PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

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

Authors

Chen, Qi-Feng; Jiang, Xiongying; Hu, Yue; Chen, Song; Lyu, Ning; Zhao, Ming

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Weng, Xiuhua**
Affiliation	**First Affiliated Hospital of Fujian Medical University, Pharmacy**
Date	**19-Dec-2024**
COI	**None**

1. How long is the period length of the model and the time horizon of the study? Did the authors extrapolate the survival time beyond follow-up? Whether different fitting methods were tested for extrapolation and why weibull function was used?

2. The source reference of utility value in the main text is [16],while that in Table 1 is [2], please check. The FOHAIC-1 trial evaluated the patient QoL by questionnaire and why the related data did not used in this study?

3. More information on how AEs were handled is needed. How long will the AEs persist? A week? A month? Could subjects get more than 1 AE at a time?

4. It should be described about assumptions of therapy in more details so that the readers can better understand how the costs and QALY of PD were calculated, e.g. the specific subsequent treatment regimens, the source of drug price, whether the AEs of subsequent treatments were considered? How the disutility of AEs were converted to the model? Severe hypertension, thrombocytopenia can also affect patients' quality of life, which did not be considered in study.

5.This study was conducted based on the trial which carried out at a single medical institution in China to compare the therapeutic effect between HAIC−FO and sorafenib on advanced HCC, could the results be generalized to all advanced HCC patients. Its scope of application and generality should be stated or discussed in limitation.

Reviewer	**2**
Name	**Mohammadnezhad, Ghader**
Affiliation	**Shahid Beheshti University of Medical Sciences, Department of clinical pharmacy**
Date	**10-Mar-2025**
COI	**None**

I read your study titled "Interventional Arterial Chemotherapy versus Sorafenib for Advanced Hepatocellular Carcinoma in China: A Health Economic Evaluation of Open-Label, Randomized, Phase 3 Study". The clinical study protocol was detailed and complete. Regarding the cost data entered into the model, please provide the exact date of extraction of the costs. There were some inconsistencies in the references related to the introduction text, which I would like to point you to references that provide more detailed and comprehensive descriptions of all economic evaluation studies in the relevant field, such as: https://link.springer.com/article/10.1007/s12029-024-01038-2 & https://link.springer.com/article/10.1007/s00228-023-03502-7. Given the value of economic evaluation studies based on real-world evidence, your study is of great value, but it is recommended that you add an implications for future research paragraph in the Discussion and state that HAIC-FO should be compared with other AHCC treatment modalities in terms of cost-effectiveness.

VERSION 1 - AUTHOR RESPONSE

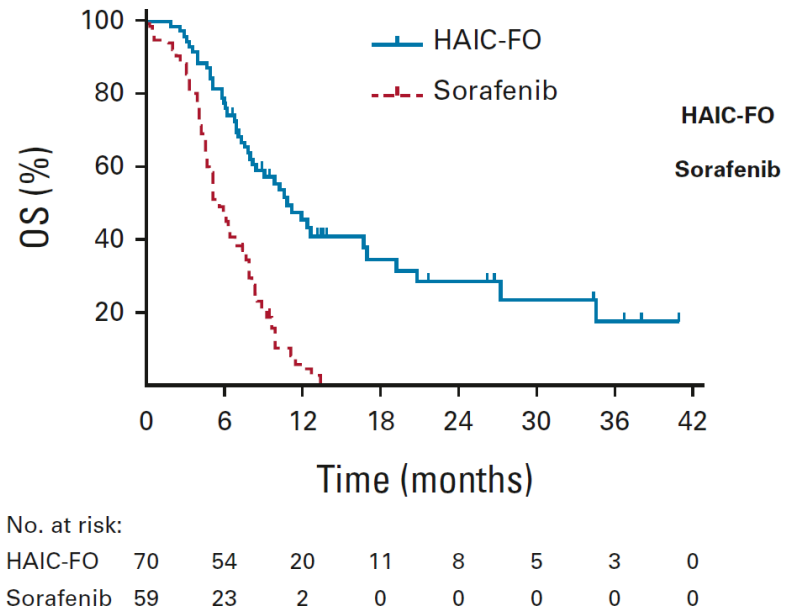
Reviewer 1

1. How long is the period length of the model and the time horizon of the study? Did the authors extrapolate the survival time beyond follow-up? Whether different fitting methods were tested for extrapolation and why weibull function was used?

Response:

Thank you for your insightful comments.

The time horizon of this model was **42 months**, which aligns with the time horizon of the FOHAIC-1 study (as shown in Fig. 1 of J Clin Oncol. 2022;40(5):468-480).



(Source: J Clin Oncol. 2022;40(5):468-480; Figure 1)

We have clarified this in the revised manuscript on Page 7, Line 1-2, by adding: "The time horizon of this model was 42 months."

Additionally, we did not extrapolate survival time beyond the follow-up period.

Regarding the choice of survival distribution, we evaluated multiple potential distributions (please refer the table below), including Weibull, Log-logistic, Log-normal, Exponential, Gompertz, and Gamma distributions. We selected the **Weibull distribution** based on the **principle of minimum Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values**, as smaller AIC and BIC values indicate a better model fit. In response to your suggestion, we have added a clarification note below Table 1 to explicitly state that the Weibull distribution was selected based on the lowest AIC and BIC values.

Survival models comparison.

	Progression-free survival				Overall survival			
	Akaike information criterion		Bayesian information Criterion		Akaike information criterion		Bayesian information Criterion	
Model	HAIC-FO	Sorafenib	HAIC-FO	Sorafenib	HAIC-FO	Sorafenib	HAIC-FO	Sorafenib
Weibull	**939.720**	**867.601**	**947.932**	**873.805**	**1014.041**	**1212.726**	**1023.253**	**1221.931**
Log-logistic	960.968	918.238	966.180	925.442	1011.346	1232.014	1019.558	1240.219

Log-normal	943.710	875.424	951.922	882.628	1020.050	1220.264	1028.261	1227.468
Gompertz	979.335	950.797	985.547	958.001	1012.809	1243.761	1019.020	1249.965
Exponential	983.321	952.285	985.927	956.887	1020.853	1243.593	1024.459	1248.195
Gamma	953.749	902.230	959.961	909.434	1013.904	1228.544	1019.116	1234.749

2. The source reference of utility value in the main text is [16], while that in Table 1 is [2], please check. The FOHAIC-1 trial evaluated the patient QoL by questionnaire and why the related data did not used in this study?

Response: We apologize for the inconsistency in reference citations. We have now standardized the citations throughout the manuscript to ensure accuracy and consistency.

Regarding the use of patient QoL data from the FOHAIC-1 trial, we acknowledge that the completion rate of the QoL questionnaire was lower than expected, which impacted subsequent analysis. The repeated administration of HAIC may have influenced patient compliance in completing the questionnaire, while in the sorafenib group, outpatient treatment without hospitalization limited face-to-face interactions, potentially affecting the accuracy of the collected QoL data.

Due to these limitations, we relied on previously published literature to define utility values as follows: 0.76 in the absence of disease progression, 0.68 for disease progression, and 0 for death.

We appreciate your understanding and will consider addressing this limitation in future research to improve data collection and analysis.

3. More information on how AEs were handled is needed. How long will the AEs persist? A week? A month? Could subjects get more than 1 AE at a time?

Response: We appreciate your insightful comments. The management of AEs is indeed crucial in both clinical practice and health economic evaluations.

In clinical practice, most AEs are short-term and manageable, with severe complications being rare. Acute reactions, such as pain and nausea, typically resolve within days. For example:

- Abdominal pain often occurs during oxaliplatin infusion and usually subsides within minutes to an hour after stopping the infusion.
- Nausea and vomiting generally decrease within 1–2 weeks post-treatment and can be effectively controlled with antiemetics.

Given the complexity of modeling each AE in detail, we followed the approach of previous study [1]. In our model, we considered grade ≥3 AEs with an incidence exceeding 1%, as documented in Lyu's study [2]. 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.

We have clarified this in the revised manuscript on Page 7, Line 15-17, with the addition:

"All AEs were assumed to be incurred during the first cycle, and subjects could experience more than one AE at a time."

Additionally, the Editorial Office considered Table 1 to be too extensive for inclusion in the main manuscript. Therefore, we have moved the data on AE costs and incidence rates to Supplementary Table S2.

Reference:

1. Wen F, Zheng H, Zhang P, Liao W, Zhou K, Li Q. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. Liver Int 2021;41:1097-1104
2. Lyu N, Wang X, Li JB, Lai JF, Chen QF, Li SL, et al. Arterial Chemotherapy of Oxaliplatin Plus Fluorouracil Versus Sorafenib in Advanced Hepatocellular Carcinoma: A Biomolecular Exploratory, Randomized, Phase III Trial (FOHAIC-1). J Clin Oncol 2022;40:468-480

4. It should be described about assumptions of therapy in more details so that the readers can better understand how the costs and QALY of PD were calculated, e.g. the specific subsequent treatment regimens, the source of drug price, whether the AEs of subsequent treatments were considered? How the disutility of AEs were converted to the model? Severe hypertension, thrombocytopenia can also affect patients' quality of life, which did not be considered in study.

Response: Thank you for your insightful question.

Subsequent treatment regimens: Please refer to the **Revised Table S1** below for detailed information on subsequent treatments. To aligned with strategies used in previous study [1] and simplify the model, we standardized subsequent treatments into a single second-line treatment approach.

Revised 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 disease progression	4 (3.1)	9 (6.8)
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;

Source of drug price: Drug costs were obtained from previously published literature [1-4].

Consideration of AEs in second-line treatment: Grade 3–4 AE-related costs for second-line treatments were not included in the model, which is consistent with the previous study [1].

Disutility of AEs in the model: All AEs were assumed to occur during the first treatment cycle, consistent with previous economic evaluation [1]. We included **AEs ≥ grade 3 with an incidence exceeding 1%**, based on Lyu's study, which covered **severe hypertension and thrombocytopenia**. We acknowledge that the potential impact of AEs on patients' quality of life was not explicitly modeled, and we will consider addressing this limitation in future research.

These clarifications have been incorporated into the revised manuscript.

Reference:

1. Wen F, Zheng H, Zhang P, Liao W, Zhou K, Li Q. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. Liver Int 2021;41:1097-1104
2. Li M, Lin S, Wilson L, Huang P, Wang H, Lai S, et al. Cost-Effectiveness Analysis of Hepatic Arterial Infusion of FOLFOX Combined Sorafenib for Advanced Hepatocellular Carcinoma With Portal Vein Invasion. Front Oncol 2021;11:562135
3. Zhao Q, Xie R, Zhong W, Liu W, Chen T, Qiu X, et al. Cost-effectiveness analysis of adding durvalumab to chemotherapy as first-line treatment for advanced biliary tract cancer based on the TOPAZ-1 trial. Cost Eff Resour Alloc 2023;21:19
4. Wong W, Yim YM, Kim A, Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, et al. Assessment of costs associated with adverse events in patients with cancer. PLoS One 2018;13:e0196007

5. This study was conducted based on the trial which carried out at a single medical institution in China to compare the therapeutic effect between HAIC−FO and sorafenib on advanced HCC, could the results be generalized to all advanced HCC patients. Its scope of application and generality should be stated or discussed in limitation.

Response: Thank you for your insightful question.

We have addressed this concern by adding the following statement to the limitations section:

"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."

Reviewer 2

1. Regarding the cost data entered into the model, please provide the exact date of extraction of the costs. There were some inconsistencies in the references related to the introduction text, which I would like to point you to references that provide more detailed and comprehensive descriptions of all economic evaluation studies in the relevant field, such as: https://link.springer.com/article/10.1007/s12029-024-01038-2 & https://link.springer.com/article/10.1007/s00228-023-03502-7.

Response: Thank you for your suggestions. The article "Atezolizumab and Bevacizumab Targeted-Therapy in Advanced Hepatocellular Carcinoma: A Systematic Review of Cost-effectiveness Analyses" is highly relevant to our study, as it discusses the high costs associated with atezolizumab and bevacizumab in advanced HCC and highlights the importance of significant price discounts for these therapies to be cost-effective. We have now added this reference to the introduction section for context and to provide a more comprehensive background on the economic evaluation of treatments for advanced HCC.

2. Given the value of economic evaluation studies based on real-world evidence, your study is of great value, but it is recommended that you add an implications for future research paragraph in the Discussion and state that HAIC-FO should be compared with other AHCC treatment modalities in terms of cost-effectiveness.

Response: Thank you for your valuable suggestion.

We have added it within the limitations to emphasize the need for further studies. Specifically, we have included the following statement:

"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."

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Weng, Xiuhua**
Affiliation Pharmacy	**First Affiliated Hospital of Fujian Medical University,**
Date	**14-Apr-2025**
COI	

1. While the manuscript presents interesting findings, significant language issues hinder the clarity of scientific communication. The text contains recurrent grammatical errors (e.g P8 Line 65: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; P9 Line 17 ：“Conversely”may not suitable), inconsistent technical terminology, and ambiguous sentence structures that frequently require re-reading to comprehend. I strongly recommend professional language editing prior to publication consideration.

2. The ICER in Abstract was not consistent with that in Results, please check.

Reviewer **2**

Name **Mohammadnezhad, Ghader**

Affiliation **Shahid Beheshti University of Medical Sciences, Department of clinical pharmacy**

Date **04-Apr-2025**

COI

Thank you.

VERSION 2 - AUTHOR RESPONSE

Reviewer 1

1. While the manuscript presents interesting findings, significant language issues hinder the clarity of scientific communication. The text contains recurrent grammatical errors (e.g P8 Line 65: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; P9 Line 17 ：“Conversely”may not suitable), inconsistent technical terminology, and ambiguous sentence structures that frequently require re-reading to comprehend. I strongly recommend professional language editing prior to publication consideration.

Response: Thank you for your valuable feedback. In response, we have employed a professional copyediting service to ensure clarity and consistency throughout the manuscript. The language has been thoroughly reviewed and revised to address grammatical issues, improve technical terminology, and enhance readability.

2. The ICER in Abstract was not consistent with that in Results, please check.

Response: Thank you for pointing this out. We have carefully reviewed the manuscript and corrected the inconsistency. The ICER value in the Abstract now matches the corresponding value in the Results section.

Reviewer 2

Comments to the Author: Thank you.

Response: Thank you for your kind comment.
