

# Cost-effectiveness of Sorafenib for hepatocellular carcinoma: a systematic review

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## Abstract

**Background:** Hepatocellular carcinoma (HCC) is the sixth common cancer (5th common cancer in men and 7th common cancer in women) worldwide. In patients who have advanced HCC, sorafenib is the first-line of treatment and showed an improvement of 37.3% in patients' overall survival. This study was aimed to systematically review the economic evaluations of sorafenib in the treatment of HCC to assist decision-makers in controlling costs and ensuring access to effective treatments within limited healthcare budgets.

**Method:** A systematic review was conducted in major databases including PubMed, Cochrane, Embase, Google scholar, Scopus, and Web of Science up to August 2018 with limitation to English full-text published articles. Articles were selected on the basis of their dealing with the economic evaluations of sorafenib. The quality of the selected studies was assessed using the Quality of Health Economic Studies (QHES) instrument.

**Results:** 13 articles were identified in databases meeting the inclusion/exclusion criteria. Five of them had compared sorafenib versus best

supportive care (BSC). The others had compared sorafenib versus different treatment strategies such as oxaliplatin plus infusional-fluorouracil/leucovorin (FOLFOX4), transarterial radioembolization (TARE), transarterial chemoembolization (TACE), and etc. This review found incremental costs per quality-adjusted life years in the range of US\$ -1,014,507 to US\$ 934,803, depending on whether the setting was considered and which comparator was utilized. In all cases, sorafenib was associated with higher cost and higher efficacy except in comparison with TACE and TARE. Sorafenib was found as a dominant and dominated strategy versus TACE and TARE, respectively.

**Conclusion:** This review revealed that sorafenib was more effective with higher cost than its comparators except TARE and could be considered as a cost-effective option for patients with metastatic HCC. The results should be interpreted with a view to the specific health care settings and willingness to pay threshold in different jurisdictions.

**Keywords:** hepatocellular carcinoma, pharmacoeconomic evaluation, sorafenib, cost-effectiveness, systematic review

## Introduction

Hepatocellular carcinoma (HCC) includes 85-90% of primary liver cancer. HCC is the sixth common cancer: 5th common cancer in men and 7th common cancer in women worldwide. In addition, the third reason of the cancer-related death after lung and stomach cancers is HCC (4).<sup>1</sup> The majority of HCC incidence are in East Asia and sub-Saharan Africa. The overall 5-year cost of care for HCC patients was approximately \$106.4 million in Canada, in 2009.<sup>2</sup> 20.9 million Disability adjusted life year (DALYs) was the result of liver cancer in 2013.<sup>3</sup> Disease is associated with a poor prognosis and just 6.9% of patients have 5-year survival mainly because a small group of patients are diagnosed in early stages.<sup>2</sup> Hepatitis B virus, hepatitis C virus, cirrhosis, environmental toxins such as aflatoxin, alcohol abuse, tobacco, type 2 diabetes mellitus, obesity are the most important risk factors of HCC.<sup>4</sup>

There are different approved treatments based on disease stage such as Stereotactic body radiotherapy (SBRT), transarterial radioembolization (TARE) transarterial chemoembolization (TACE), liver transplantation (LT), radiofrequency ablation (RFA), microwave ablation, percutaneous ethanol or acetic acid ablation, cryoablation, systemic chemotherapy, and molecularly targeted therapies such as doxorubicin for hepatocellular carcinoma.<sup>1</sup> In patients who have advanced HCC, sorafenib is recommended as the first-line of treatment in different guidelines.<sup>5-7</sup> Sorafenib were helped to improve overall survival around 37.3%.<sup>8</sup>

Sorafenib is a multi-kinase inhibitor such as vascular endothelial growth factor receptor (VEGFR) that decreases tumor cell proliferation. Sorafenib was approved in 2007 for hepatocellular carcinoma as an oral medication administrated 400mg twice daily. However, according to recent studies, dose-adjusted sorafenib regimen results in better efficacy-safety balanced.<sup>9</sup>

In light of the ever-increasing costs of the healthcare system and a great expense of the newly introduced treatments, it has become more crucial than ever before to choose more cost-effective treatments among different alternatives. Cost-effectiveness studies may provide healthcare decision-makers with the requisite insights to make informed choices.

Hence, this study was aimed to systematically review the economic evaluations of SFN in the treatment of HCC to assist decision-makers in controlling costs and ensuring access to effective treatments within limited healthcare budgets.

## Methods

### Literature search strategy

A systematic literature search in EMBASE, MEDLINE, PUBMED, Google Scholar, and the Scopus database was conducted between November 2004 and August 2018. Table 1 shows key words which have been used in our search strategy.

**Table 1** Search strategy and keywords in which used

<b>Keywords</b>	1. Sorafenib	8. HCC
	2. Nexavar	9. economic evaluation
	3. Hepatocellular	10. pharmacoeconomic evaluation
	4. Liver	11. cost-effectiveness
	5. Carcinoma	12. cost-utility
	6. Cancer	13. cost-benefit
	7. Hepatoma	14. cost-minimization
<b>Search strategy</b>	(1 OR 2) AND (((3 OR 4) AND (5 OR 6)) OR 7 OR 8) AND (11 OR 12 OR 13 OR 14)	

**Inclusion or exclusion criteria:**

The search was limited to articles published in English. In addition, studies were omitted if the full-text was not available. The included studies should also meet the following inclusion criteria:

**Table 2** The Quality of Health Economics Studies (QHES) instrument

	Questions	Points
1.	Was the study objective presented in a clear, specific, and measurable manner?	7
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4
3.	Were variable estimates used in the analysis from the best available sources (i.e., randomized control trial - best, expert opinion - worst)?	8
4.	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9
6.	Was incremental analysis performed between alternatives for resources and costs?	6
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear and transparent manner?	8
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7
14.	Did the author(s) explicitly discuss the direction and magnitude of potential biases?	6
15.	Were the conclusions/recommendations of the study justified and based on the study results?	8
16.	Was there a statement disclosing the source of funding for the study?	3
	<b>Total Points</b>	<b>100</b>

- Adult with intermediate or advanced hepatocellular carcinoma as patient population.
- Taking into account both cost and clinical consequences.
- Representing sorafenib-containing therapy as one of the treatments arm

**Study selection**

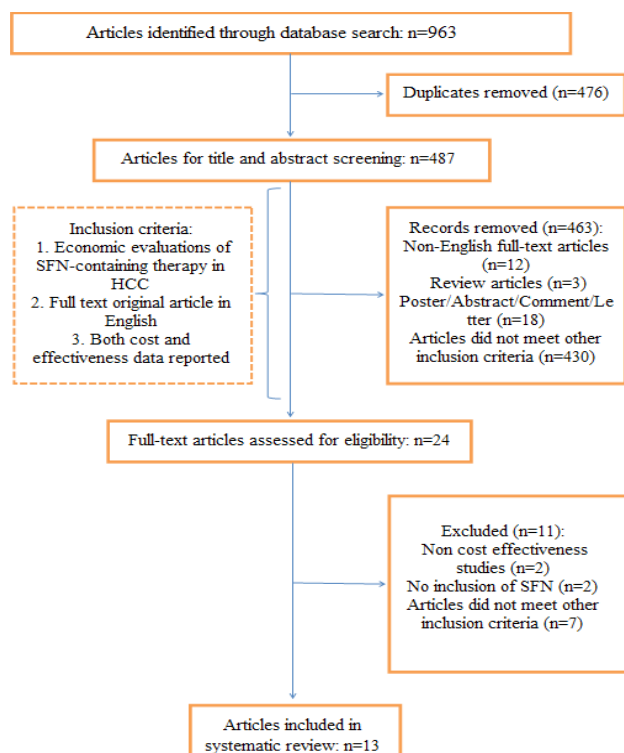
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used to carry out the systematic review.<sup>10</sup> Then, selected articles were transferred to the Mendeley reference manager software and duplicated documents found in different databases were counted out. Then, the full text of the articles were screened by two reviewers ensure compliance with the inclusion and exclusion criteria and, finally, the data from eligible studies were extracted onto an Excel spreadsheet. In case of disagreement between researchers, a third reviewer decided on discrepancies of the articles.

To evaluate the quality of the included studies, the Quality of Health Economic Studies (QHES) instrument, which is shown in Table 2, was used. QHES score shows the quality of economic studies as follows: poor (QHES score <50), fair (QHES score  $\geq 50$  and <75), and good (QHES score  $\geq 75$  and  $\leq 100$ ).<sup>11</sup>

## Results

### Overview

In this comprehensive systematic review 487 articles were identified. After primary evaluation by screening the titles and abstracts, according to the inclusion criteria, 24 articles were selected for full-text evaluation. Finally, 13 articles were selected for final analysis whose characteristics have been presented in Tables 3 and 4. Six of the selected studies had compared sorafenib versus best supportive care (BSC). Other studies had compared sorafenib versus SBRT, TACE, FOLFOX4, TARE, and other therapies. The PRISMA flow chart of this study is given in Figure 1.



**Figure 1** The PRISMA

The cost-effectiveness analyses of sorafenib-containing therapy were conducted in five different countries including USA ( $n = 3$ ), Italy ( $n = 3$ ), Canada ( $n=1$ ), Taiwan ( $n=2$ ), and China ( $n=5$ ). All of them except one study were developed in a single country. Markov model was applied for all of the studies in a 2 year to life-time time horizon. However, Parikh et al.<sup>20</sup> did not report model, time horizon and perspective of study. 10 studies disclosed their source of funding.

The question of studies was focusing on the comparison of SFN, SBRT, FOLFOX4, TARE, TACE or Best Supportive Care (BSC) in the treatment of HCC in terms of cost-effectiveness. Three studies were sponsored by Sanofi Bayer. Four studies declined any financial support. Three studies did not announce, obviously. Three studies were supported by universities in China and Italy.

### Sorafenib versus best supportive care

Muszbec et al.<sup>12</sup> developed a Markov cohort model to evaluate the cost-effectiveness of sorafenib versus BSC as first-line treatment in advanced HCC employing data from SHARP<sup>24</sup> study. Costs were

calculated in 2007 Canadian dollars with a time horizon of lifetime and a 5% discount rate from Canadian provincial Ministry of Health perspective in Canada. The resources used on medical costs were based on publicly available sources, and in the absences of published data experts' opinion were used. The result illustrated that sorafenib was associated with the incremental effectiveness of 0.49 life years gained (LYG). As a result, the incremental cost effectiveness ratio (ICER) was estimated as Can\$75,759 per LYG. Sensitivity analysis showed that the model is sensitive to overall survival (OS), time to progression (TTP) and BSC costs after progression. Finally, the authors who disclosed that supporting by Bayer HealthCare Pharmaceuticals, concluded that although sorafenib is more effective than BSC, it is not cost effective at the threshold of \$50,000.

Vitale et al.<sup>13</sup> compared sorafenib with no therapy before LT employing a Markov model. The model was run in a 10-year time horizon given a payer perspective in 2008. The result indicated an incremental quality adjusted life days (QALD) of 94 (1350 versus 1244 QALD) resulting in an ICER of €197/QALD. The calculated WTP of sorafenib in Italy was €346 per QALD. In conclusion, Sorafenib neoadjuvant therapy was found to be cost-effective in comparison to no therapy for patients waiting for LT.

In another study, Carr et al.<sup>14</sup> adopted a Markov model to assess the cost-effectiveness of sorafenib versus BSC for advanced HCC from the perspective of third-party payer. OS and progression free survival (PFS) of sorafenib was derived from SHARP study. Costs were reported in 2007 dollar over a lifetime horizon. LYs was calculated as 1.58 for sorafenib and 1.05 for BSC, respectively. In addition, sorafenib was associated with an incremental cost of \$32,835 compared to BSC (\$40,639 versus \$7,804) resulting in an ICER of \$62,473/LYG. The economic evaluation showed that sorafenib was cost-effective compared BSC in USA. One-way sensitivity analysis found OS for sorafenib and BSC to be the most sensitive variables, followed by TTP with sorafenib, the cost of first-line treatment with sorafenib—no progression, and the cost of first-line treatment with BSC—no progression.

Cammà et al.<sup>15</sup> compared cost-effectiveness of sorafenib full dose and sorafenib adjusted dose with BSC using a Markov model. Costs were calculated in 2012 euro with a time horizon of 5-year and a 3% discount rate from third-party managed-care payer perspective in Italy. The resources used on medical costs were based on the DRG tariffs and national ambulatory fees. The result illustrated that sorafenib dose adjusted in Barcelona Clinic Liver Cancer (BCLC) B and C stage was associated with the incremental effectiveness of 0.41 life years gained (LYG) and 0.28 QALYs. As a result, ICER was estimated as €25,874 per LYG and €34,534 per QALY for sorafenib dose-adjusted in BCLC B,C. Sensitivity analysis showed that the model is sensitive to an assumption on survival rates of BSC patients, sorafenib treatment duration, and type of survival distribution. Finally, the authors concluded that dose-adjusted sorafenib is more effective than BSC which was lower than the generally accepted societal WTP threshold.<sup>15</sup>

Similarly, Zhang et al.<sup>16</sup> analyzed sorafenib and BSC in the treatment of advanced HCC. A Markov model was developed using 3% discount rate with the payer's perspective. All costs were measured in US dollars. The result demonstrated an incremental QALY of 0.18 (0.45 versus 0.27 QALY) together with an incremental cost of \$18,597.84 (\$19,495.05 versus \$897.21) resulting in an ICER of \$101,399.11/QALY. The sensitivity analysis indicated that the model is sensitive to

the cost of sorafenib, and duration of the PFS state for the sorafenib group. This study showed sorafenib is not a cost-effective strategy at a WTP of \$20 301.00/QALY in China. The study was not been sponsored.<sup>16</sup>

**Table 3** Characteristics of articles assessing cost-effectiveness of Sorafenib in hepatocellular carcinoma

Study (year)	Country	Perspective	Currency/year	Economic model type	Time horizon	Discount rate	Funding source
Muszbek et al. (2008) <sup>12</sup>	Canada	Canadian provincial Ministry of Health	Canadian dollars/ 2007	Markov	Lifetime	5%	Bayer HealthCare Pharmaceuticals
Vitale et al. (2010) <sup>13</sup>	Italy	Payer	Euro/ 2008	Markov	10 year	3%	Not reported
Carr et al. (2010) <sup>14</sup>	USA	Third-party-payer	Dollars/ 2007	Markov	Lifetime	3%	Bayer HealthCare Pharmaceuticals
Cammà et al. (2013) <sup>15</sup>	Italy	Third-party managed-care payer	Euro/ 2012	Markov	5 year	3%	Not reported
Zhang et al. (2015) <sup>16</sup>	China	Chinese payer	Dollars/ NA	Markov	NA	3%	No
Zhang et al. (2016) <sup>17</sup>	China	Chinese societal	Dollars/NA	Markov/ cohort	10 year	Not reported	No
Leung et al. (2016) <sup>18</sup>	Taiwan	National Health Insurance	NT\$/2015	Markov	5 year	3%	No
Rognoni et al. (2017) <sup>19</sup>	Italy	Healthcare system	Euro/2016	Markov	Lifetime	3.5%	ASBM Srl through an unrestricted grant to CERGAS, Bocconi University
Parikh et al. (2017) <sup>20</sup>	USA	Medicare	Dollars/ 2015	NA	2 year	NA	NOT reported
Zhao et al. (2017) <sup>21</sup>	China	Healthcare system	Dollars/ 2015	Markov/ cohort	Lifetime	3%	No
Chen et al. (2018) <sup>9</sup>	China/ USA	Healthcare system	Dollars/ 2016	Markov/ cohort	2 year	3%	National Natural Science Foundation of China and Pearl River S&T Nova Program of Guangzhou, China
Ho et al. (2018) <sup>22</sup>	Taiwan	Healthcare payer	NT\$/2014	Markov	5 year	3%	China Medical University grant
Qin et al. (2018) <sup>23</sup>	China	Healthcare system/ patients	Dollars/ 2017	Markov	Lifetime	5%	Sanofi china

**Table 4** Cost-effectiveness results of SFN in metastatic renal cell carcinoma

Study	Population	Comparator	Type of cost included	Cost	Effectiveness	ICER
Muszbek et al. (2008) <sup>12</sup>	Advanced HCC	SFN vs BSC	Hospitalization, Medical staff, visits Lab tests, AE, drug and supportive care Radiological tests	Can\$47,272 vs Can\$10,309	LYs: 1.51 vs 1.02	Can\$ 75,759/LYG
Vitale et al. (2010) <sup>13</sup>	Waiting list for liver transplantation	SFN+LT vs LT	Sorafenib, Percutaneous ablation, Chemoembolization, Follow-up, Transplantation, indirect cost, drugs	NA	QALD: 1.350 vs 1.244	€197/QALD
Carr et al. (2010) <sup>14</sup>	Advanced HCC	SFN vs BSC	Drugs, physician visits, laboratory tests, scans, and hospitalizations	\$US40,639 vs \$US7,804	LYs: 1.58 vs 1.05	\$62,473/LYG
Cammà et al. (2013) <sup>15</sup>	Intermediate and Advanced HCC	SFN full dose vs BSC SFN adjusted dose vs BSC	Drugs, diagnostic exams, visits, hospitalization	€16,081 vs 4,142 €19,944 vs 4,142	QALY: 0.16 vs 0.012 QALY: 0.44 vs 0.017	€69,344/QALY €34,534/QALY
Zhang et al. (2015) <sup>16</sup>	Advanced HCC	SFN vs BSC	Drugs, tests, and grade 3/4 AE	\$19,495 vs \$897	QALY: 0.45 vs 0.27	\$101,399/QALY
Zhang et al. (2016) <sup>17</sup>	Advanced HCC	SFN vs FOLFOX4	Drugs, administration, venous access management, nursing care, tests, hospitalization, AE, indirect costs	\$18,748 vs \$6,876	QALY: 0.3935 vs 0.3808	\$934,801/QALY

Table Continued

Study	Population	Comparator	Type of cost included	Cost	Effectiveness	ICER
Leung et al. (2016) <sup>18</sup>	Unresectable advanced HCC	SFN vs SBRT	drug costs, laboratory test, physician visits, pharmacy dispensing fee, administration and nursing care fee, AE	NT\$ 2,166,079 VS NT\$1,197,039	QALY: 3.07 vs 2.81	NT\$426,117 / QALY
Rognoni et al. (2017) <sup>19</sup>	Intermediate HCC Advanced HCC	TARE vs SFN	Drug costs, Exam, procedure, DRG	€29,289 vs €31,149 €30,750 vs €21,961	QALY: 0.638 vs 1.178 QALY: 0.568 vs 0.639	€3,302/QALY (dominatd) TARE dominant
Parikh et al. (2017) <sup>20</sup>	Advanced HCC	SFN vs No therapy	Diagnosis to the end of follow-up, drugs	NA	NA	\$224,914/LYG
Zhao et al. (2017) <sup>21</sup>	Unresectable HCC	SFN+TACE vs TACE	Included inpatient visit, diagnostic and laboratory testing, medications, and procedures	\$44,542 vs \$26,951	QALY: 1.02 vs 0.71	\$56,745/QALY
Chen et al. (2018) <sup>9</sup>	Advanced HCC	Full dose SFN vs TACE	Direct medical costs in China Direct medical costs in USA	\$16,703 vs \$10,642 \$34,190 vs \$95,061	QALY: 0.435 vs 0.375 QALY: 0.435 vs 0.375	\$101,028.83/ QALY SFN Dominant
Ho et al. (2018) <sup>22</sup>	Advanced HCC	SFN vs SFN+Other	Direct medical costs accrued from inpatient and outpatient care, and pharmacy visits	NT\$522,695 vs NT\$957,483	QALY: 0.3837 vs 0.5432	NT\$2,725,943/ QALY
Qin et al. (2018) <sup>23</sup>	Intermediate and Advanced HCC	SFN vs FOLFOX4	Drugs, General ward, tests, AE treatment	\$12,798 vs \$8,428	QALY: 0.42 vs 0.38	\$128,559 /QALY

HCC: Hepatocellular carcinoma, SFN: sorafenib, BSC: Best supportive care, LYG: life year gain, LT: liver transplantation, QALD: quality-adjusted life days, QALY: quality-adjusted life year, SBRT: Stereotactic body radiotherapy, TARE: transarterial radioembolization, TACE: transarterial chemoembolization, DRG: diagnosis related group, FOLFOX4: oxaliplatin plus infusional-fluorouracil/leucovorin

Parikh et al.<sup>20</sup> investigated the cost-effectiveness of sorafenib in patients with advanced stage HCC using Medicare beneficiaries with HCC diagnoses from 2007-2009 in USA included 228 sorafenib-treated patients and 870 control patients. ICERs were calculated for sorafenib-treated and control patients. All costs were measured in US dollars in 2015. The results illustrated the median survival of the sorafenib-treated patients was 150.5 days versus 62 days for control patients. The median survival benefit was 31 days and sorafenib was not found to be cost-effective with an ICER of \$224,914 per life year gained.

### Sorafenib versus SBRT

Leung et al.<sup>18</sup> stated sorafenib was effective in comparison with SBRT in patients with advanced HCC; however, due to the higher costs, it was not found to be cost-effective. Costs were calculated in 2015 new Taiwan dollars with 5-year time horizon and a 3% discount rate with National Health Insurance perspective. The results indicated that SFN was associated with the incremental effectiveness of 0.26 QALYs. The ICER was estimated \$114,795 per QALY for sorafenib versus SBRT. Sensitivity analysis demonstrated that the model is sensitive to the utility of progressive disease for the sorafenib treatment, utility of PFS for SBRT, utility of PFS for sorafenib, utility of PFS to progression disease for SBRT and transition probability of progressive disease to death for SBRT. Leung et al.<sup>18</sup> stated that the study had not any sponsor.

### Sorafenib versus FOLFOX4

Zhang et al.<sup>17</sup> compared the cost and effectiveness of sorafenib versus FOLFOX4 in 2016 from a Chinese societal perspective in the first-line treatments for advanced hepatocellular carcinoma. A Markov cohort model was used with a 10-year time horizon. ICERs of FOLFOX4 versus sorafenib was calculated to be \$934,801.57/

QALY. The sensitivity analysis showed that the model is sensitive to duration of PFS state for sorafenib group, cost of PFS state for sorafenib group, cost of sorafenib and utility of PD state. It was resulted that FOLFOX4 was cost-effective compared to SFN. The study demonstrated sorafenib is not a cost-effective strategy at a WTP of \$20,301.00/QALY in China.

In another study, Qin et al.<sup>23</sup> compared FOLFOX4 versus sorafenib in 2017 from healthcare system and patient's perspective for advanced HCC in China. A Markov model was developed using 5% discount rate over a lifetime time horizon. The results demonstrated that FOLFOX4 dominated sorafenib with lower costs (FOLFOX4: US\$ 8428 sorafenib: US\$ 12,798) and higher QALYs (FOLFOX4: 0.42; sorafenib: 0.38) per patient. Sorafenib was not found to be a cost-effective strategy at a WTP of \$22,073/QALY in China. According to one-way sensitivity analyses, the result was most sensitive to FOLFOX4 and sorafenib survival (PFS and OS) and the cost of sorafenib therapy.

### Sorafenib versus TARE

Rognoni et al.<sup>19</sup> estimated the cost-effectiveness of TARE versus sorafenib in intermediate and advanced HCC using LY and QALY. Costs were calculated in 2016 euro with a lifetime horizon and a 3.5% discount rate from healthcare system perspective. In intermediate stage, the result indicated an incremental QALY of 0.540 (1.178 versus 0.638 QALY) together with an incremental cost of €1,782 (€31,071 versus €29,289) resulting in an ICER of €3,300/QALY. In advanced stage, the results showed that sorafenib was dominated compared to TARE due to its higher cost and lower efficacy in Italy. This study which was funded by ASBM Srl through an unrestricted grant to CERGAS, Bocconi University (Milan, Italy).

### Sorafenib versus TACE

Chen et al.<sup>9</sup> developed a Markov model to judge the cost-effectiveness of sorafenib versus TACE for advanced HCC. Costs were calculated in 2016 dollars with a 2-year time horizon and a 3% discount rate from healthcare system perspective. The most important parameter that has affected the results was the mortalities of compensated cirrhotic patients without and with progression taking dose-adjusted sorafenib, in both countries. In this study, full dose and adjusted dose were compared with TACE. Full and dose-adjusted earned 0.435 and 0.482 QALY, respectively while TACE gained 0.375 QALY. The ICER of full-dose sorafenib versus TACE was \$101,028.83/QALY in China whereas full-dose sorafenib was a dominant strategy (ICER of -\$1,014,507.20/QALY) compared with TACE in the USA. Compared to full-dose sorafenib, dose-adjusted sorafenib was the dominant strategy with the negative ICERs in both China (-\$132,238.94/QALY) and the USA (-\$230,058.09/QALY). Chen et al. disclosed that the study sponsored by National Natural Science Foundation of China and Pearl River S&T Nova Program of Guangzhou, China.

### Sorafenib + TACE versus TACE

Zhao et al.<sup>21</sup> analyzed TACE in comparison to TACE plus sorafenib in unresectable hepatocellular carcinoma. A Markov cohort model was adopted using 3% discount rate from a healthcare system perspective in China. All the costs were measured in 2015 US dollars with a lifetime time horizon. The result demonstrated an incremental QALY of 0.31 (1.02 versus 0.71 QALY) together with an incremental cost of \$17,591 (\$44,542 versus \$26,951) resulting in an ICER of \$56,745/QALY. In conclusion, TACE was found to be cost-effective strategy in comparison with TACE plus sorafenib. The sensitivity analyses showed the cost post TACE-sorafenib therapy with stable state was most influence factor on ICER. This study has not been sponsored.

### Sorafenib versus sorafenib + other therapy

Ho et al.<sup>22</sup> evaluated the cost-effectiveness of sorafenib versus sorafenib plus other therapy in patients with advanced HCC. A Markov model was developed using 3% discount rate with 5-year time horizon. All costs were calculated in 2014 new Taiwan dollar with healthcare system perspective. Analysis showed that combination treatment with sorafenib was associated with an incremental cost of NT\$434,788 and produced 0.1595 QALY resulting in an ICER of NT\$2,725,943/QALY. Thus, SFN plus other therapy was not cost-effective treatment in Taiwan at a WTP of NT\$ 2,213,145/QALY. The sensitivity analyses demonstrated that the model was sensitive to health utility values and monthly costs accrued in the progression-free survival state of the combination therapy group. this study funded by China Medical University grant.

### Quality assessment (QHES)

The results of the quality assessment using the QHES instrument have been presented in Table 5. It was found that the quality of the included studies was at a high level (Mean QHES Score: 92.4). The objectives of studies were clearly presented in all studies (Question 1). The perspective of the analysis had been stated in all studies. However, just one study had state justification for the reasons of selection (Question 2). The best available source of data was utilized by all the studies (Question 3). When subgroup analyses were conducted, the groups were pre-specified (Question 4) and all studies handle uncertainty in an appropriate way but three studies including Zhang et al., Zhao et al. and Parikh et al.<sup>20</sup> conduct only a one-way sensitivity analysis (Question 5). All studies performed incremental analysis between alternatives for effectiveness and costs (Question 6). In addition, all of the studies provided detailed information on the methods used to derive effectiveness (Question 7 & Question 8). Moreover, all studies measured costs appropriately (Question 9).

**Table 5** Quality assessment of studies using the QHES instrument

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Score
Muszbek et al. <sup>12</sup>	√	±	±	√	√	√	√	√	√	√	√	√	√	√	√	√	94
Vitale et al. <sup>13</sup>	√	±	√	√	√	√	√	√	√	±	√	√	√	√	√	×	92
Carr et al. <sup>14</sup>	√	±	√	√	√	√	√	√	√	√	√	√	√	√	√	√	98
Cammà et al. <sup>15</sup>	√	±	√	√	√	√	√	√	√	√	√	√	√	√	√	×	95
Zhang et al. <sup>16</sup>	√	±	√	√	±	√	√	±	√	√	√	±	√	√	√	√	86
Zhang et al. <sup>17</sup>	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	100
Leung et al. <sup>18</sup>	√	±	√	√	√	√	√	±	√	√	√	±	√	√	√	√	90.5
Rognoni et al. <sup>19</sup>	√	±	√	√	√	√	√	√	√	√	√	√	√	√	√	√	98
Parikh et al. <sup>20</sup>	√	±	√	√	±	√	√	√	√	√	√	±	√	√	√	√	89.5
Zhao et al. <sup>21</sup>	√	√	±	√	±	√	±	±	√	±	√	×	±	√	√	×	68
Chen et al. <sup>9</sup>	√	±	√	√	√	√	√	√	√	√	√	√	√	√	√	√	98
Ho et al. <sup>22</sup>	√	±	√	√	√	√	√	±	√	√	√	√	√	√	√	√	94.5
Qin et al. <sup>23</sup>	√	±	√	√	√	√	√	√	√	√	√	√	√	√	√	√	98

The primary outcome measures had been clearly stated in all studies and other relevant outcomes were addressed except Vitale et al. study (Question 10). In addition, the reliability and validation of health outcome measures had been tested before (Question 11). The model had been clearly explicated by the authors of all studies (Question 12). Then, the justification for the choice of the model and discussion on results, assumptions, and limitations had been given by all the studies (Question 13). The direction and magnitude of potential bias had also been discussed by the authors of all studies (Question 14), and the conclusions drawn by the authors of all studies were based on the study results and sounded reasonable (Question 15). Finally, Vitale et al., Camma et al. and Parikh et al. do not disclose the source of funding for the study (Question 16).

## Discussion

This study is the first systematic review of the economic evaluation studies of sorafenib in HCC treatment. The cost-effectiveness of sorafenib has been evaluated in several stages of disease against various treatment regimens. The findings in this study point to an incremental cost per QALY in the range of \$-1,014,507 to \$934,801, depending on whether the disease stage is advanced or not and which comparator is utilized.

Overall, the results indicated that Sorafenib could be considered as a cost-effective treatment option for patients with HCC. Briefly, compared to BSC, sorafenib is associated with higher cost and higher efficacy. However, the resulting ICERs were higher than WTP thresholds. Nevertheless, the best result was achieved when BSC compared to adjusted dose of sorafenib<sup>15</sup>. The highest ICER resulted when comparing sorafenib to FOLFOX<sup>17</sup>. TARE was selected as dominant strategy<sup>19</sup>, while TACE was dominated in comparison to sorafenib in USA.<sup>9</sup>

Most of studies mentioned that the model was sensitive to clinical effectiveness (OS or PFS) and drug acquisition cost. In addition, some of them also showed sensitivity to health state utility<sup>17,18,22</sup>. Not only being sensitive to clinical effectiveness somewhat makes the result questionable, but also extrapolating clinical efficacy and treatment persistency from short-term RCTs to a long treatment period carries significant uncertainty and requires additional assumptions that are not well acknowledged in the literature.

For transferability of the results of these studies, in addition to noting different health care settings, different costs, different medical procedures, etc., willingness to pay should also be considered an important contributing factor. It should be also noted that willingness to pay threshold is not a rigid cutoff all over the world. For example, in the United States, a threshold of \$50,000 per QALY is generally accepted to assess the cost-effectiveness of an intervention. Furthermore, health care authorities in China and Taiwan consider a treatment as a cost-effective strategy if it results in an ICER of  $\leq \$20,301/\text{QALY}$  and  $\leq \text{NT}2,213,145/\text{QALY}$ , respectively. In Italy, a cut-off at an ICER of  $\leq \text{€}38,000/\text{QALY}$ . So, the results should be interpreted with a view to the specific willingness to pay threshold in different jurisdictions.

Generalizability of the trials to the wider patient population is another limitation in targeted studies. Most of the patients included in the clinical trials have had good performance and prognosis. Accordingly, the generalizability of estimated overall survival to the wider patient population can prove a limiting factor. In addition, the generalizability of cost-effectiveness studies, which have been conducted in a specific

country, to other health care settings may be limited due to the differences in costs between different countries such as developed and developing countries.

## Conclusion

In sum, this review revealed that sorafenib was more effective with higher cost than its comparators except TARE and could be considered as a cost-effective treatment option for patients with metastatic HCC. The results should be interpreted with a view to the specific health care settings and willingness to pay threshold in different jurisdictions.

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No funding has been received for this research.

## Conflict of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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