness has not been thoroughly evaluated.

Concerns about the economic value of the T+A regimen persist, prompting exploration of alternative therapies with improved cost-effectiveness. This study compared the cost-effectiveness of HAIC-FO and sorafenib in Chinese patients with advanced HCC.

Materials and Methods

FOHAIC-1 trial

The Institutional Review Board approved this study (IRB No.SB5010-2017-015). All participants provided informed consent. Patients and the public were not involved in the design, conduct, reporting, or dissemination of our research plans. The trial, carried out at a medical institution in China, was a phase 3 randomized study comparing the therapeutic effects of HAIC-FO and sorafenib in advanced hepatocellular carcinoma (HCC) [13]. The primary inclusion criterion was a dominant liver mass, with additional criteria detailed in ClinicalTrials.gov (registration ID: 03164382). From 2017 to 2020, a total of 262 eligible patients were randomized into 2 groups: 130 received HAIC-FO, and 132 received sorafenib therapy (1:1 ratio; **Figure 1**). Among these, 89.3% had hepatitis B virus (HBV) infection and 82.8% exhibited macrovascular invasion. In the HAIC-FO arm, the regimen consisted of sequential infusions of oxaliplatin (130 mg/m^2), leucovorin (200 mg/m^2), fluorouracil (400 mg/m^2), and fluorouracil (2,400 mg/m^2) administered via catheter every 3 weeks. The HAIC-FO procedure and treatment-associated adverse events (AEs) have been previously described [13-15]. Patients in the sorafenib control group received 800 mg of sorafenib orally per day, divided into 2 doses, with dosage adjustments as needed. Subsequent treatments are detailed in **Table S1.**

Economic evaluation using Markov model

TreeAge 2011 software was adopted in this study, following the CHEERS reporting guidelines for constructing a Markov model for cost-effectiveness analysis [16]. In this model, the health status was categorized into 3 types: stable, progressive, and death. Patients underwent HAIC-FO or sorafenib therapy in the stable disease stage, while during disease progression, they received second-line therapy until death. The time horizon of the model was 42 months. This study deemed HAIC-FO to be economically viable if the incremental cost-effectiveness ratio (ICER) was under a certain willingness-to-pay (WTP) threshold. Specifically, WTP thresholds refer to WTP per quality-adjusted life-years (QALYs). Based

on previous research, we set WTP thresholds in China to $30,492 per QALY [17]. **Table 1 and Table S2** provide details of the model parameters and their corresponding sources. When patients received HAIC-FO treatment, hospitalization was necessary, and they were responsible for covering the hospitalization cost. However, if the patient received sorafenib treatment, hospitalization was not required, and the cost did not increase. Furthermore, when patients received HAIC-FO treatment, they needed to pay an additional fee apart from the hospitalization cost. The present study assigned QALY values as follows: 0.76 in the absence of disease progression, 0.68 with disease progression, and 0 upon death [17]. This research considered grade ≥3 AEs—including elevated total bilirubin, hypertension, fatigue, neutropenia, thrombocytopenia, and elevated aspartate aminotransferase (AST)/alanine transaminase (ALT)—with an incidence exceeding 1% as documented in Lyu's study [13]. To simplify the modeling, we assumed that all AEs occurred during the first treatment cycle and that subjects could experience more than one AE simultaneously.

Statistical analysis

During the cost-effectiveness analysis, we performed a sensitivity analysis to evaluate how uncertainties in treatment effectiveness, costs, and utilities influenced the final ICER. Model parameters were derived from relevant literature, with values varied by ±20% from baseline to define parameter ranges. The discount rate was set at 0%–5%. In Monte Carlo simulations, 1,000 iterations were conducted, and each key parameter was assigned a probability distribution (e.g., costs modeled using gamma distributions, utilities modeled using beta distributions).

Patient and public involvement statement

Patients and the public were not involved in the design or conduct of this study.

Results

Base case results

In the base-case analysis, the HAIC-FO arm incurred a total cost of $18,470.98 and yielded 1.0 quality-adjusted life-year (QALY). The sorafenib group had a total cost of $15,011.73, and yielded 0.66 QALY (**Table 2**). Compared with sorafenib, HAIC-FO resulted in an incremental cost-effectiveness ratio (ICER) of $10,235.56 per QALY, which was below the willingness-to-pay (WTP) threshold in China (**Figure 2A**).

Subgroup analyses revealed that the ICERs for HAIC-FO compared with sorafenib were below the WTP threshold across all analyzed subgroups. These included tumor size (>10 vs. ≤10 cm), tumor number (1–3 vs. >3), tumor burden (≥50% vs. <50%), portal vein tumor thrombosis (Vp4 vs. Vp1–3), macrovascular invasion (yes vs. no), gender (male vs. female), etiology (hepatitis B virus [HBV] vs. non-HBV), extrahepatic spread (yes vs. no), Child-Pugh score (B vs. A), age (>55 vs. ≤55 years), and alpha-fetoprotein level (>400 vs. ≤400 ng/ml) (**Figure 2B**). Specifically, the ICER was $7,003.33 per QALY for patients with Vp4 portal vein tumor thrombus and $7,382.86 per QALY for those with a high tumor burden.

One-way sensitivity analysis

We conducted a one-way sensitivity analysis to identify key parameters influencing the cost-effectiveness comparison between HAIC-FO and sorafenib. **Figure 3A** presents a tornado diagram illustrating variations in the cost-effectiveness of HAIC-FO versus sorafenib across modeled parameters. The tornado diagram confirmed that HAIC-FO maintained an ICER below the $30,492 per QALY WTP threshold across all parameters compared with sorafenib.

Parameters related to adverse events (AEs) had the smallest impact on ICER variability, with fluctuations of less than $11.50 per QALY. Consequently, AE parameters were excluded from **Figure 3A**.

Probabilistic sensitivity analysis

Based on Monte Carlo analysis, the HAIC-FO strategy was cost-effective in 99.9% simulations in China (**Figure 3B**). As shown in **Figure 3C**, probabilistic sensitivity analysis demonstrated that as the WTP threshold per incremental QALY increased, the proportion of modeled scenarios favoring HAIC-FO as the cost-effective strategy rose correspondingly, while the proportion favoring sorafenib declined. At a WTP threshold of $10,000 per QALY, HAIC-FO was the preferred strategy in 48.9% of simulations; this increased to 97.2% at $20,000, 99.9% at $30,000 and 100.0% at $40,000.

Discussion

The cost of hepatocellular carcinoma (HCC) treatment constitutes a substantial portion of cancer-related healthcare expenditure, underscoring the need to evaluate health-economic implications of HAIC-FO. This study employed a Markov model to compare the cost-effectiveness of HAIC-FO and sorafenib in patients with advanced HCC. Our findings indicate that HAIC-FO is a cost-effective therapeutic option from the perspective of Chinese payers. These results provide valuable insights for policymakers, clinicians, and patients regarding the role of HAIC-FO in HCC management from a health-economic perspective (**Figure 4**).

Recent clinical benefits offered by HAIC-FO have garnered wide attention from physicians and patients [18]. However, few cost-effectiveness studies comparing HAIC-FO or HAIC-FO based therapy with sorafenib for advanced HCC have been published, contributing to uncertainty in healthcare decision-making [19-21]. Our findings demonstrate that HAIC-FO is a cost-effective therapeutic alternative to sorafenib for advanced HCC, a conclusion supported by results across a wide range of parameters. Li et al. previously reported that combining HAIC-FO with sorafenib was not cost-effective compared with sorafenib

monotherapy for HCC with portal vein invasion [17]. However, this conclusion requires cautious interpretation, as their model assumed continuous HAIC-FO administration until disease progression. The authors modeled HAIC-FO treatment over 8 years—a duration far exceeding real-world clinical practice, where HAIC-FO is typically administered every 3 weeks for 6–8 months (8 sessions). This discrepancy suggests potential overestimation of HAIC-FO costs in their analysis. For instance, in patients surviving beyond 8 months, the model used by Li et al. would inflate HAIC-FO-related expenses. In contrast, our study limited HAIC-FO treatment to 6–8 cycles, aligning with clinical trials protocols and real-world clinical guidelines.

HAIC was cost-effective compared to sorafenib when adverse events (AEs)—including neutropenia, elevated AST, and thrombocytopenia—were incorporated into the Markov model for incremental cost-effectiveness ratio (ICER) calculation. One-way sensitivity analysis further confirmed that AEs had minimal impact on cost-effectiveness outcomes (excluded from tornado plot). Despite their limited influence on cost-effectiveness, AEs retain clinical significance as they directly affect patients health-related quality of life and treatment adherence. Kudo et al. [22], reported higher rates of ≥ grade 3 AEs with HAIC-based therapy; however, these were manageable through treatment interruption or dose reduction. Future research should prioritize evaluating the efficacy, safety, and economic benefits of HAIC combination therapies, which are emerging as key focus in HCC management.

While our findings indicate HAIC-FO as a more cost-effective option than sorafenib, it is important to acknowledge that sorafenib—an orally administered medication—offers advantages in convenience and independence from medical facilities or specialized personnel. Therefore, given regional disparities in healthcare infrastructure across China [23], interventional procedures like HAIC-FO may be less feasible in areas with limited equipment

or insufficient trained staff compared to oral or intravenous therapies. Furthermore, the National Healthcare Security Administration of China has actively reduced drug costs through centralized procurement and volume-based pricing [24]. Our analysis accounted for potential drug price fluctuations and confirmed the cost-effectiveness superiority of HAIC-FO over sorafenib under these dynamic conditions.

Several limitations of this study should be acknowledge. First, most patients presented high liver tumor burden at initial diagnosis, which is frequently linked to hepatitis B virus (HBV) infection. Notably, sorafenib demonstrates limited efficacy in HBV-infection related HCC, but significantly improves survival in hepatitis C virus (HCV)-related HCC [25]. Consequently, the health-economics evaluation of HAIC-FO and sorafenib remains uncertain in regions where HCC etiology differs (e.g., HCV infection or alcohol use). Additionally, this single-center study was conducted in China, limiting generalizability to regions with distinct healthcare systems, treatment protocols, or economic conditions [26]. Second, chemotherapeutic regimens exhibit considerable heterogeneity [13, 27-29]. Further research is needed for rigorously evaluating the cost-effectiveness and safety of diverse HAIC strategies across populations. Third, Markov modeling carries inherent limitations related to assumptions and input data quality. However, our findings remained robust across sensitivity analysis, suggesting minimal impact from alternative inputs. Finally, future studies should compare HAIC-FO cost-effectiveness with other advanced HCC therapies—including emerging systemic treatments—to enable comprehensive economic evaluations.

In summary, the HAIC-FO strategy demonstrates greater cost-effectiveness than sorafenib for advanced HCC in Chinese patients, particularly among individuals with Vp4 portal vein tumor thrombus or high tumor burden.

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Author contribution:

- Conceptualization: Qi-Feng Chen and Ming Zhao
- Data curation: Qi-Feng Chen and Xiong-Ying Jiang
- Formal analysis: Qi-Feng Chen, Xiong-Ying Jiang, Yue Hu, and Song Chen
- Funding acquisition: Qi-Feng Chen, Ning Lyu and Ming Zhao
- Investigation: Qi-Feng Chen, Xiong-Ying Jiang, Yue Hu, and Song Chen
- Methodology: Qi-Feng Chen and Xiong-Ying Jiang
- Project administration: Ming Zhao
- Resources: Ming Zhao
- Software: Ming Zhao
- Supervision: Ming Zhao
- Validation: Qi-Feng Chen, Xiong-Ying Jiang, Yue Hu, and Song Chen
- Visualization: Qi-Feng Chen and Xiong-Ying Jiang
- Writing-original draft: Qi-Feng Chen and Xiong-Ying Jiang
- Writing-review & editing: Ming Zhao
- Ming Zhao is the guarantor

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Competing interests: None declared.

Patient consent for publication: Not applicable.

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Figure Legends

Figure 1. Study flow diagram.

Figure 2. Base-case and subgroup analysis results. (A) Incremental cost-effectiveness ratio (ICER) for hepatic artery infusion chemotherapy with fluorouracil, leucovorin, and oxaliplatin (HAIC-FO) compared with sorafenib: $10,235.56 per quality-adjusted life-year (QALY). (B) Subgroup analysis of cost-effectiveness. AFP, alpha-fetoprotein; EHS, extrahepatic spread; HBV, hepatitis B virus; ICER, incremental cost-effectiveness ratio; MVI, macrovascular invasion; PVTT, portal vein tumor thrombus; QALYs, quality-adjusted life-years.

Figure 3. Sensitivity analysis. (A) Tornado diagram of the one-way sensitivity analysis for the incremental cost-effectiveness ratio (ICER) comparing hepatic artery infusion chemotherapy with fluorouracil, leucovorin, and oxaliplatin (HAIC-FO) and sorafenib, with parameters ranked by their impact on ICER variability. (B) Probabilistic sensitivity analysis (1,000 Monte Carlo simulations) demonstrating the cost-effectiveness of HAIC-FO. Dots below the line represent simulations where the cost per quality-adjusted life-year (QALY) gained was below the willingness-to-pay (WTP) threshold. Input parameters and distributions are detailed in Table 1. (C) Cost-effectiveness acceptability curves for HAIC-FO and sorafenib across varying WTP thresholds.

Figure 4. Schematic diagram of the study.

Tables

Table 1. Markov inputs in cost-effectiveness analysis.

Variable	Baseline	Range low	Range high	Distribution	Reference
Survival input					
HR of HAIC-FO vs sorafenib for OS	0.408	0.301	0.553	Normal	[13]
HR of HAIC-FO vs sorafenib for PFS	0.451	0.340	0.598	Normal	[13]
Weibull OS survival model with HAIC-FO	λ 0.0170272, γ 1.3635872				[13]
Weibull PFS survival model with HAIC-FO	λ 0.071169, γ 1.037127				[13]
Weibull OS survival model with sorafenib	λ 0.0151598, γ 1.8083652				[13]
Weibull PFS survival model with sorafenib	λ 0.0888648, γ 1.3537234				[13]
Utility input					
utility of PFS	0.760	0.610	0.910	Beta	[17]
utility of PD	0.680	0.540	0.820	Beta	[17]
disutility due to neutropenia	0.090	0.006	0.120	Beta	[30]
disutility due to fatigue	0.073	0.037	0.110	Beta	[30]
Cost input					

sorafenib (per month)	3077.760	2462.208	3693.312	Gamma	[17]
oxaliplatin (per month)	364.413	291.531	437.296	Gamma	[17]
cisplatin (per month)	14.310	11.448	17.172	Gamma	[31]
fluorouracil (per month)	686.200	548.960	823.440	Gamma	[17]
leucovorin (per month)	31.653	25.323	37.984	Gamma	[17]
HAIC procedure (per month)	2422.707	1938.165	2907.248	Gamma	[17]
hospitalization (per month)	502.560	402.048	603.072	Gamma	[17]
test (per month)	469.587	375.669	563.504	Gamma	[17]
second_line (per month)	959.160	767.328	1150.992	Gamma	[9]
Body surface area	1.720	1.380	2.060	Normal	[17]
Discount rate	0.030	0.000	0.050	Fixed	[17]

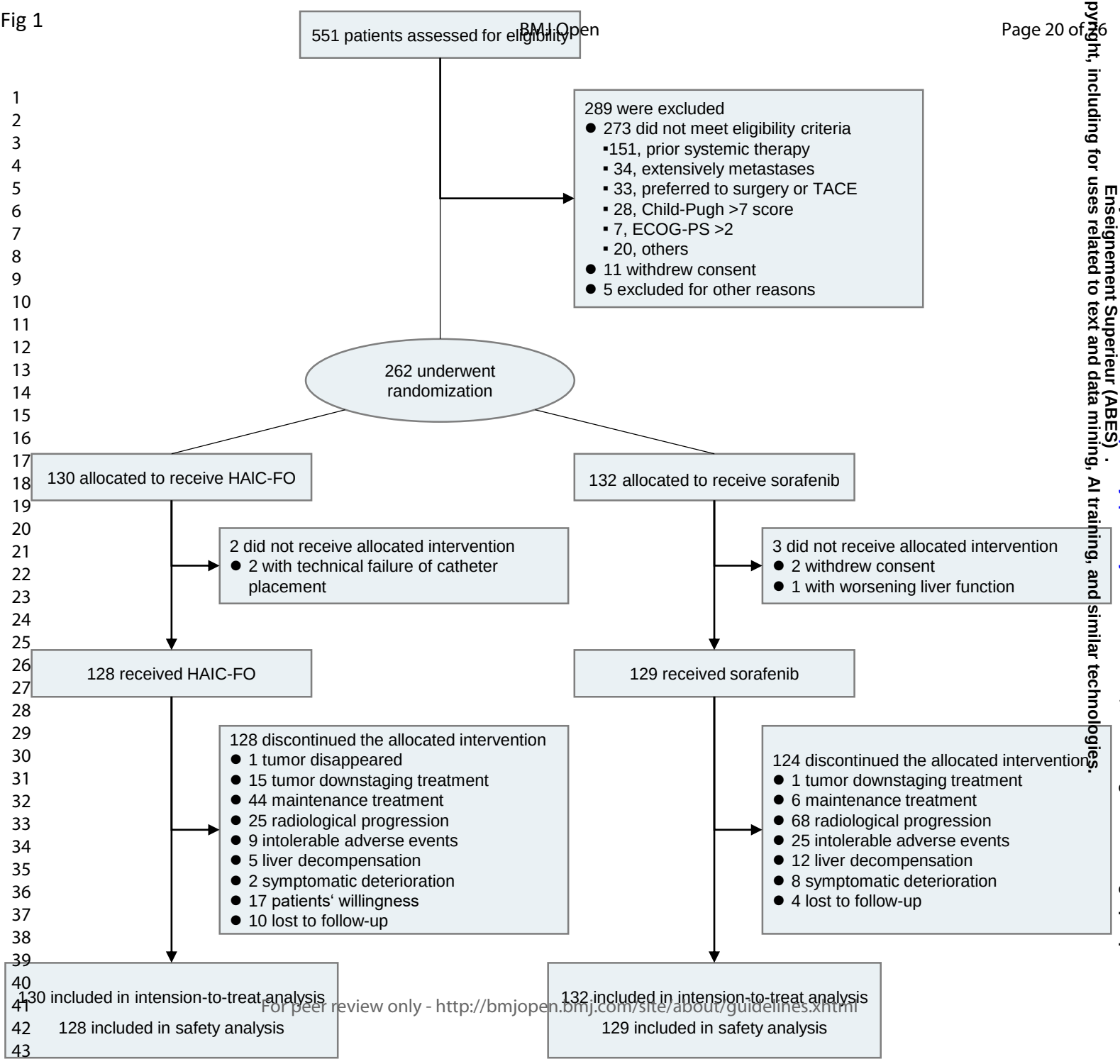
Note: Regarding the choice of survival distribution, we evaluated multiple potential distributions, including Weibull, log-logistic, log-normal, gamma, Gompertz, and exponential distributions. We selected the Weibull distribution based on the principle of minimum Akaike Information Criterion (AIC) and Bayesian Information Criterion values, as smaller AIC and BIC values indicate a better model fit.

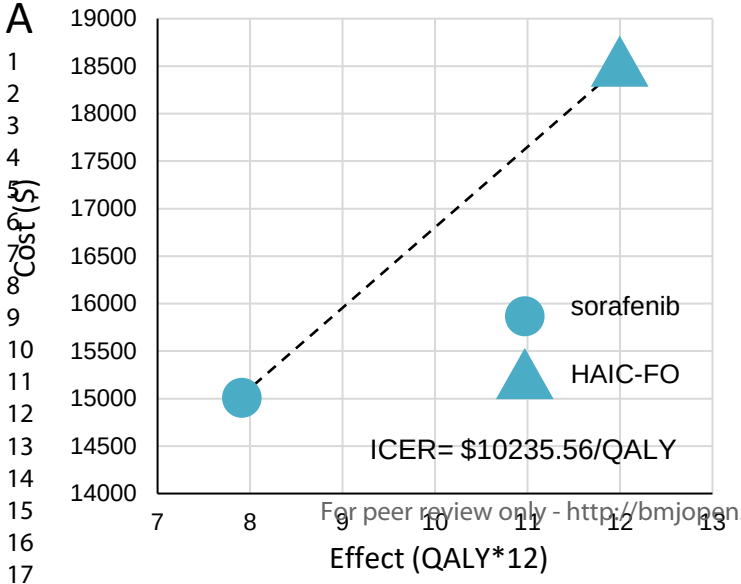
HR, hazard ratio. HAIC, hepatic arterial infusion chemotherapy. FO, oxaliplatin+fluorouracil. OS, overall survival. PFS, progression-free survival. PD, progression disease. AST, aspartate aminotransferase.

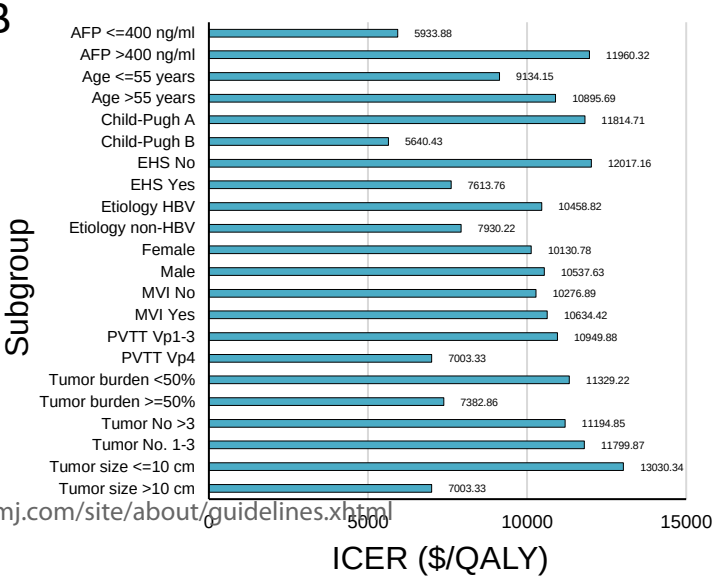
Table 2. Cost-effectiveness results.

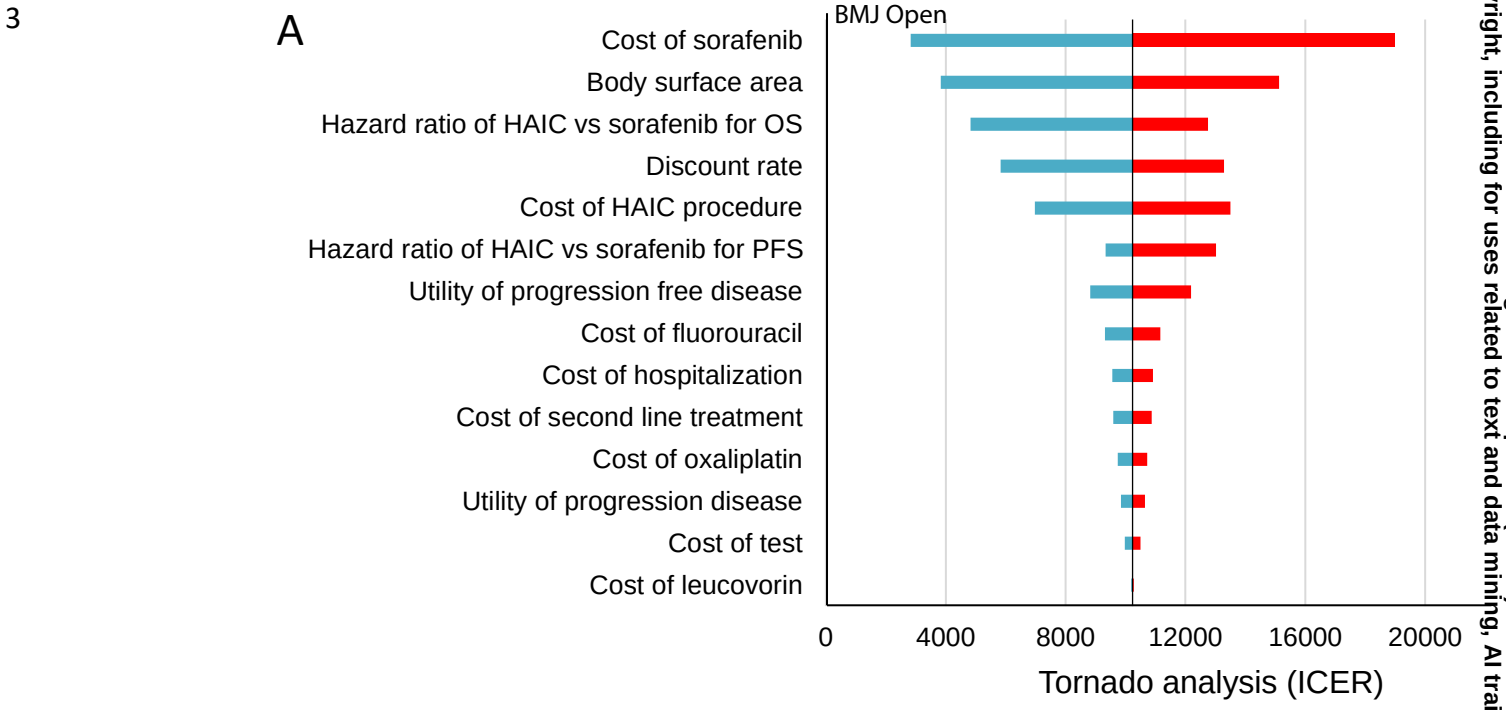
	QALYs	Total cost ($)	ICER ($/QALY)
Sorafenib	0.66	15011.73	/
HAIC-FO	1.00	18470.98	10235.56

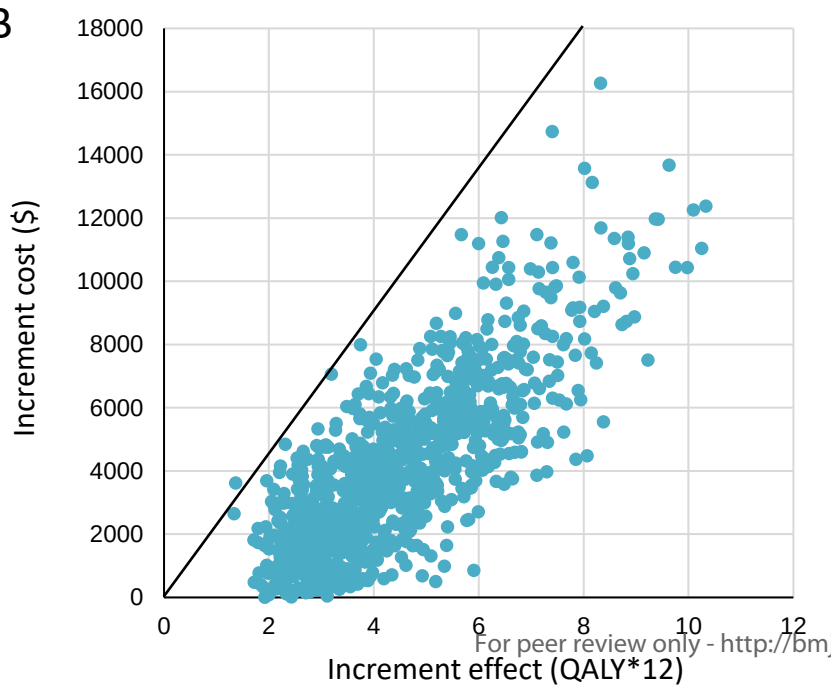
HAIC-FO: hepatic artery infusion chemotherapy of fluorouracil, leucovorin, and oxaliplatin; QALYs: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio.

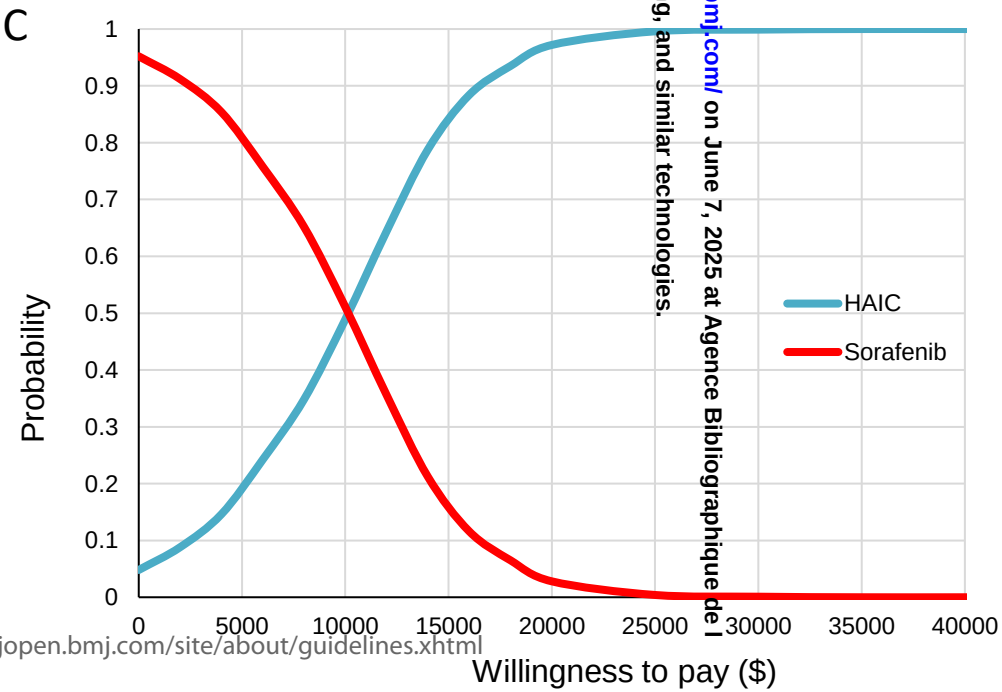










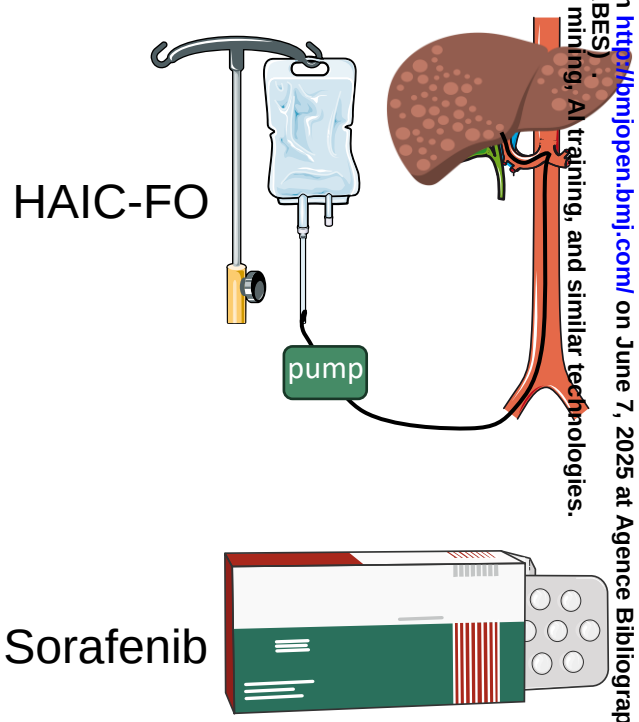


Cost-effectiveness of HAIC-FO versus Sorafenib for Advanced HCC

Study Population

Eligibility Criteria	Details
Age	≤18 years
Condition	Locally advanced or unresectable HCC confirmed histologically or with cirrhosis diagnosed clinically
Dominant Mass	Present in the liver with or without extrahepatic oligometastasis
Suitability for Other Treatments	Unsuitable for surgery, ablation, or transarterial chemoembolization, or progressive disease after such therapies
Prior Systemic Treatment	No
Child-Pugh Grade	≤7
ECOG Performance Status	0-2

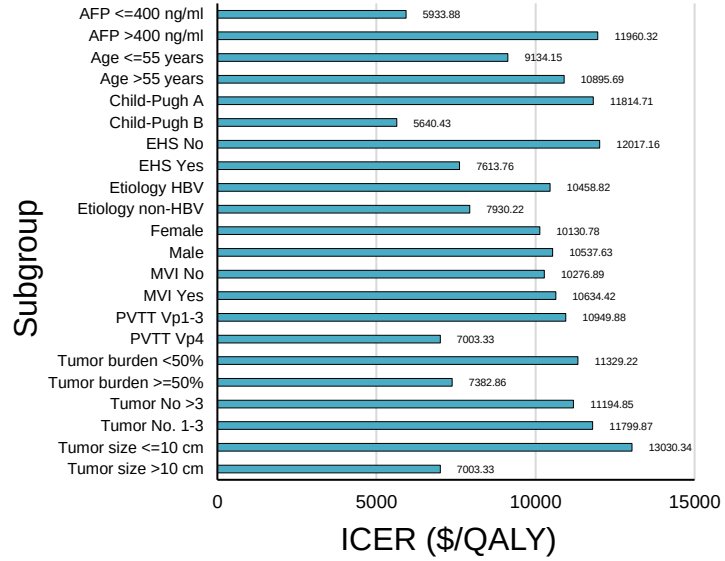
Intervention



Outcome

HAIC-FO is cost-effective compared to sorafenib

	QALYs	Cost ($)	ICER ($/QALY)
Sorafenib	0.66	15011.73	/
HAIC−FO	1.00	18470.98	10235.56



clinicaltrials.gov, NCT03164382

Supplementary tables

Table S1. Subsequent treatment regimens.		
	HAIC-FO group (n = 130)	**Sorafenib group (n = 132)**
	No. (%)	**No. (%)**
Number of patients with at least one 2-line treatment after disease progression	25 (19.2)	41 (31.1)
Percutaneous thermal ablation	1 (0.8)	0 (0)
Surgical resection	0 (0)	0 (0)
Transarterial chemoembolization	2 (1.5)	5 (3.8)
HAIC-FO	0 (0)	6 (4.5)
Radiotherapy for vascular invasion	0 (0)	2 (1.5)
Tyrosine kinase inhibitor	14 (10.8)	20 (15.2)
Anti-PD-1 immune checkpoint inhibitor	5 (3.8)	5 (3.8)
Tyrosine kinase inhibitor + Anti-PD-1 immune check point inhibitor	1 (0.8)	2 (1.5)
Tislelizumab + Bevacizumab	1 (0.8)	1 (0.8)
Number of patients with at least one 3-line treatment after	4 (3.1)	9 (6.8)

disease progression		
Percutaneous thermal ablation	0 (0)	0 (0)
Surgical resection	0 (0)	0 (0)
Transarterial chemoembolization	1 (0.8)	0 (0)
HAIC-FO	1 (0.8)	0 (0)
Radiotherapy for vascular invasion	0 (0)	0 (0)
Tyrosine kinase inhibitor	2 (1.5)	5 (3.8)
Anti-PD-1 immune check point inhibitor	0 (0)	3 (2.3)
Tyrosine kinase inhibitor + Anti-PD-1 immune check point inhibitor	0 (0)	0 (0)
Tislelizumab + Bevacizumab	0 (0)	1 (0.8)
Note: Percentage in the parenthesis was calculated as the accrual number of patients receiving such treatment divided by the total number of patients receiving treatment. Abbreviations: HAIC-FO, hepatic arterial infusion chemotherapy of FOLFOX regimens; PD-1, programmed cell death protein-ligand 1;		

Table S2. Markov inputs in cost-effectiveness analysis.

Variable	Baseline	Range low	Range high	Distribution	Reference
Cost input					
hypertension	1.350	1.080	1.620	Gamma	[9]
elevated total bilirubin	113.530	90.824	136.236	Gamma	[9]
neutropenia	82.390	65.912	98.868	Gamma	[17]
fatigue	64.120	51.296	76.944	Gamma	[32]
elevated AST	42.540	34.032	51.048	Gamma	[17]
thrombocytopenia	1054.220	843.376	1265.064	Gamma	[32]
Incidence of adverse events					
hypertension with sorafenib	0.101	0.081	0.121	Beta	[13]
elevated total bilirubin with sorafenib	0.070	0.056	0.084	Beta	[13]
neutropenia with sorafenib	0.062	0.050	0.074	Beta	[13]

fatigue with sorafenib	0.062	0.050	0.074	Beta	[13]
elevated AST with sorafenib	0.031	0.025	0.037	Beta	[13]
thrombocytopenia with sorafenib	0.023	0.018	0.028	Beta	[13]
hypertension with HAIC	0.000	0.000	0.050	Beta	[13]
elevated total bilirubin with HAIC	0.055	0.044	0.066	Beta	[13]
neutropenia with HAIC	0.078	0.062	0.094	Beta	[13]
fatigue with HAIC	0.000	0.000	0.050	Beta	[13]
elevated AST with HAIC	0.109	0.087	0.131	Beta	[13]
thrombocytopenia with HAIC	0.109	0.087	0.131	Beta	[13]
HAIC, hepatic arterial infusion chemotherapy. AST, aspartate aminotransferase.					