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SYSTEMATIC REVIEW

A Systematic Review of Cost-Effectiveness Analyses for Hepatocellular Carcinoma Treatment

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Abstract

Background Hepatocellular carcinoma (HCC) is associated with significant financial burden for patients and payers. The objective of this study was to review economic models to identify, evaluate, and compare cost-effectiveness estimates for HCC treatments.

Methods A systematic search of the PubMed, Embase, and Cochrane Library databases to identify economic evaluations was performed and studies that modeled treatments for HCC reporting costs and cost effectiveness were included. Risk of bias was assessed qualitatively, considering costing approach, reported study perspective, and funding received. Intervention costs were adjusted to 2021 US dollars for comparison. For studies reporting quality-adjusted life-years (QALYs), we conducted analyses stratified by comparison type to assess cost effectiveness at the time of the analysis.

Results A total of 27 studies were included. Non-curative versus non-curative therapy comparisons were used in 20 (74.1%) studies, curative versus curative comparisons were used in 5 (18.5%) studies, and curative versus non-curative comparisons were used in 2 (7.4%) studies. Therapy effectiveness was estimated using a QALY measure in 20 (74.1%) studies, while 7 (25.9%) studies only assessed life-years gained (LYG). A health sector perspective was used in 26 (96.3%) of the evaluations, with only 1 study including costs beyond this perspective. Median intervention cost was $53,954 (range $4550–$4,760,835), with a median incremental cost of $6546 (range − $72,441 to $1,279,764). In cost-utility analyses, 11 (55%) studies found the intervention cost effective using a $100,000/QALY threshold at the time of the study, with an incremental cost-effectiveness ratio (ICER) ranging from − $1,176,091 to $1,152,440 when inflated to 2021 US dollars.

Conclusion The majority of HCC treatments were found to be cost effective, but with significant variation and with few studies considering indirect costs. Standards for value assessment for HCC treatments may help improve consistency and comparability.

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Key Points for Decision Makers

In this systematic review of 27 unique economic evaluations, the median intervention cost was $53,954, with a median incremental cost of $6546. Of the 20 studies that included a quality-adjusted life-year (QALY) measure, 11 found the intervention to be cost effective using a $100,000/QALY threshold at the time of the study but with significant variation and with few studies considering indirect costs.

Standards for future value assessment for hepatocellular carcinoma treatments could improve consistency and comparability, and patient engagement may ensure models reflect actual patient experiences.

1 Introduction

Hepatocellular carcinoma (HCC) has one of the highest mortality rates out of all cancers and is the fourth leading cause of cancer-related deaths worldwide [1, 2]. In addition to mortality, patients with HCC may experience a variety of challenges impacting their overall quality of life (QoL), such as pain, lethargy, difficulty sleeping, alopecia, weight loss, etc. [3, 4]. The disease prognosis, treatment options, and patient experience further depends on the staging of the disease and the degree of liver dysfunction [4]. HCC also comes with a significant financial burden for both patients and payers [5, 6]. Many patients not eligible for transplant or resection may also forgo treatment due to high costs and limited benefits of other existing therapies [3].

Cost-effectiveness analysis (CEA) methods have been considered the 'gold standard' for developing objective estimates of the value of health interventions to inform decision making [7, 8]. While best practices and recommendations for CEAs exist, there are several researcher decisions, methodological approaches, and data sources that can introduce variability in the ultimate cost-effectiveness determination [9, 10]. For example, a 'societal perspective' that includes informal care (e.g., caregiver burden, time, travel) and non-healthcare costs (e.g., absenteeism, presenteeism) has traditionally been recommended [11] for CEAs, but most analyses focus on payer decisions that only incorporate formal healthcare costs (e.g., inpatient, outpatient, pharmacy, laboratory) [10]. Other researcher-level decisions can have a major influence on CEA results, such as population, comparator selection, time horizon, and health outcome measures. In order to accurately assess and compare the value of different innovations in the prevention, diagnosis, and treatment of HCC, these methodological considerations must be evaluated to determine the appropriateness of HCC-specific standards for economic evaluation. The objective of this systematic review was to identify, evaluate, and compare cost-effectiveness estimates for different treatment approaches for HCC.

2 Methods

We performed a systematic search on 1 May 2020 to identify economic evaluations using the PubMed (PubMed.gov), Embase (Embase.com), and Cochrane Library (WileyOnline) databases.

2.1 Search Strategy

The search strategy for each database is provided in eAppendix 1. The review focused on answering the following questions.

1. What are the costs and incremental cost effectiveness of both curative and non-curative therapies for HCC?
2. What types of costs are frequently identified when comparing different HCC interventions?
3. What research methods are commonly used to evaluate cost effectiveness for HCC therapies?

2.2 Selection Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines were used for study eligibility criteria, quality assessment, and analysis of results [12, 13]. The following inclusion criteria were used to screen articles.

1. Articles must be written in English.
2. Articles need to model interventions aimed at treating HCC in adults.
3. Articles must report economic information, including costs and cost effectiveness.

All abstracts were reviewed by at least two reviewers using Covidence [14] systematic review software to track discrepancies, with conflicts resolved by one of the authors (TJM). Full-text review was completed by at least two reviewers, with all papers reviewed by TJM. Inclusion disagreements were discussed until consensus was reached.

2.3 Data Extraction and Evidence Synthesis

Data extraction included the following variables: article citation details (year, author, title), study type, study description, country, population description, intervention and comparators, and measure of effectiveness—quality-adjusted life-year (QALY) or life-years gained (LYG), description of costing methods, time horizon, discount rate, currency, description of sensitivity analysis, costs reported, and effectiveness reported. Using this extracted data, we identified the HCC stage based on the Barcelona Clinic Liver Cancer (BCLC) staging system [15], type of intervention (curative or non-curative), intervention costs adjusted to 2021 US dollars (US$) using currency conversion and a 3% discount rate for inflation [16], and whether the intervention would be considered cost-effective using a $100,000/QALY threshold [17] at the time of the analysis. Curative therapies included liver transplant, resection, or radiofrequency ablation (RFA), while non-curative therapies included tyrosine kinase inhibitors (e.g., sorafenib, cabozantinib, lenvatinib), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiotherapy (SBRT), and any palliative care or best supportive care [18, 19]. Considering the potential for authors to report a study perspective that is not consistent with current recommendations, we used the costing methods described in the article to confirm the study perspective as either a health sector (direct costs only) or societal perspective (including any costs beyond direct medical costs in the health sector perspective such as productivity, time, consumption, etc.) [20].

For studies that report a QALY outcome, we conducted further exploratory analyses to compare cost effectiveness across this similar subset of CEAs commonly referred to as cost-utility analyses. In this comparison, the primary outcome of interest was the ICER (cost/QALY) calculated in US$ at the time of the study. Since interpretation of positive and negative ICER values depends on the directionality of the numerator (intervention more or less costly) and denominator (intervention more or less effective), we plotted the incremental costs (y-axis) and incremental effects (x-axis) with the $100,000 theoretical willingness-to-pay threshold for cost effectiveness, to illustrate which ICERs should be interpreted as cost effective (i.e., below the diagonal threshold) [21].

2.4 Risk-of-Bias Assessment

Risk of bias was assessed qualitatively, considering costing approach, reported study perspective, and type of funding received. Specifically, the authors considered how study perspective, intervention/comparator selection, length of time, and outcomes included might impact the study's ultimate cost-effectiveness conclusion.

3 Results

3.1 Overview of Studies

The economic literature search identified a total of 5816 records, with a total of 4304 remaining after duplicates were removed (Fig. 1). After abstract screening using the inclusion criteria, a total of 50 full-text articles were reviewed for inclusion, resulting in 27 unique studies included for extraction and synthesis (Table 1) [22–48].

3.2 Modeling Methods

Most economic evaluations were conducted for a single country (22/27, 81.5%), with 5 (18.5%) studies evaluating the cost effectiveness in multiple countries. Models were limited to advanced HCC patients in 11 (40.7%) studies, early HCC only in 6 (22.2%) studies, and a combination of multiple HCC stages in the remaining 10 (37.0%) studies. Non-curative versus non-curative (including supportive care) therapy comparisons were used in 20 (74.1%) studies, curative versus curative comparisons were used in 5 (18.5%) studies, and curative versus non-curative comparisons were used in 2 (7.4%) studies. Therapy effectiveness was estimated using a QALY measure in 20 (74.1%) studies, while 7 (25.9%) studies only assessed LYG. A health sector perspective was used in 26 (96.3%) of the evaluations, with only 1 study including costs beyond the health sector perspective [39]. In terms of funding received, 16 (59.3%) studies either had no funding or did not disclose any funding sources, while 7 (25.9%) received government-funded grants and 4 (14.8%) were funded by industry or for-profit sources.

3.3 Costs of Treatment

A total of 25 (92.6%) studies calculated the total costs of the intervention and comparator to assess the incremental costs, while 2 studies [26, 36] only reported the marginal costs for treatments assessed. The median intervention cost adjusted to 2021 US$ was $53,954 (range $4550–$4,760,835), with a median incremental cost of $6546 (range − $72,441 to $1,279,764).

3.4 Cost-Utility Analyses

Of the 20 studies that included a QALY measure, 11 (55%) found the intervention to be cost effective using a $100,000/QALY threshold at the time of the study, and 10 (50%) found the intervention to be cost effective when inflating to 2021 US$ (Table 2). When comparisons included two curative therapies ($n = 4$), median incremental costs were $48,249 (range −$10,000 to $163,006), with median incremental

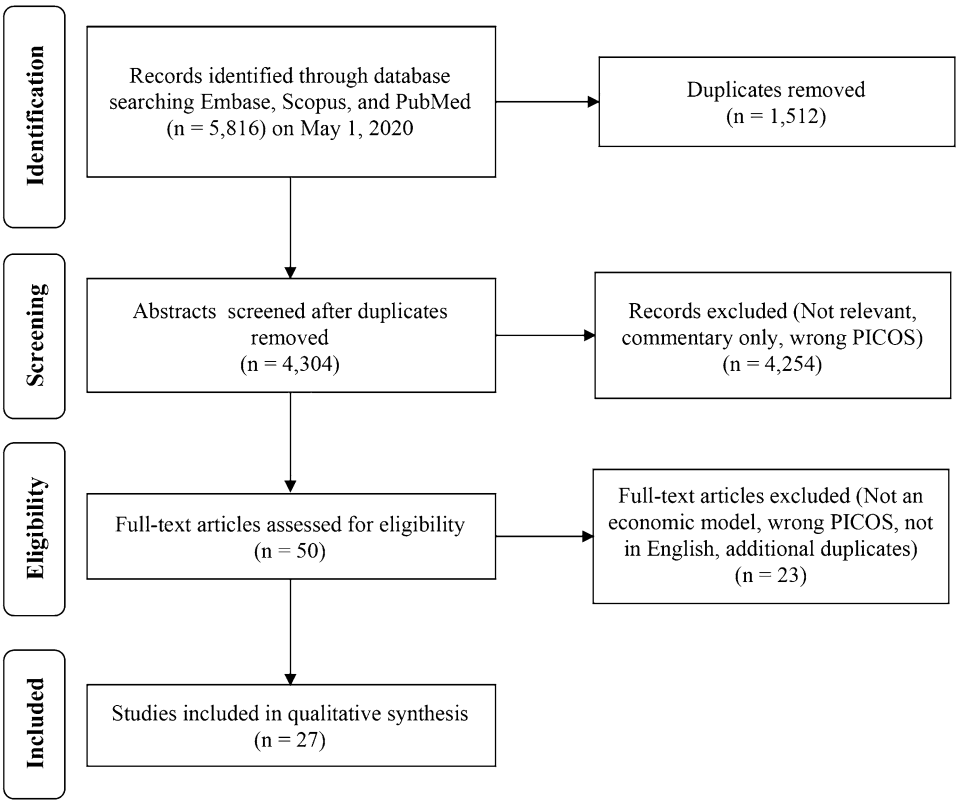

Fig. 1 Review flow diagram according to the PRISMA statement. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *PICOS* population, intervention, control and outcomes

effects of 1.2 QALYs gained (range 0.3–2.4). When comparisons included two non-curative therapies ($n = 16$), median incremental costs were \$2839 (range − \$60,870 to \$1,137,054), with median incremental effects of 0.14 QALYs gained (range − 0.26 to 3.97). The median ICERs were \$53,168 and \$47,102 for 'curative vs. curative' and 'non-curative vs. non-curative' comparisons, respectively (Fig. 2).

3.5 Risk of Bias

While no quantitative assessment of bias within or across studies was performed, we did note areas where potential bias could exist or limit the interpretation of the analysis. We found the types of costs included in each analysis were frequently limited. Nearly all included studies focused primarily on health sector or payer perspective costs, likely underestimating the total costs for both the interventions and comparators selected. The majority of studies also used a lifetime model time horizon. While this is a perfectly acceptable time horizon selection, longer time horizons introduce more uncertainty with the underlying model assumptions and make the model results more sensitive to discount rate selections.

4 Discussion

4.1 Summary of the Findings

To our knowledge, this systematic review is the first to assess economic models for therapies used in patients with HCC. We found a wide variety of cost-effectiveness methods used, making it difficult to compare across studies even when limiting to cost-utility analyses only. Methodological considerations such as population, disease severity, time horizon, discount rate, types of costs included, health outcomes assessed, and comparator selection can have a major influence on estimating whether HCC treatment is cost effective or not. One common theme found across HCC economic models was the use of a payer or health sector perspective that only focuses on direct costs of care (e.g., hospitalization, outpatient visits, medications). The only study that included indirect costs was in a comparison of leucovorin + fluorouracil + oxaliplatin (FOLFOX) versus sorafenib for an advanced HCC population in China [39]. In this analysis, the authors only included productivity costs due to absenteeism by multiplying days of work missed by the minimum wage for the province [39]. Additionally, two studies were inappropriately described as societal perspective analyses as they

Table 1 Summary of the included economic studies

Authors	Year	Model type	Country	Population	Intervention	Comparator	Effectiveness	Funding
Cammà et al. [22]	2013	Markov model	Italy	Caucasian males, age 67 years, not eligible/failed ablative therapy	Sorafenib	Best supportive care	QALY, LYG	None disclosed
Carr et al. [23]	2010	Markov model	USA	Adults (> 18 years of age), life expectancy ≥ 12 weeks, ≥ 1 tumor lesions not previously treated	Sorafenib	Best supportive care	LYG	Industry
Chen et al. [34]	2018	Markov model	Multiple	Adults, BCLC stage C, Child–Pugh class A/B	Sorafenib	TACE	QALY, LYG	Government
Cucchetti et al. [42]	2013	Markov model	Italy	Early HCC patients who underwent HR, Child–Pugh class A or RFA	Liver resection	RFA	QALY, LYG	None disclosed
Gupta et al. [43]	2019	Markov model	India	Cohort starting at age 40 years; BCLC Stage C	Sorafenib	Best supportive care	QALY, LYG	None disclosed
Hamdy et al. [44]	2019	Markov model	Egypt	Adults, median age 60 years, no previous treatment	Sorafenib	Best supportive care	QALY	None disclosed
Kim et al. [45]	2020	Markov model	Canada	Patients with unresectable HCC; BCLC stage B or C, Child–Pugh A	Lenvatinib	Sorafenib	QALY	Government
Landman et al. [47]	2011	Markov model	USA	Child–Pugh class A, single nodule ≤ 5 cm or up to 3 nodules ≤ 3 cm	Liver transplant	Liver resection	QALY	Government and industry
Leung et al. [48]	2016	Markov model	Taiwan	Unresectable, advanced HCC	SBRT	Sorafenib	QALY	None disclosed
Liao et al. [24]	2019	Markov model	Multiple	Patients who received sorafenib first-line	Cabozantinib	Best supportive care	QALY	Government
Lim et al. [25]	2015	Markov model	Multiple	Patients aged 55 years with early HCC, Child–Pugh A/B cirrhosis	Liver transplant	Liver resection	QALY, LYG	Government
Llovet et al. [26]	2002	Markov model	Spain	Child–Pugh A and A/B; waiting for transplant	Liver resection	No treatment	LYG	Government
Kobayashi et al. [46]	2019	Partitioned-survival model	Japan	Adults, BCLC stage B or C	Lenvatinib	Sorafenib	QALY	None disclosed
Muszbek et al. [27]	2008	Markov model	Canada	Adults (> 18 years); life expectancy of at least 12 weeks; unsuitable for surgery	Sorafenib	Best supportive care	LYG	Industry
Naugler and Sonnenberg [28]	2010	Markov model	USA	Newly diagnosed HCC < 2 cm in diameter	TACE or RFA	Monitoring	LYG	None disclosed

Table 1 (continued)

Authors	Year	Model type	Country	Population	Intervention	Comparator	Effectiveness	Funding
Pollom et al. [29]	2017	Markov model	USA	60 year old, localized HCC not eligible for resection or transplant; Child–Pugh A/B, 1–2 lesions < 3 cm	SBRT-SBRT	RFA-SBRT	QALY	Government
Qin et al. [30]	2018	Markov model	China	Adults (> 18 years), mean age 50 years; 80–90% male, Child–Pugh A/B	Sorafenib	FOLFOX4	QALY	Industry
Rognoni et al. [31]	2017	Markov model	Italy	Adults, mean age 70 years, 80% male	TARE	Sorafenib	QALY, LYG	Industry
Rognoni et al. [32]	2018	Markov model	Italy	Mean age 68 years, intermediate only	TARE + TACE ± sorafenib	TARE + sorafenib	QALY, LYG	None disclosed
Rostambeigi et al. [33]	2014	Decision analysis	USA	BCLC classification system (A, B, or C)	TARE	TACE	LYG	None disclosed
Sarasin et al. [35]	1998	Markov model	USA	Age < 60 years, Child–Pugh class A, single nodule ≤ 5 cm or up to 3 nodules ≤ 3 cm	Liver transplant	Liver resection	LYG	None disclosed
Shetty et al. [36]	2001	Decision analysis	USA	46 patients from a single clinic, with literature review	RFA	Best supportive care	LYG	None disclosed
Sieg et al. [37]	2020	Markov model	Multiple	Adult patients who showed progression under prior sorafenib therapy	Cabozantinib	Best supportive care	QALY, LYG	None disclosed
Spolverato et al. [38]	2015	Markov model	Multiple	Age 55 years, Child–Pugh class A, single nodule ≤ 5 cm or up to 3 nodules ≤ 3 cm	Liver transplant	RFA	QALY	None disclosed
Zhang et al. [39]	2016	Markov model	China	Median age 50 years, 85%+ male, Child–Pugh A/B	FOLFOX	Sorafenib	QALY	None disclosed
Zhang et al. [40]	2015	Markov model	China	Adults (> 18 years), 85%+ male, Child–Pugh A/B	Sorafenib	Best supportive care	QALY	None disclosed
Zhao et al. [41]	2017	Markov model	China	Adults (> 18 years), BCLC stage B or C, Child–Pugh A/B	TACE-sorafenib	TACE	QALY	None disclosed

HCC hepatocellular carcinoma, *QALY* quality-adjusted life-year, *LYG* life-years gained, *BCLC* Barcelona Clinic Liver Cancer, *TARE* transarterial radioembolization, *TACE* transarterial chemoembolization, *RFA* radiofrequency ablation, *SBRT* stereotactic body radiation therapy, *FOLFOX* 5-fluorouracil, leucovorin, and oxaliplatin, *HR* hepatic resection

Table 2 Cost-utility analyses with costs converted to 2021 US dollars and the cost-effectiveness threshold set at $100,000/QALY

Authors	Country	Stage	Comparison type	Incremental costs reported	Incremental costs (2021)	Incremental effects	Incremental cost-effectiveness ratio	Is it cost effective?
Chen et al. (2018) [34]	Multiple	Advanced	Non-curative vs. non-curative	(60,870.43)	(70,565.51)	0.06	(1,176,091.86)	Yes (Dominant)
Kim et al. (2020) [45]	Canada	Intermediate and advanced	Non-curative vs. non-curative	(18,336.71)	(20,037.02)	0.132	(151,795.59)	Yes (Dominant)
Rognoni et al. (2017) [31]	Italy	Intermediate and advanced	Non-curative vs. non-curative	(9711.85)	(11,596.45)	0.071	(163,330.29)	Yes (Dominant)
Qin et al. (2018) [30]	China	Advanced	Non-curative vs. non-curative	4370.00	4918.47	− 0.04	(122,961.84)	No (Comparator Dominant)
Kobayashi et al. (2019) [46]	Japan	Intermediate and advanced	Non-curative vs. non-curative	(5052.90)	(5,687.09)	0.23	(24,726.46)	Yes (Dominant)
Rognoni et al. (2018) [32]	Italy	Intermediate	Non-curative vs. non-curative	(6933.74)	(8038.11)	0.448	(17,942.20)	Yes (Dominant)
Landman et al. (2011) [47]	USA	Very early and early	Curative vs. curative	(10,000.00)	(14,685.34)	2.4	(6118.89)	Yes (Dominant)
Gupta et al. (2019) [43]	India	Advanced	Non-curative vs. non-curative	1409.90	1586.86	0.19	8351.89	Yes
Cucchetti et al. (2013) [42]	Italy	Early	Curative vs. curative	4216.00	5500.92	0.3	18,336.41	Yes
Cammà et al. (2013) [22]	Italy	Intermediate and advanced	Non-curative vs. non-curative	16,481.68	21,504.85	0.44	48,874.67	Yes
Zhao et al. (2017) [41]	China	Intermediate and advanced	Non-curative vs. non-curative	17,591.00	21,004.57	0.31	67,756.69	Yes
Spolverato et al. (2015) [38]	Multiple	Early	Curative vs. curative	92,282.00	120,407.08	1	120,407.08	No
Zhang et al. (2015) [40]	China	Advanced	Non-curative vs. non-curative	18,252.00	21,793.84	0.18	121,076.90	No
Lim et al. (2015) [25]	Multiple	Early	Curative vs. curative	163,006.00	212,685.86	1.4	151,918.47	No
Leung et al. (2016) [48]	Taiwan	Advanced	Non-curative vs. non-curative	(30,757.33)	(36,725.86)	− 0.26	141,253.31	No
Hamdy Elsisi et al. (2019) [44]	Egypt	Advanced	Non-curative vs. non-curative	1,137,054.00	1,279,764.29	3.97	322,358.76	No
Pollom et al. (2017) [29]	USA	Early	Non-curative vs. non-curative	4269.00	5097.41	0.007	728,201.32	No
Liao et al. (2019) [24]	Multiple	Advanced	Non-curative vs. non-curative	108,521.00	122,141.34	0.13	939,548.78	No
Zhang et al. (2016) [39]	China	Advanced	Non-curative vs. non-curative	(11,872.00)	(14,175.79)	− 0.0127	1,116,203.85	No

Table 2 (continued)

Authors	Country	Stage	Comparison type	Incremental costs reported	Incremental costs (2021)	Incremental effects	Incremental cost-effectiveness ratio	Is it cost effective?
Sieg et al. (2020) [37]	Multiple	Advanced	Non-curative vs. non-curative	172,866.00	183,393.54	0.15	1,222,623.60	No

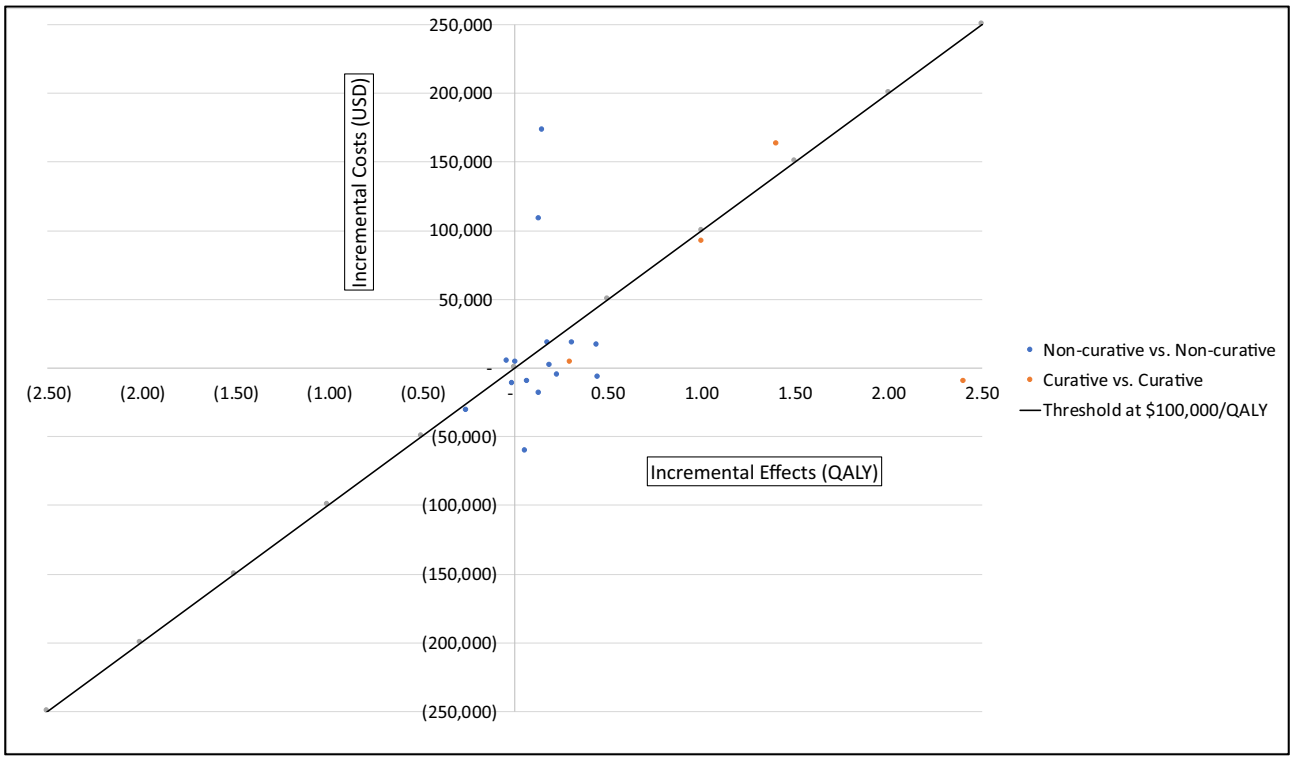

Fig. 2 Incremental cost-effectiveness ratios for 'non-curative vs. non-curative' and 'curative vs. curative' comparisons with a cost-effectiveness threshold at $100,000/QALY. *QALY* quality-adjusted life-year, *USD* US dollars

failed to include any indirect costs or costs outside the more narrow payer perspective [43, 47].

In terms of cost effectiveness, ICERs reported varied widely from − $1,176,091 [34] to $1,152,440 [37], demonstrating how difficult it is to compare ICERs across studies without limiting the comparison to studies with nearly identical evaluation methods. For example, Chen et al. aimed to compare dose-adjusted sorafenib versus TACE in a limited advanced-stage HCC population using lifetime costs, resulting in the lowest ICER reported [34]. In contrast, Sieg et al. compared cabozantinib versus best supportive care as a 'second-line therapy' in a similar advanced-stage HCC, resulting in the highest ICER reported [37]. Selecting a very low-cost 'supportive care' treatment as a comparator seems to be a driving factor for such a large ICER in treatment only, adding an estimated 9.4 weeks of life (0.18 LYG). This demonstrates how economic evaluations can vary widely within a similar population based on the clinical scenario and treatment comparisons.

Future CEAs for HCC treatments should consider the use of an impact inventory that explicitly shows the direct and indirect costs included and which perspective includes each cost type [9]. Health economists may also want to consider engaging HCC patients and caregivers in the CEA process to validate that the model structure chosen reflects the patient experience, identify appropriate comparators and outcomes, and identify which costs are most important to patients [49–51]. While evidence suggests HCC and other types of cancer cause significant burdens on family and caregivers, no studies in our analysis have considered the potential spillover effects of the disease on the supportive network around the patient [3, 52].

When considering the potential risk of bias within and across studies included, the most glaring source of bias

comes from the limited types of costs included in each analysis. This health sector or payer perspective focus for HCC evaluations likely underestimates the total costs for both the interventions and comparators selected. Since this underestimation is applied to both intervention and comparator, the final direction and size of the introduced bias when assessing incremental costs or an ICER may be difficult to predict. Most studies selected a lifetime time horizon for the primary analysis, with 10- and 5-year horizons commonly selected for studies shorter than lifetime. This modeling decision may be appropriate to the individual research question, however longer time horizons create greater uncertainty beyond the bounds of the underlying data inputs and put greater importance on the discount rate selection.

4.2 Limitations

Since our systematic review focused on economic evaluations, the heterogeneity of methods made it inappropriate to use traditional meta-analysis methods to pool results. We described costs and cost-effectiveness results, categorizing and comparing where appropriate and providing qualitative assessment of different components. We did attempt to draw comparisons on reported costs by exchanging the currency used to US$ and then inflating to 2021 US$ using a flat 3% discount rate, similar to discount approaches applied by many health technology assessment bodies [53]. However, we did not apply different inflation rates across studies, which may better reflect price changes for non-tradable resources where the study was conducted but can potentially overestimate the adjusted cost [54]. Additionally, the generalizability of any pooled results may be limited when considering the differences in health system structures across countries or when considering the within-study differences described in this article. While we reported descriptive statistics for costs and ICERs reported, the usefulness of a mean or median statistic may be less than the range of reported values, demonstrating how important methodological considerations are when interpreting economic evaluations. Finally, for treatment categorization purposes, we did not differentiate based on dosage or the variability in transplantation or resection procedures. In our analysis, these groupings were broadly defined. Studies may also include wide variations in 'standard of care' or 'best supportive care' that were not assessed in this review. This review may help guide future researchers interested in estimating the value or cost effectiveness of different treatment options in HCC patients and encourage the use of existing recommendations and best practices in the conduct and reporting of CEAs [9].

5 Conclusions

Economic evaluations for the treatment of HCC are conducted using a variety of methods and modeling decisions that make it difficult to compare across studies. For cost-utility analyses specifically, the majority of HCC treatments were found to be cost effective at a $100,000/QALY willingness-to-pay threshold, but with a wide range and with very few studies considering indirect costs. Future value assessment for HCC treatments should incorporate multiple perspectives and engage patients and caregivers to ensure the evaluation reflects the true patient experience.

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Conflicts of interest TJM reports receiving consultant fees from PhRMA, NHC, and Johns Hopkins University, all unrelated to this research. Sydney Yuen, Adaeze Q. Amaefule, Hannah H. Kim, Breanna-Verissa Owoo1, and Emily F. Gorman report no conflicts of interest.

Data availability statement All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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