




A systematic review of comparative economic analyses of systemic therapies for hepatocellular carcinoma

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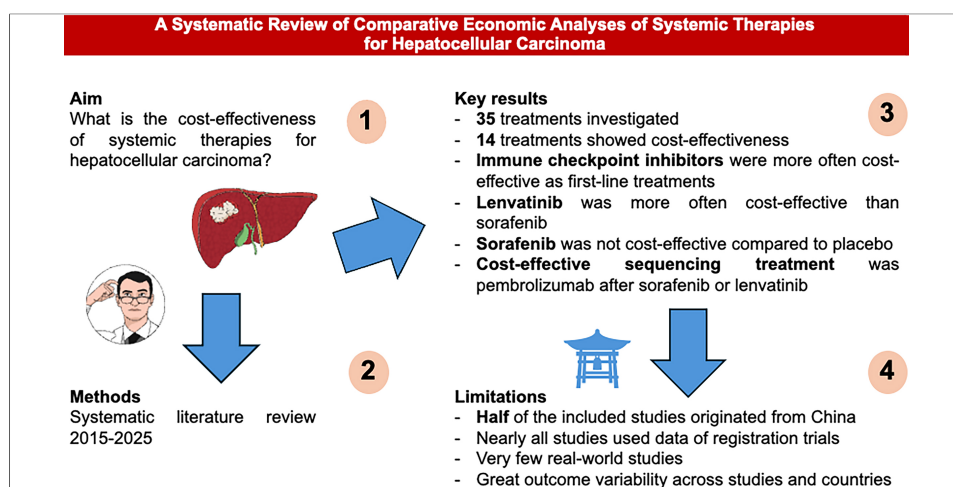
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Abstract

Aim: We conducted a systematic synthesis of comparative economic evaluations assessing systemic therapies for hepatocellular carcinoma (HCC) to establish their cost-effectiveness.

Methods: We searched six bibliographic databases for English-language studies published from 2015 through June 2025. Extracted endpoints included counts and types of regimens deemed cost-effective, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), and ICER relative to national willingness-to-pay (WTP) thresholds.

Results: Fifty-four studies met the inclusion criteria, producing four treatment subgroupings

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and 35 distinct treatment comparisons. QALYs were reported in 96.3% of articles, ICERs in 90.7%, and WTP thresholds in 92.6%. Fourteen regimens (40.0% of comparisons) were judged cost-effective. Regimens that included immunotherapy were more often cost-effective, while lenvatinib outperformed sorafenib in most analyses. Nearly all studies (94.4%) relied, to varying degrees, on data from 14 randomized controlled trials; 48.1% focused on the Chinese healthcare environment; 27.8% used a lifetime horizon; and 38.9% reported a median [interquartile range (IQR)] horizon of 10 (9) years. Only 5.5% adopted a societal perspective.

Conclusion: Less than half of the evaluated systemic therapies were cost-effective, focusing mainly on immunotherapy-based regimens. Harmonized methodological standards are needed to ensure that economic evaluations keep pace with real-world practice as systemic treatments become more widely adopted. [International Platform of Systematic Review and Meta-Analysis Protocols (INPLASY) registration number: 2025100049].

INTRODUCTION

Understanding the costs and cost drivers of medical treatments is vital to maintaining the viability of modern health systems in an era of constrained resources^[1]. This concern is especially acute in oncology, where rising expenditures do not always correspond to substantial improvements in survival or quality of life^[2,3]. Containing healthcare spending remains a persistent challenge, and expenditures are expected to continue climbing^[4].

Management of hepatocellular carcinoma (HCC) now spans image-guided procedures, surgical resection, liver transplantation (LT), systemic drugs, and multimodal combinations^[5-7], with associated costs steadily increasing^[8,9]. One cost-control approach is to match patients to the therapies most likely to achieve a cure, prioritizing treatments with curative potential regardless of cost^[1]. Another strategy emphasizes earlier diagnosis and rapid initiation of care^[1]. Global surveillance recommendations for patients with chronic liver disease have improved early tumor detection and the chance for curative therapy^[10]. Screening of asymptomatic high-risk individuals can uncover HCC at stages suitable for potentially curative interventions^[11,12] thereby reducing treatment costs and improving outcomes^[8].

Over the last decade, systemic options for HCC have expanded to include oral targeted therapies, tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) pathway inhibitors (VEGFi), and immune checkpoint inhibitors (ICIs)^[13]. Agents that improve response rates, progression-free survival (PFS), and overall survival (OS) have become first-line choices for advanced (aHCC), unresectable (uHCC), or metastatic (mHCC) HCC^[14]. They are also being integrated in combined or sequential approaches with interventional radiology to pursue curative aims, facilitate conversion to resection, or serve as adjuvant/neoadjuvant therapies^[15,16].

Despite their clinical importance, formal economic evaluations are mostly missing from major HCC management guidelines. The Barcelona Clinic Liver Cancer (BCLC)^[5], the Japanese Society of Hepatology-HCC (JSH-HCC)^[17], the Chinese guidelines^[18], the European Association for the Study of the Liver (EASL)^[19], and the American Association for the Study of Liver Disease (AASLD)^[20] do not systematically include cost-effectiveness analyses. Differences in costing methods across studies, countries, and systems make it difficult to include economic data in effectiveness research. However, gaining a better understanding of the financial factors affecting HCC management could help clinicians make informed decisions within budget limits and involve administrators, payers, policymakers, patients, and other stakeholders in the process.

To address this gap, we reviewed comparative economic studies of contemporary HCC therapies, exploring differences by patient characteristics, tumor stage, institution, and geography. This paper concentrates on systemic agents used as first- or second-line therapies for advanced HCC.

METHODS

Research design

This work is a systematic review of comparative economic evaluations of therapeutic approaches for HCC. The interpretation of review findings draws upon the principles described by Sukhera in 2022^[21]. This approach was selected to provide a critical, sometimes subjective appraisal of available evidence and to offer perspectives on how the field might progress from diverse vantage points^[21,22]. Accordingly, we followed the five key steps outlined in prior publications^[21-23].

Rationale for the review

Evaluating the cost-effectiveness of HCC treatments is crucial for guiding clinical decisions. As new drugs and regimens are introduced rapidly, assessments of the economic value of systemic therapies need frequent updates^[5,13,15]. The goals of this study were to gather evidence on: (1) the comparative economic effectiveness, utility, and benefits of HCC treatment options; and (2) factors that influence treatment costs, including perspectives from clinicians, hospital managers, policymakers, patients, and stakeholders. The review also examined international differences in financial aspects among providers, payers, and regions. In this scope, we specifically focused on first- and second-line systemic therapies.

Research question

The primary research question of the entire project was: What are the most cost-effective treatments for patients with HCC?

Within this framework, the research question of the current study was: What are the most cost-effective first- and second-line systemic therapies for patients with HCC?

Boundaries and definitions

We used the P (patients/disease), I (interventions), C (comparators), and O (outcomes) framework, where patients were those affected by HCC; interventions included all active strategies for treating HCC, both curative and palliative; comparisons involved best supportive care (BSC) or comparisons across treatments; and outcomes measured economic treatment metrics. Therapeutic interventions were based on the 2025 EASL guidelines for HCC treatment. These were categorized into (1) ablation; (2) intra-arterial therapies; and (3) systemic therapies^[19]. Ablation includes conventional or drug-enhanced radiofrequency ablation (RFA) or microwave ablation (MW), selective internal radiotherapy (SIRT), stereotactic body radiation therapy (SBRT), liver resection (LR), and LT. Intra-arterial therapies included hepatic artery infusion chemotherapy (HAIC) and trans-arterial chemoembolization (TACE). We also expanded the research to include treatments not yet fully explored by the EASL guidelines, such as carbon ion therapy (CIT). Based on the available studies, these treatments were considered either alone or in combination.

Comparative economic evaluations were defined per international standards as cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-of-illness analysis (COIA)^[24,25]. COIA papers were excluded because they lacked a comparator population^[25,26]. Considerable overlap exists among these methods, particularly between CEA and CUA, and classifications vary across authors^[27-29].

Inclusion criteria

PubMed (PubMed.gov), Google Scholar (<https://scholar.google.com/>), Cochrane (Wiley Online), Scopus, Web of Science (WoS), and Embase (Embase.com) were searched on July 1, 2025. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines were used to define the study's eligibility criteria, conduct quality assessment, and analyze the results^[30,31]. A PRISMA checklist for the abstract and paper is provided as [Supplementary Materials](#).

The search terms used to retrieve the studies are illustrated in the [Supplementary Materials](#). Only full-length articles in English or in English translations were included. Systematic reviews, commentaries, empirical articles, gray literature, trade publications, and digital media communications were excluded and used only to retrieve additional references not included in the original search strategy. Owing to various factors, such as the rising healthcare costs of HCC treatment^[4,8], advancements in recent medical technologies for HCC, shifts in liver disease epidemiology with the emergence of metabolic dysfunction-associated liver disease (MASLD), and the increasing number of publications on HCC, the literature review was limited to studies published between 2015 and June 30, 2025. However, if the thematic coverage was insufficient, a second search was conducted without date restrictions, and key or seminal papers on the topic, along with other relevant manuscripts, were considered, regardless of their publication date.

Only articles comparing first- or second-line systemic treatments to active comparators, placebo, or BSC were included in the final analysis. Studies involving neoadjuvant or adjuvant therapies administered before or after radiology-assisted interventions or surgery, and systemic therapies compared with intrahepatic arterial infusion, were excluded.

The references were initially evaluated independently by two investigators (Longo D and De Simone P) based on the face value of their abstracts, with any disagreements resolved by a third reviewer (Peritore D). The reference lists of the articles were also checked for additional literature (snowballing). An artificial intelligence (AI)-based Rayyan platform was used to sort articles, assess abstracts and texts, and eliminate duplicates (<https://www.rayyan.ai/>). A shared Google Drive repository was used to collect and review articles from all team members.

Data extraction and interpretation

Extracted variables included year, authors, title, study type, country, population, interventions and comparators, and effectiveness measures [quality-adjusted life-years (QALYs) or life-years saved (LYS)]. Costing methods, time horizons, discount rates, currencies, sensitivity analyses, reported costs, and economic metrics were also recorded. HCC stage was classified according to the BCLC system, and interventions were categorized as curative or non-curative. International currencies were converted to US dollars using a currency converter^[32]. No inflation adjustments were made to reported monetary values. Outcomes were assessed using three primary metrics: (1) QALYs and LYS as measures of clinical benefit; (2) incremental cost-effectiveness ratio (ICER) per QALY/LYS [or incremental cost-utility ratio (ICUR)] to show additional cost per unit benefit; and (3) ICER/willingness-to-pay (WTP) ratio to indicate cost-effectiveness, using WTP values reported in the studies or, when absent, the World Health Organization (WHO) guidance calculating WTP as three times the per capita gross domestic product (GDP)^[33]. Data interpretation followed Sukhera^[21].

Evaluation of the risk of bias

At least three investigators independently reviewed the included papers^[34-37]. The risk of bias was first appraised using the Joanna Briggs Institute (JBI) checklist by three team members experienced in research quality assessment^[38]. The JBI checklist comprises 11 items evaluating general and specific study attributes^[38].

No minimum JBI score was required for inclusion; all studies meeting eligibility criteria were analyzed, though potential biases affecting cost-effectiveness outcomes were noted. Given that JBI does not cover all economic evaluation needs, we also assessed studies using the ECOBIAS checklist^[89].

Data description and analysis

Clinical and demographic variables were described using reported means, standard deviations (SDs), medians, and percentages. Missing data were not imputed. Means were weighted across series when appropriate; medians were pooled via meta-analytic techniques when raw data were lacking, using a random-effects model with inverse-variance weighting to account for heterogeneity. Monetary values are those reported in the original articles; foreign currencies were converted to 2025 US dollars^[32]. Data were tabulated (author, year, country assessed, treatments/comparators, QALYs/LYs, WTPs, and methodological notes) [Tables 1-4]^[34-87]. For clarity and to mirror clinical practice, data were stratified by treatment type and number of active regimens (immunotherapy, multiple comparators, oral agents, second-line *vs.* placebo/BSC). A methodological summary combining JBI and ECOBIAS inputs appears in Tables 5 and 6.

Ethic issues

The current study was exempt from ethics committee review under Italian national regulations. This study was registered with the International Platform of Systematic Review and Meta-Analysis Protocols (INPLASY) at www.inplasy.com (#INPLASY2025100049; DOI: 10.37766/inplasy2025.10.0049).

RESULTS

Quantitative analysis

The article-sorting algorithm is illustrated in Figure 1. We began with 30,500 references retrieved from the databases using “cost of treatment for HCC” as the primary keyword combination. Of these, 842 (100%) were retained, and their abstracts were screened for potential alignment with the study framework’s objectives, based on general hints of economic considerations. Finally, 164 (19.5%) references were selected for full-text review because they included economic analyses.

Of the 164 studies (100%), 38 (23.2%) were excluded: 15 (9.1%) lacked a clear treatment comparator, 9 (5.5%) involved non-patients of interest, 7 (4.3%) were systematic reviews, 4 (2.3%) were duplicates, and one each focused on several cancer types (0.6%), did not include HCC patients (0.6%), or lacked suitable economic outcomes (0.6%). Ultimately, 126 studies (76.8%) were comparative economic analyses consistent with the research framework.

Of these 126 (100%) studies, 72 (57.1%) were excluded because 16 (12.7%) focused on SIRT, 11 (8.7%) on TACE, 10 (7.9%) on surgical resection, 7 (5.6%) on transplantation, 7 (5.6%) on SBRT, 6 (4.8%) on RFA, 5 (3.4%) on HAIC, 4 (3.2%) on combination treatment, 4 (3.2%) on different treatment modalities, and 2 (1.6%) on HAIC ± systemic chemotherapy. Finally, 54 (42.8%) studies focused solely on systemic therapies and formed the core of this evaluation [Figure 1 and Tables 1-4]^[34-87].

Most of these studies examined the cost-effectiveness outcomes in China (26, 48.1%), six in the USA (11.1%), four in both China and the USA (7.4%), two in Taiwan (3.7%), two in Canada (3.7%), two in Japan (3.7%), two in Israel (3.7%), and one each in Germany and the USA (1.8%), Singapore (1.8%), Thailand (1.8%), Italy (1.8%), France (1.8%), China, USA, and Europe (1.8%), Australia (1.8%), Egypt (1.8%), India (1.8%), and Brazil (1.8%) [Tables 1-5, 7 and 8].

Owing to differences in study designs and drugs explored, we divided the retrieved comparative economic analyses into four categories: (1) head-to-head comparisons of ICIs as first-line therapy [usually against sorafenib (SORA)] as comparator [Table 1]^[34-58]; (2) studies that simultaneously compared multiple ICI- and

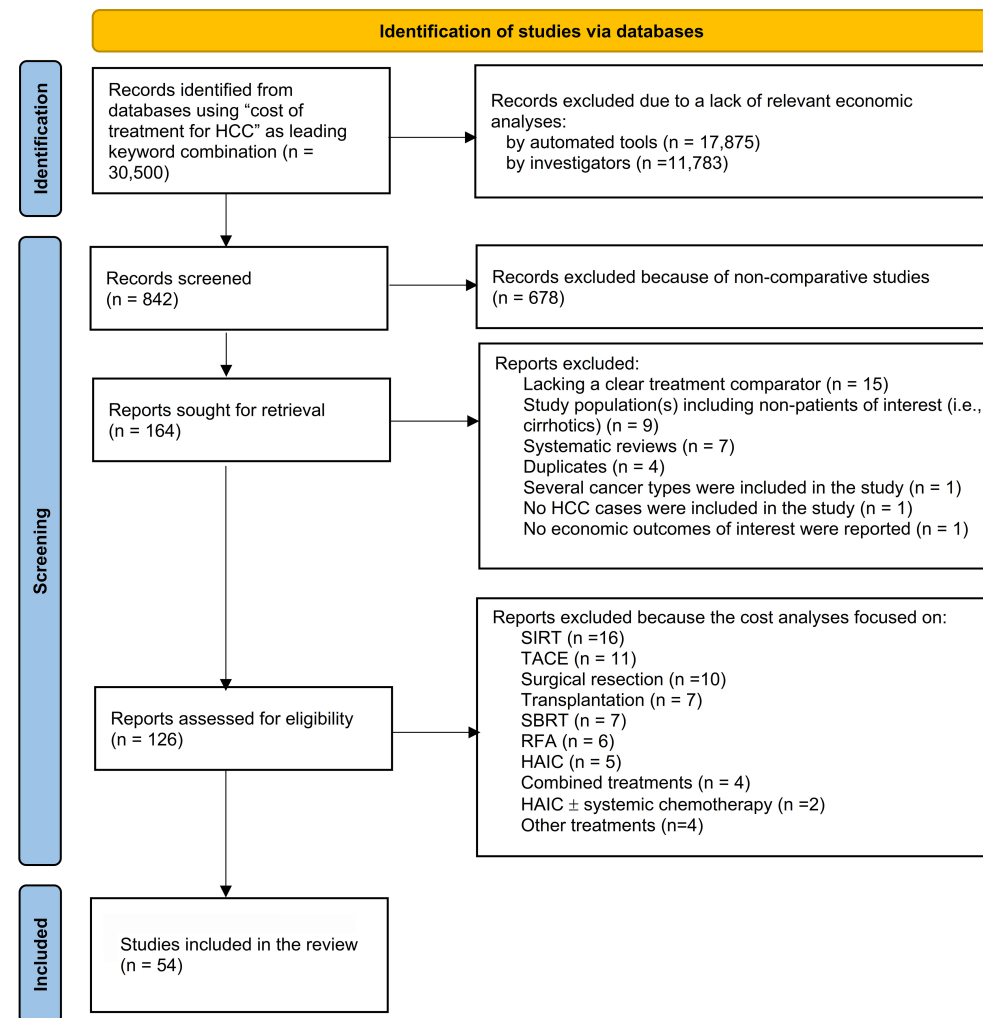


Figure 1. The literature references selection algorithm. HAIC: Hepatic artery infusion therapy; HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; SIRT: selective internal radiation therapy; TACE: trans-arterial chemoembolization.

Table 1. Results of comparative economic studies on head-to-head comparisons of ICI as first-line therapy

#	Author ^[Ref.]	Year	Country	Indication	Treatments	QALY ^a	ICER ^b	WTP ^c	ICER/WTP ^d	Remarks
Atezolizumab + Bevacizumab										
1	Chang <i>et al.</i> ^[34]	2025	Taiwan	aHCC	ATE + BEVA vs. SORA	0.57	US\$117,000	US\$92,579.9	1.2	Data extracted from the IMBrave150 trial Partitioned survival analysis with a 20-year horizon The perspective was that of the National Health Insurance Administration Discount 0%-5%
2	Liu <i>et al.</i> ^[35]	2025	USA & China	aHCC	ATE + BEVA vs. SORA	0.57 (USA) 0.47 (China)	US\$253,247.07 (USA) US\$181,552,71 (China)	US\$150,000 (USA) US\$38,201.19 (China)	1.68 (USA) 4.75 (China)	Data extracted from the IMBrave150 trial Partitioned survival analysis with a life-time horizon Discount 3% in USA and 5% in China
3	Chee <i>et al.</i> ^[36]	2024	Singapore	uHCC	ATE + BEVA vs. SORA	1.09	US\$80,676.9	US\$89,432.5	0.9	Data extracted from the IMBrave150 trial Partitioned survival model with a 10-year horizon Data were extracted from a network meta-analysis of published studies
4	Sripchoosanaphan <i>et al.</i> ^[37]	2024	Thailand	uHCC	ATE + BEVA vs. SORA	0.8309	US\$54,589	US\$4,678	11.66	Markov model with a life-time horizon Societal perspective Annual discount rate 3%
5	Tseng <i>et al.</i> ^[38]	2023	Taiwan	uHCC	ATE + BEVA vs. SORA	1.7	US\$75,192	US\$92,579.9	0.81	Data were extracted from the IMBrave-105 trial Partitioned survival analysis with a 15-year horizon Annual discount rate %

6	Gaugain <i>et al.</i> ^[39]	2023	France	a/uHCC	ATE + BEVA vs. SORA	0.61	€131,163 (i.e. US\$155,352)	€150,000 (US\$177,663)	0.87	Data were extracted from the French national real-world dataset and IMBrave150 Partitioned survival model over a lifetime horizon
7	Li <i>et al.</i> ^[40]	2022	China	a/uHCC	ATE + BEVA vs. NIV	0.69 (1.13 LYS)	US\$113,892	Note: this WTP threshold is higher than what is used by most Chinese authors	0.75	Data were extracted from a network meta-analysis integrating IMBrave150 and CheckMate459 trials Partitioned survival analysis with a 10-year horizon
8	Zhang <i>et al.</i> ^[41]	2021	China	u/mHCC	ATE + BEVA vs. SORA	0.484 (0.623 LYS)	US\$322,500	US\$100,000-150,000	3.22-2.15	Data were extracted from the IMBrave105 trial Partitioned survival analysis with a 6-year horizon The US payor perspective was used
9	Chiang <i>et al.</i> ^[42]	2021	Hong Kong	uHCC	ATE + BEVA vs. SORA	0.44	US\$179,729	US\$100,000-150,000	1.79-1.19	Reducing the price of both drugs by 20% and 29% would satisfy the WTP thresholds (both scenarios) Markov model with a lifetime horizon US payor's perspective
10	Su <i>et al.</i> ^[43]	2021	USA	uHCC	ATE + BEVA vs. SORA	0.530 (1.297 LYS)	US\$169,223 (ICUR)	US\$150,000	1.12	Cost-effectiveness can be improved by reducing the cost of either drug and adapting schedules to patients' risk factors Data extracted from the IMBrave105 trial and additional trials Partitioned survival analysis Annual discount rate 3%
11	Wen <i>et al.</i> ^[44]	2021	China	uHCC	ATE + BEVA vs. SORA	0.53	US\$145,546.21 (China) US\$168,030.21 (USA)	US\$28,527.00 (China) US\$150,000 (USA)	5.1 1.12	Data extracted from IMBrave105 Markov model Chinese and US perspectives were considered
Sintilimab + Bevacizumab or Bevacizumab biosimilar										
12	Xu <i>et al.</i> ^[45]	2023	China	uHCC	SIN + BEVAb (IBI305) ^a vs. SORA	0.33	US\$52,817.89	US\$38,334	1.37	Data were extracted from the ORIENT-32 trial Markov model Chinese payors perspective

										Data were extracted from the ORIENT-32 trial
13	Peng <i>et al.</i> ^[46]	2022	China	uHCC	SIN + BEVAb vs. SORA	1.27 (1.84 LYS)	US\$23,352	US\$30,552	0.76	Markov model with a lifetime horizon
									1.9	Chinese healthcare system's perspective
14	Zhou <i>et al.</i> ^[47]	2022	China	u/mHCC	SIN + BEVAb vs. LEN	0.493	US\$24,462	US\$12,516 (low-income areas) US\$37,547 (national average)	0.65	Data were extracted from ORIENT-32 and REFLECT trials
										Partitioned survival analysis with a lifetime horizon
										Chinese healthcare system perspective
15	Zhou <i>et al.</i> ^[48]	2021	China	uHCC	SIN + BEVA vs. SORA	0.5	US\$20,968	US\$33,592	0.62	Data were extracted from the ORIENT-32 trial
										Partitioned survival analysis with a lifetime horizon
										Chinese healthcare system's perspective
										Cost-effectiveness may further increase by reducing the dosage of BEVA to 7.5 mg/kg
										STRIDE (Single dose tremelimumab and regular interval durvalumab)
16	Cheng <i>et al.</i> ^[49]	2025	USA	uHCC	TREM + DUR (STRIDE) vs. SORA	0.57	US\$19,239	US\$150,000	0.13	Data extracted from the HIMALAYA trial and network meta-analysis of published trials
										Partitioned survival analysis with a 20-year horizon
										Payer perspective
17	Xiong <i>et al.</i> ^[50]	2024	USA	uHCC	1. TREM + DUR (STRIDE) 2. DUR alone vs. SORA	0.2 (0.27 LYS) 0.08 (0.15 LYS)	1.US\$97,995.5 (STRIDE vs. SORA) 2.US\$754,408 (STRIDE vs. DUR alone)	US\$150,000	0.65 5.02	Data extracted from the HIMALAYA protocol and STRIDE strategy
										Partitioned survival analysis with a 48-month horizon
										US societal perspective
18	Liao <i>et al.</i> ^[51]	2024	China	uHCC High AFP	TREM + DUR (STRIDE) vs. SORA	0.29	US\$72,762	US\$150,000	0.48	Data extracted from the HIMALAYA protocol and STRIDE strategy
										Markov model
										Camrelizumab + Rivoceranib

19	Zhao <i>et al.</i> ^[52]	2024	China	uHCC	CAM + RIV vs. SORA	0.80	US\$9,150.75	US\$16,426.80 (low-income regions) US\$34,319.01 (medium-income regions) US\$81,036.63 (high-income regions)	0.56 0.27 0.11	Data extracted from the CARES-310 trial Markov state transition model Sensitivity analysis stratified based on regions income
20	Wei <i>et al.</i> ^[53]	2024	USA & China	uHCC	CAM + RIV vs. SORA	0.71 (USA) 0.64 (China)	US\$122,388.62 (USA) US\$30,410.56 (China)	US\$100.000-150.000,00 (USA) US\$23,932.5-35,898.8 (China)	1.22- 0.81 1.27- 0.84	Data extracted from the CARES-310 trial USA and Chinese payors perspective Partitioned survival model with a 15-year time horizon
Tislelizumab										
21	Sun <i>et al.</i> ^[54]	2024	China USA Europe	uHCC	TIS vs. SORA	0.56 (USA and Europe) 0.52 (China)	US\$108,812.5 (USA) US\$94,880.40 (Europe) US\$14,206.80 (China)	US\$150.000(USA) US\$100.000(Europe) US\$38,186 (China)	0.72 0.94 0.37	Data extracted from the RATIONALE-301 trial Partitioned survival model Monte Carlo simulation
22	Zheng <i>et al.</i> ^[55]	2024	China	uHCC	TIS vs. SORA	0.18	US\$10413.17	US\$37,304.34	0.27	Data extracted from the RATIONALE-301 trial Partitioned survival model with a 10-year survival horizon
23	Chen <i>et al.</i> ^[56]	2024	China	uHCC	TIS vs. SORA	0.568	US\$ 22,869.64	\$37,653	0.60	Data extracted from the RATIONALE-301 trial Partitioned survival model with a lifetime horizon National Health Service perspective
Nivolumab										
24	Shu <i>et al.</i> ^[57]	2023	China	aHCC	NIV vs. SORA	0.27	US\$236,765.93	US\$38,201.1	6.19	Data were extracted from the CheckMate-459 trial Partitioned survival model Chinese healthcare system perspective

25	Li et al. ^[58]	2022	China	aHCC	NIV vs. SORA	0.32 (0.50 LYS)	US\$220,864	US\$150,000	1.47	Data were extracted from CheckMate459 trial Partitioned survival analysis with a 10-year lifetime horizon
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^aQALY is expressed as an increase or decrease versus the comparator; ^bICER is expressed per QALY unit; ^cWTP is expressed per QALY unit; ^dIf ICER/WTP > 1, the treatment is not cost-effective in the context explored; ^eBI305 is a bevacizumab biosimilar. Cost-effective treatments are highlighted in bold. QALY: Quality-adjusted life year; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay; ICI: immune checkpoint inhibitor; aHCC: advanced hepatocellular carcinoma; uHCC: unresectable hepatocellular carcinoma; mHCC: metastatic hepatocellular carcinoma; ATE: atezolizumab; BEVA: bevacizumab; SORA: sorafenib; NIV: nivolumab; LYS: life-years saved; HCC: hepatocellular carcinoma; SEER: Surveillance, Epidemiology, and End Results; ICUR: incremental cost-utility ratio; SIN: sintilimab; BEVAb: bevacizumab biosimilar; LEN: lenvatinib; STRIDE: single tremelimumab regular interval durvalumab; TREM: tremelimumab; DUR: durvalumab; HCV: hepatitis C virus; AFP: alpha-fetoprotein; CAM: camrelizumab; RIV: rivoceranib; TIS: tislelizumab; BCLC: Barcelona Clinic Liver Cancer.

Table 2. Results of economic studies comparing simultaneously multiple ICI- and TKI/VEGFi-based regimens as first-line therapy irrespective of the used comparator(s)

#	Author	Year	Country	Indication	Treatments	QALY ^a	ICER ^b	WTP ^c	ICER/WTP ^d	Remarks
Sequencing treatments										
26	Sherrow et al. ^[59]	2020	USA	uHCC 1st and 2nd-line treatment	8 different 1st- and 2nd-line sequences using: SORA, REGO, CABO, PEM, NIV, LEN (SORA-REGO; SORA-CABO; SORA-NIV; SORA-PEM ; LEN-REGO; LEN-CABO; LEN-NIV; LEN-PEM)	Not applicable due to multiple comparators	The strategies with the highest cost-effectiveness were TKI followed by ICI The 2 most cost-effective strategies were: SORA-PEM (US\$227,741.03) LEN-PEM (US\$230,371.17)	US\$150,000-300,000	A sequencing strategy of 1st-line TKI followed by 2nd-line ICI is more cost-effective than TKI-TKI SORA-PEM and LEN-PEM are the most cost-effective but well above the WTP threshold of US\$150,000	Data extracted from RCT on all drugs included in the study Markov model with 9 possible states
Multiple regimens comparisons										
27	Lian et al. ^[60]	2024	China USA	uHCC	1. ATE + BEVA; 2. TREM + DUR (STRIDE); 3. DUR ; 4. LEN vs. SORA	1. 1.92 (2.73 LYS) 2. 1.67 (2.40 LYS) 3. 1.52 (2.18) 4. 1.406 (2.05 LYS)	1. US\$196,704 2. US\$800,755 3. Reported as dominant due to lower cost than SORA (US\$178,200 vs. 202,831) 4. US\$2,032,756	US\$150,000,00	1. 1.31 2. 5.33 3. Dominant 4. 13.55	Data extracted from literatures studies and network meta-analysis Partitioned survival analysis with a 10-year horizon US healthcare and societal perspectives

28	Wen <i>et al.</i> ^[61]	2024	China	uHCC	1. TREM + DUR (STRIDE); 2. ATE + BEVA; 3. SIN + BEVAb ; 4. CAM + RIV ; 5. PEM + LEN	1 = 0.73 2 = 0.90 3 = 1.12 4 = 0.91 5 = 0.83	1. US\$115,887.68 2. US\$78,872.289 3. US\$24,072.86 4. US\$13,306.89 5. US\$66,725.94	US\$35,526.9	3.2 2.2 0.67 0.37 1.87	Data extracted from HIMALAYA, IMBrave150, ORIENT-32, CARES-310, and LEAP-002 trials Markov model with a 10-year horizon Monte Carlo simulations
29	Sun <i>et al.</i> ^[62]	2022	China, USA	aHCC	(China) 1. ATE + BEVA 2. SIN + BEVA 3. LEN 4. DONA 5. SORA (USA) 1. ATE + BEVA 2. LEN 3. NIV 4. SORA	(China) Compared with DONA 1. 0.46 2. 1.25 3. 0.77 4. -1.08 (USA) Compared with NIV 1. 3.76 2. 4.29 3. 1.92	(China) Compared with DONA 1. US\$85,607.88 2. US\$12,109.27 3. US\$1,651.47 (USA) Compared with NIV 1. 47,896.93 2. 25,022.13 3. 89,972.04	US\$11,101.70 (China) US\$69,375.0 (USA) NOTE: the WTP thresholds are lower than what is reported by other authors and correspond to the lowest range of WHO's recommendations	(China) Compared to DONA 1. 7.71 2. 1.09 3. 0.14 (USA) Compared to NIV 1. 0.69 2. 0.36 3. 1.29	Network meta-analysis based on RCTs Markov model Annual discount rate 0%-8% in China and 0%-5% in USA
30	Li <i>et al.</i> ^[63]	2022	China	uHCC	1. SIN + BEVAb 2. ATE + BEVA vs. SORA	1. 0.617 2. 0.596	1. US\$39,766.86 2. US\$103,037.66	US\$33,500	1. 1.18 2. 3.07 SIN + BEVAb cost-effectiveness is favorable in the context of a patient-assisted program scenario	Data were extracted from IMBrave150 and ORIENT-32 trials Partitioned survival model with a 15-year lifetime horizon Annual discount rates 5% A patient-assisted program was included in sensitivity analysis
31	Gong <i>et al.</i> ^[64]	2022	China	aHCC	1. LEN 2. ATE + BEVA 3. SIN + IBI305 ^a vs. SORA	1. 0.04 2. 0.31 3. 0.87	1. US\$188,625 2. US\$75,150.3 3. US\$144,513	US\$36,600	1. 5.15 2. 2.05 3. 3.94	Partitioned survival model Interviews with clinicians were used to derive costs Annual discount rate of 5%

32	Wang et al. ^[65]	2022	China	aHCC	<ol style="list-style-type: none"> SUN LEN DONA SORA + ERL SIN + IBI305^a LIN BRIVA ATE + BEVA vs. SORA 	<ol style="list-style-type: none"> 0.78 0.45 0.83 0.81 0.82 0.82 0.85 0.85 	<ol style="list-style-type: none"> US\$551 US\$121,059 US\$68,869 US\$95,545 US\$115,760 US\$128,527 US\$115,760 US\$160,049 	US\$37,654.5	<ol style="list-style-type: none"> 0.01 3.21 1.82 2.53 3.07 3.41 3.07 4.2 	<p>A theoretical model for first-line therapies was constructed based on SHARP and NCT00492752 trials</p> <p>Markov model with a 10-year time horizon</p> <p>Chinese payors perspective and only direct costs included</p>
33	Guan et al. ^[66]	2022	China	uHCC	<ol style="list-style-type: none"> DONA SORA LEN 	<ol style="list-style-type: none"> 1.106 (1.755 LYS) 0.999 (1.577 LYS) 0.915 (1.410 LYS) 	<ol style="list-style-type: none"> US\$42,116 US\$44,261 US\$43,193 	US\$31,315	<ol style="list-style-type: none"> 1.34 1.41 1.37 	<p>Data were extracted from network meta-analysis using ZGDH-3 phase 2 and 3 trials and REFLECT trial</p> <p>Partitioned survival analysis with a lifetime horizon</p>
34	Zhao et al. ^[67]	2022	China	uHCC	<ol style="list-style-type: none"> SORA LEN DONA SIN + BEVAb ATE + BEVA 	<p>Compared to SORA:</p> <p>LEN = 0.16 (0.25 LYS)</p> <p>DONA = 0.19 (0.30 LYS)</p> <p>SIN + BEVAb = 0.51 (0.95 LYS)</p> <p>ATE + BEVA = 0.86 (1.46 LYS)</p>	<p>Compared to SORA:</p> <p>LEN = US\$40,667.92</p> <p>DONA = US\$27,630.63</p> <p>SIN + BEVAb = US\$51,877.36</p> <p>ATE + BEVA = US\$130,508.44</p>	US\$33,521	<p>LEN = 1.21</p> <p>DONA = 0.82</p> <p>SIN + BEVAb = 1.54</p> <p>ATE + BEVA = 3.89</p>	<p>Network meta-analysis of 4 trials (IMBrave105, REFLECT, ORIENT-32, ZGDH-3)</p> <p>Partitioned survival analysis</p> <p>Chinese healthcare system's perspective</p>
35	Giuliani et al. ^[68]	2021	Italy	aHCC	<ol style="list-style-type: none"> LEN ATE + BEVA vs. SORA 	Not reported	<p>€139.24 (per month of PFS)</p> <p>€9198.82 (per month of PFS)</p>	Not reported	Not reported	<p>Survival model not clearly indicated</p> <p>PFS rather than overall survival was used to compute ICER</p> <p>Perspective of a National Health System hospital facility</p>

^aQALY is expressed as an increase or decrease versus the comparator; ^bICER is expressed per QALY unit; ^cWTP is expressed per QALY unit; ^dIf ICER/WTP > 1, the treatment is not cost-effective in the context explored; ^eIBI305 is a bevacizumab biosimilar. Cost-effective treatments are indicated in bold. QALY: Quality-adjusted life year; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay; ICI: immune checkpoint inhibitor; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitors or antagonists; uHCC: unresectable hepatocellular carcinoma; aHCC: advanced hepatocellular carcinoma; SORA: sorafenib; REGO: regorafenib; CABO:

cabozantinib; PEM: pembrolizumab; NIV: nivolumab; LEN: lenvatinib; RCT: randomized controlled trial; ATE: atezolizumab; BEVA: bevacizumab; TREM: tremelimumab; DUR: durvalumab; STRIDE: single tremelimumab regular interval durvalumab; LYS: life-years saved; SIN: sintilimab; BEVAb: bevacizumab biosimilar; CAM: camrelizumab; RIV: rivocecanib; DONA: donafenib; WHO: World Health Organization; IBI305: bevacizumab biosimilar IBI305; SUN: sunitinib; ERL: erlotinib; LIN: linifanib; BRIVA: brivanib; PFS: progression-free survival; ICUR: incremental cost-utility ratio.

Table 3. Results of economic studies on head-to-head comparison of TKI/VEGFi-based regimens only as first-line therapy irrespective of the used comparator(s)

#	Author	Year	Country	Indication	Treatments	QALY ^a	ICER ^b	WTP ^c	ICER/WTP ^d	Remarks
TKI/VEGFi										
36	Meng <i>et al.</i> ^[69]	2022	China	u/mHCC	DONA vs. SORA	0.184	US\$41,081.52 US\$13,439.10 (if the branded price of SORA was considered)	US\$10,499.74 TKI/VEGFi TKI/VEGFi 31,499.23	3.9-1.3 1.2- 0.42 (if a reduced DONA price is considered)	Data were extracted from network using ZGDH-3 phase 2 and 3 trials Partitioned survival analysis with a lifetime horizon Chinese healthcare system's perspective Annual discount rates 5% Scenario analysis with the brand and generic price of SORA
37	Meyers <i>et al.</i> ^[70]	2021	Canada	uHCC	LEN vs. SORA	0.17 (0.22 LYS)	-US\$5021 (as ICUR)	Not reported	LEN is dominant on SORA due to its reduced cost	Data extracted from the REFLECT trial Partitioned survival analysis over a 10-year horizon Canadian health provider's perspective Data extracted from the Japanese population of the REFLECT trial
38	Ikeda <i>et al.</i> ^[71]	2021	Japan	uHCC	LEN vs. SORA	0.31	-JPY156799 (US\$1060,15)	Not reported	LEN dominates on SORA due to reduced costs and improved QALY	Partitioned survival model with a lifetime horizon Japanese healthcare system's perspective Annual discount rate of 2% Data extracted from the REFLECT trial
39	Saiyed <i>et al.</i> ^[72]	2020	Australia	uHCC	LEN vs. SORA	0.119	A\$33,028 (US\$21,792.3)	AU\$50,000 (US\$32,990.7)	0.66	Partitioned survival model with a 10-year horizon A health-system perspective was adopted

40	Cai et al. ^[73]	2020	China	uHCC	LEN vs. SORA	1.122 (< 60 kg) 1.122 (60 kg)	US\$11,825.94 (< 60 kg) US\$28,627.12 (60 kg)	US\$29,306.37	0.40 0.97	Data extracted from the REFLECT trial Chinese patients Markov model with transition states Annual discount rate 3% The China National Healthcare Medical Administration perspective was used
41	Kim et al. ^[74]	2020	Canada	aHCC	LEN vs. SORA	0.132	In the full-price SORA scenario, LEN dominated on SORA and was associated with a 23,719.34US\$ cost saving In the 90%-discount SORA scenario, LEN ICER was US\$104,668.71	US\$0-50,000	LEN is cost-saving as compared to SORA and its cost-effectiveness is well below the WTP threshold in the full-price SORA scenario However, introduction of a generic SORA formulation or SORA discounted price might reduce LEN cost savings	Data extracted from the REFLECT trial State-transition model with a 5-year horizon Annual discount rate 1.5% Different scenarios were considered based on SORA discount rates (20%-90% discount rate)
42	Kobayashi et al. ^[75]	2019	Japan	uHCC	LEN vs. SORA	0.23 (0.27 LYS)	-JPY406,307 (US\$2,745.67)	JPY5,000,000 (US\$33,788.1)	LEN is associated with cost savings vs. SORA and improved QALY	Data were extracted from the REFLECT trial Partitioned survival analysis with a lifetime horizon

^aQALY is expressed as an increase or decrease versus the comparator; ^bICER is expressed per QALY unit; ^cWTP is expressed per QALY unit; ^dIf ICER/WTP > 1, the treatment is not cost-effective in the context explored; ^eBI305 is a bevacizumab biosimilar. Cost-effective treatments are indicated in bold. TKI: Tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitors or antagonists; uHCC: unresectable hepatocellular carcinoma; mHCC: metastatic hepatocellular carcinoma; aHCC: advanced hepatocellular carcinoma; DONA: donafenib; SORA: sorafenib; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay; LEN: lenvatinib; LYS: life-years saved; ICUR: incremental cost-utility ratio; JPY: Japanese yen.

oral-based regimens as first-line treatment [Table 2]^[59-68]; (3) studies on head-to-head comparison of oral agents only as first-line therapy [Table 3]; and (4) studies on first- or second-line therapies versus placebo and/or BSC [Table 4].

ICI as first-line therapy

A total of 25 studies were included in this category [Table 1]^[34-58]. Eleven studies focused on atezolizumab (ATE) [a programmed death-ligand 1 (PD-L1) inhibitor] + bevacizumab (BEVA) (a VEGF-A protein chain inhibitor)^[34-44]; four studies examined sintilimab (SIN) + BEVA or BEVA biosimilar versus TKI/VEGFi [SORA in three cases, lenvatinib (LEN) in one]^[45-48]; three studies compared the single tremelimumab (TREM) and regular-interval durvalumab (DUR) (STRIDE regimen) versus SORA^[49-51]; two studies evaluated a combination of camrelizumab (CAM) + rivoceranib (RIV) against SORA^[52,53]; three studies assessed tislelizumab (TIS) versus SORA^[54-56]; and two studies compared nivolumab (NIV) with SORA [Table 1]^[57,58].

Table 4. Results of comparative economic studies on first- or second-line therapies with placebo and/or BSC as the comparator

#	Author	Year	Country	Indication	Treatments	QALY ^a	ICER ^b	WTP ^c	ICER/WTP ^d	Remarks
Second-line cabozantinib										
43	Sieg <i>et al.</i> ^[76]	2020	Germany USA	aHCC second-line treatment	CABO vs. BSC	0.15 (0.18 LYS)	US\$375,470 (Germany) US\$1,189,796 (US pricing)	US\$163,371 (Germany) US\$150,000 (USA)	2.29 7.93	Data extracted from the CELESTIAL trial Markov model with a lifetime horizon German statutory health insurance perspective compared with the US scenario and prices
44	Shlomai <i>et al.</i> ^[77]	2019	Israel	aHCC second-line treatment	CABO vs. placebo	0.16 (0.22 LYS)	US\$469,374	US\$230,000	2.04	Data extracted from the CELESTIAL trial Markov model with a 5-year time horizon National health system perspective
45	Liao <i>et al.</i> ^[78]	2019	China	aHCC second-line treatment	CABO vs. placebo	0.13	US\$833,497 (USA) US\$304,177 (UK) US\$156,437 (China)	US\$150,000 (USA) US\$76,671 (UK) US\$26,481 (China)	5.55 3.96 5.91	Data extracted from the CELESTIAL trial Markov model with a 10-year horizon China, US and UK payors' perspectives were used
46	Soto-Perez-de-Celis <i>et al.</i> ^[79]	2019	Brazil	aHCC second-line treatment	CABO vs. placebo	0.067	US\$1,040,675	US\$100,000	10.41	Data extracted from the CELESTIAL trial Decision-analytic model with 3 mutually exclusive health states US healthcare system's perspective
Second-line regorafenib										
47	Shlomai <i>et al.</i> ^[80]	2018	Israel	uHCC second-line treatment after SORA	REGO + BSC vs. placebo + BSC	0.25 (0.38 LYS)	US\$201,797-268,506	US\$150,000	1.34-1.79	Data extracted from the RESORCE trial Markov model Annual discount rate 3%

48	Parikh <i>et al.</i> ^[81]	2017	USA	aHCC	REGO vs. BSC	0.18	US\$224,362	US\$100,000	2.24	Reducing REGO price would increase acceptability	Data extracted from RESORCE trial Markov model US healthcare perspective
Second-line pembrolizumab											
49	Chiang <i>et al.</i> ^[82]	2021	China	uHCC second line after SORA	PEM vs. placebo (both with BSC)	0.138	US\$340,409	US\$150,000 NOTE: the authors used the US national WTP	2.26	The model was sensitive to cost of PEM, OS, PFS, and health utility of placebo	Data extracted from the KEYNOTE-240 trial. Quality measures were extracted from a bladder cancer trial. Health utility measures of placebo were extracted from the RESORCE trial (regorafenib vs. placebo as second line therapy) Markov model with a lifetime horizon
Second-line ramucirumab											
50	Zheng <i>et al.</i> ^[83]	2019	China	aHCC second-line treatment	RAMU vs. placebo in patients with AFP 400 ng/mL	0.07	US\$782,104.57	US\$100,000 NOTE: the authors used a WTP threshold different than 3 times the per capita GDP	7.82		Data extracted from the REACH-2 trial Markov model and a 10-year horizon USA payors' perspective
First-line sorafenib vs. placebo/BSC											
51	Gupta <i>et al.</i> ^[84]	2018	India	aHCC	SORA vs. placebo	0.19 (0.25 LYS)	US\$7861	Not reported		SORA cost-effectiveness is 4.2 higher than GDP	Data were extracted from the Asia-Pacific SORA trial Markov model with a lifetime horizon Societal perspective
52	Hamdy Elsisy <i>et al.</i> ^[85]	2018	Egypt	aHCC	SORA vs. placebo	3.96	US\$286,776	US\$41,372	6.9		Data extracted from the SHARP trial Markov model with a 4-year horizon Data were extracted from MEDICARE beneficiary's dataset (SEER)
53	Parikh <i>et al.</i> ^[86]	2017	USA	aHCC8 (stage III/IV AJCC)	SORA vs. no treatment	0.24	US\$224,914	US\$100,000	2.24		Treated patients were matched with controls through PSM Univariate and multivariate analyses were used to identify predictors of survival

54	Zhang <i>et al.</i> ^[87]	2015	China	aHCC	SORA vs. BSC	0.18	US\$101,399.11	US\$20,301.00	4.99	Data extracted from medical records
										Costs are sensitive to Child-Pugh status
										Markov model

^aQALY is expressed as an increase or decrease versus the comparator; ^bICER is expressed per QALY unit; ^cWTP is expressed per QALY unit; ^dIf ICER/WTP > 1, the treatment is not cost-effective in the context explored; ^eBI305 is a bevacizumab biosimilar. CABO: Cabozantinib; BSC: best supportive care; aHCC: advanced hepatocellular carcinoma; QALY: quality-adjusted life year; LYS: life-years saved; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay; USA: United States of America; UK: United Kingdom; REGO: regorafenib; uHCC: unresectable hepatocellular carcinoma; SORA: sorafenib; PEM: pembrolizumab; OS: overall survival; PFS: progression-free survival; RAMU: ramucirumab; AFP: alpha-fetoprotein; GDP: gross domestic product; AJCC: American Joint Committee on Cancer; SEER: Surveillance, Epidemiology, and End Results; PSM: propensity score matching.

Table 5. Summary of the risk bias evaluation of the 54 included studies according to the JBI^[88]

Item	Remarks
Is there a well-defined question?	In all included studies
Is there comprehensive description of alternatives?	Only studies with multiple comparators ^[59-67] - All included studies except for references [39,86,87] extracted data from previous phase II/III trials - References [29,86,87] used real-world data without comprehensive description of alternatives
Are all important and relevant costs and outcomes for each alternative identified?	In all included studies
Has clinical effectiveness been established?	In all included studies
Are costs and outcomes measured accurately?	In all included studies except for references [59,68] where ICERs were not clearly reported
Are costs and outcomes valued credibly?	In all studies except for references [40,62,58,68,70,71,82-84] - Studies [40,58,82,83] used higher WTPs than those recommended - Reference [62] used a lower WTP than what usually recommended - References [68,70,71,84] did not report any WTP
Are costs and outcomes adjusted for differential timing?	In all included studies
Is there an incremental analysis of costs and consequences?	In all studies except for references [59,68]
Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	In all included studies except for reference [68]
Do study results include all issues of concern to users?	Only in studies [37,50,84]
Are the results generalizable to the setting of interest in the review?	With caution - References [35,40-42,44-48,51-58,60-67,69,73,78,82,83,87] originate from or focus on the Chinese health market and may have a limited transferability to other international settings - References [45-48,52-56,61,65-67,69] included or focused on drugs that are currently limited to the Chinese healthcare market To assist in evaluation of current evidence, please refer to Supplementary Table 1 for a list of drugs approved in the Chinese (NMPA), US (FDA) and European (EMA) markets

JBI: Joanna Briggs Institute; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay; NMPA: National Medical Products Administration; FDA: Food and Drug Administration; EMA: European Medicines Agency.

Table 6. Summary of qualitative evaluations of included comparative economic studies on systemic therapies for HCC obtained from the ECOBIAS toolkit^[89]

Item	N (%) studies
Type of studies	
CEA/CUA*	54 (100)
CBA	0 (0)
Countries explored	
China (%)	26 (48.1)
USA (%)	6 (11.1)
China-USA (%)	4 (7.4)
Taiwan (%)	2 (3.7)
Canada (%)	2 (3.7)
Japan (%)	2 (3.7)
Israel (%)	2 (1.8)
Germany-USA (%)	1 (1.8)
Singapore (%)	1 (1.8)
Thailand (%)	1 (1.8)
Italy (%)	1 (1.8)
France (%)	1 (1.8)
China-USA-Europe (%)	1 (1.8)
Australia (%)	1 (1.8)
Egypt (%)	1 (1.8)
India (%)	1 (1.8)
Brazil (%)	1 (1.8)
Data sourcing	
National/international registration trials	51 (94.4) ^[34-38,40-85]
Real-world	3 (5.6) ^[39,86,87]
Economic metrics	
Outcomes	
QALYs (%)	52 (96.3) ^[34-58,67,69-87]
LYS (%)	15 (27.8) ^[40,41,43,46,50,58,60,66,67,70,75-77,80,84]
ICER (%)	49 (90.7) ^[34-42,44-65,67-69,71-87]
ICUR (%)	2 (3.7) ^[43,70]
Alternative outcome measures (%)	3 (5.5) ^[66,68,74]
WTP (%)	50 (92.6%) ^[34-67,69,72-83,85-87]
Methodology	
Partitioned survival analysis (%)	28 (51.8) ^[34-36,38-41,43,47-50,53-58,60,63,64,66,67,69,70-72,75]
Markov model (%)	23 (42.6) ^[37,42,44-46,51,52,59,61,62,65,73,74,76-78,80-85,87]
Other/not clearly reported (%)	3 (5.6) ^[68,79,86]
Lifetime horizon (%)	15 (27.8) ^[35,37,39,42,46-48,56,66,69,71,75,76,82,84]
Defined horizon (%)	21 (38.9) ^[34,36,38,40,41,49,50,53,55,58,60,61,63,65,70,72,74,77,78,83,85]
Median (IQR) years	10 (9)
Perspective	
National/regional healthcare (%)	18 (33.3) ^[34,44,46-48,56,57,60,67,68,70-73,76,77,79,81]
Payor (%)	9 (16.7) ^[41-43,45,49,65,78,83,85]
Societal (%)	3 (5.5) ^[37,50,84]
Not clearly indicated (%)	24 (44.4) ^[35,36,38-40,51-55,58,59,61-64,66,69,74,75,80,82,86,87]

*Most CEA reported utility metrics. Therefore, a clear distinction between CEA and CUA is not an applicable measure. HCC: Hepatocellular carcinoma; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; CBA: cost-benefit analysis; QALY: quality-adjusted life year; LYS: life-years saved; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; WTP: willingness to pay; IQR: interquartile range.

ATE + BEVA

The comparator was SORA in 10 (90.9%) studies^[34-39,41-44], and NIV in one (0.9%)^[40]. All these studies based their economic analyses on the IMBrave-105 trial^[90]. The analysis comparing ATE + BEVA vs. NIV also used data from the CheckMate-459 trial^[91]. The studies were published between 2021 and 2025 and examined cost-effectiveness in China in four (36.4%), Taiwan in two (0.18%), and Thailand (0.9%), Singapore (0.9%), France (0.9%), the USA (0.9%), and both the USA and China (0.9%). The adjusted mean (SD) of ATE +

Table 7. Summary of treatments examined in the current systematic review

	Treatments*	N (%) studies	
First-line	ATE + BEVA versus SORA	17 (31.5) ^[34-39,41-44,60,62-68]	
	ATE + BEVA with multiple comparators	1 (1.8) ^[61]	
	ATE + BEVA versus NIV	1 (1.8) ^[40]	
	SIN + BEVAb versus SORA	8 (14.8) ^[45,46,48,62-67]	
	SIN + BEVAb with multiple comparators	1 (1.8) ^[61]	
	SIN + BEVAb versus LEN	1 (1.8) ^[47]	
	Immunotherapy	STRIDE versus SORA	4 (7.4) ^[49-51,60]
		STRIDE with multiple comparators	1 (1.8) ^[61]
		DUR versus SORA	2 (3.7) ^[50,60]
		CAM + RIV versus SORA	2 (3.7) ^[52,53]
CAM + RIV with multiple comparators		1 (1.8) ^[61]	
PEM + LEN with multiple comparators		1 (1.8) ^[61]	
TIS versus SORA		3 (5.6) ^[54-56]	
NIV versus SORA		3 (5.6) ^[57,58,62]	
SORA versus BSC/placebo		4 (7.4) ^[84-87]	
LEN versus SORA		12 (22.2) ^[60,62,64-68,70-75]	
TKI/VEGFi	DONA versus SORA	5 (9.2) ^[62,65-67,69]	
	DONA versus LEN	1 (1.8) ^[66]	
	SUN versus SORA	1 (1.8) ^[65]	
	LIN versus SORA	1 (1.8) ^[65]	
	BRIVA versus SORA	1 (1.8) ^[65]	
	SORA + ERL versus SORA	1 (1.8) ^[65]	
	Second-line	CABO versus BSC/placebo	4 (7.4) ^[76-79]
		REGO versus BSC/placebo	2 (3.7) ^[80,81]
		PEM versus BSC/placebo	1 (1.8) ^[82]
		RAMU versus BSC/placebo	1 (1.8) ^[83]
Sequencing treatments	REGO after SORA	1 (1.8) ^[59]	
	CABO after SORA	1 (1.8) ^[59]	
	NIV after SORA	1 (1.8) ^[59]	
	PEM after SORA	1 (1.8) ^[59]	
	REGO after SORA	1 (1.8) ^[59]	
	CABO after LEN	1 (1.8) ^[59]	
	NIV after LEN	1 (1.8) ^[59]	
	PEM after LEN	1 (1.8) ^[59]	
Active treatment by country/region explored**			

	China = 18 active treatments	
	ATE + BEVA	11 (20.4) ^[35,40,41,44,60-65,67]
	SIN + BEVAb	10 (18.5) ^[45-48,61-65,67]
	STRIDE	
	DUR	3 (5.6) ^[51,60,61]
	CAM + RIV	1 (1.8) ^[60]
	TIS	2 (3.7) ^[52,53]
	NIV	4 (25.9) ^[54-56,61]
	LEN	2 (3.7) ^[57,58]
	PEM + LEN	12 (22.2) ^[60,62,64-67,70-75]
	DONA	1 (1.8) ^[61]
	SUN	5 (9.2) ^[62,65-67,69]
	SORA + ERL	1 (1.8) ^[65]
	LIN	1 (1.8) ^[65]
	BRIVA	1 (1.8) ^[65]
	CABO	1 (1.8) ^[65]
	PEM	1 (1.8) ^[78]
	RAMU	1 (1.8) ^[82]
	SORA	1 (1.8) ^[83]
ASIA		1 (1.8) ^[87]
	Japan = 2 active treatments	
	LEN	2 (3.7) ^[71,75]
	Taiwan = 1 active treatment	
	ATE + BEVA	2 (3.7) ^[34,38]
	Hong Kong = 1 active treatment	
	ATE + BEVA	1 (1.8) ^[42]
	Singapore = 1 active treatment	
	ATE + BEVA	1 (1.8) ^[36]
	Thailand = 1 active treatment	
	ATE + BEVA	1 (1.8) ^[37]
	India = 1 active treatment	
	SORA	1 (1.8) ^[84]
Asia-Pacific	Australia = 1 active treatment	
	LEN	1 (1.8) ^[72]
	USA = 17 active treatments	
	ATE + BEVA	3 (5.6) ^[35,43,62]
	NIV	1 (1.8) ^[62]
	STRIDE	2 (3.7) ^[49,50]
	DUR	1 (1.8) ^[50]
	TIS	1 (1.8) ^[54]
	LEN	1 (1.8) ^[62]
	SORA-REGO	1 (1.8) ^[59]
	SORA-CABO	1 (1.8) ^[59]
	SORA-NIV	1 (1.8) ^[59]
	SORA-PEN	1 (1.8) ^[59]
	LEN-REGO	1 (1.8) ^[59]
	LEN-CABO	1 (1.8) ^[59]
	LEN-NIV	1 (1.8) ^[59]
	LEN-PEM	1 (1.8) ^[59]
	CABO	1 (1.8) ^[76]
	REGO	1 (1.8) ^[81]
	SORA	1 (1.8) ^[86]
North America		
	Canada	
	LEN	2 (3.7) ^[70,74]
	Israel = 2 active treatments	
	CABO	1 (1.8) ^[77]
	REGO	1 (1.8) ^[80]
Middle East		
	Egypt = 1 active treatment	
	SORA	1 (1.8) ^[85]
Africa		

	Europe = 1 active treatment TIS	1 (1.8) ^[54]
	France = 1 active treatment ATE + BEVA	1 (1.8) ^[39]
Europe	Italy = 2 active treatments ATE + BEVA	1 (1.8) ^[68]
	LEN	1 (1.8) ^[68]
	Germany = 1 active treatment CABO	1 (1.8) ^[76]
South America	Brazil = 1 active treatment CABO	1 (1.8) ^[79]

*As monotherapy, combined therapies or sequencing treatments; **SORA was considered only as an active treatment when the comparator was placebo or supportive care. ATE: Atezolizumab; BEVA: bevacizumab; NIV: nivolumab; SIN: sintilimab; BEVAb: bevacizumab biosimilar; LEN: lenvatinib; STRIDE: single tremelimumab regular interval durvalumab; DUR: durvalumab; CAM: camrelizumab; RIV: rivoiceranib; PEM: pembrolizumab; TIS: tislelizumab; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitors or antagonists; SORA: sorafenib; BSC: best supportive care; DONA: donafenib; SUN: sunitinib; LIN: linifanib; BRIVA: brivanib; ERL: erlotinib; CABO: cabozantinib; REGO: regorafenib; RAMU: ramucirumab.

Table 8. Summary of cost-effective treatments based on the results of the systematic review

Treatments*	N (%) studies	Countries explored
First-line		
Immunotherapy		
ATE + BEVA vs. SORA	5 (9.2) ^[36,38,39,62]	China (1), Singapore (1), Taiwan (1), USA (1), France (1)
ATE + BEVA vs. NIV	1 (1.8) ^[40]	China (1)
SIN + BEVAb vs. SORA	3 (5.6) ^[46,47,48]	China (3)
SIN + BEVAb vs. multiple comparators	1 (1.8) ^[61]	China (1)
STRIDE vs. SORA	3 (5.6) ^[49,50,51]	USA (2), China (1)
CAM + RIV vs. SORA	2 (3.7) ^[52,53]	China (2), USA (1) (study #53 explored both the Chinese and the US market)
CAM + RIV vs. multiple comparators	1 (1.8) ^[61]	China (1)
TIS vs. SORA	3 (5.6) ^[54,55,56]	China (3), USA (1), Europe (1) (study #54 explored China, USA, and Europe)
DUR vs. SORA	1 (1.8) ^[60]	China (1), USA (1) (study #60 explored both China and USA)
TKI/VEGFi		
LEN vs. SORA	7 (12.9) ^[62,70,71,72,73,74,75]	China (3), USA (1), Canada (2), Japan (2), Australia (1) (study #62 explored both China and USA)
DONA vs. SORA	1 (1.8) ^[67]	China (1)
SUN vs. multiple comparators	1 (1.8) ^[65]	China (1)
Sequencing treatments		
SORA-PEM	1 (1.8) ^[59]	USA (1)
LEN-PEM	1 (1.8) ^[59]	USA (1)

*As monotherapy, combined therapies or sequencing treatments. ATE: Atezolizumab; BEVA: bevacizumab; NIV: nivolumab; SIN: sintilimab; BEVAb: bevacizumab biosimilar; STRIDE: single tremelimumab regular interval durvalumab; CAM: camrelizumab; RIV: rivoiceranib; TIS: tislelizumab; DUR: durvalumab; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitors or antagonists; LEN: lenvatinib; DONA: donafenib; SUN: sunitinib; SORA: sorafenib; PEM: pembrolizumab.

BEVA QALYs was 0.70 ± 0.36 , and the adjusted mean \pm SD of LYS was 1.21 ± 0.11 . The adjusted mean \pm SD ICER/WTP ratio is 2.71 ± 3.07 . Finally, ATE + BEVA was cost-effective (i.e., ICER/WTP < 1) compared to the comparator in four studies (three versus SORA and one versus NIV) [Table 1]^[36,38,39,40].

SIN + bevacizumab biosimilar

Four studies published between 2021 and 2023 examined the cost-effectiveness of SIN (a PD-1 receptor antagonist approved for HCC in China) in combination with BEVA or a BEVA biosimilar (IBI3015)^[44-48]. All

of these studies were conducted by Chinese authors, with SORA as the comparator in three studies and LEN in one study^[44-48]. The studies derived data for analysis from previous trials, that is ORIENT-32^[92], and REFLECT^[93]. The adjusted mean \pm SD of the SIN + BEVA biosimilar QALYs was 0.64 ± 0.42 , and the reported LYS (measured in only one study) was 1.84. The adjusted mean \pm SD ICER/WTP ratio is 1.06 ± 0.55 . Finally, the SIN + BEVA biosimilar was cost-effective in three studies (two versus SORA, and one versus LEN) [Table 1].

STRIDE

The STRIDE regimen was studied in three research projects between 2023 and 2025, involving scholars from the US (2 cases) and China (one)^[49-51]. All studies used data from the HIMALAYA trial^[94]. One study also compared DUR monotherapy with STRIDE^[50]. The mean \pm SD adjusted QALY for STRIDE was 0.35 ± 0.19 , and the reported LYS (measured in only one study) was 0.27. The mean \pm SD adjusted ICER/WTP ratio was 0.42 ± 0.26 , and STRIDE proved cost-effective across all included studies, regardless of the TKI/VEGFi comparator^[49-51].

CAM + RIV

A regimen combining CAM (a PD-1 inhibitor approved in China) with RIV (a VEGF-2 inhibitor approved in China and pending approval in other countries) was studied in two research projects by Chinese scholars, one examining China's healthcare system and the other exploring both the US and Chinese healthcare systems [Table 1]^[52,53]. Data were derived from the CARES-310 trial in both cases^[95]. The adjusted mean \pm SD QALY for CAM + RIV was 0.71 ± 0.08 , and the adjusted mean \pm SD ICER/WTP ratio was 0.71 ± 0.43 . CAM + RIV was found to be cost-effective in both published studies^[52,53].

TIS

A single-agent regimen with TIS, a PD-1 inhibitor, was compared with SORA in three studies conducted by Chinese researchers, examining cost-effectiveness in China (two publications) and across China, the USA, and Europe (one publication) [Table 1]^[54-56]. In all studies, data were derived from the RATIONALE-301 trial^[96], and the comparator was SORA. The adjusted mean \pm SD QALY for TIS was 0.46 ± 0.18 , and the adjusted mean \pm SD ICER/WTP ratio was 0.58 ± 0.27 . The regimen was cost-effective in all studies and across all international scenarios [Table 1]^[54-56].

NIV

A single-agent regimen with NIV, a PD-1 inhibitor, was compared with SORA in two studies conducted between 2022 and 2023, both of which evaluated its cost-effectiveness in China^[57,58]. Population data were obtained from the CheckMate-459 trial for each case^[91]. Despite its improved clinical efficacy over SORA (i.e., adjusted mean \pm SD QALY of 0.29 ± 0.03), NIV was not considered cost-effective in any of the studies (adjusted mean \pm SD ICER/WTP ratio 3.83 ± 3.33) [Table 1]^[57,58].

Simultaneous comparison of multiple regimens

Ten studies examined multiple first-line regimens simultaneously against a common comparator, usually SORA [Table 2]^[59-68].

Sequencing treatments

In 2020, a US study examined eight different sequences of first- and second-line drugs using VEGFi and/or TKI agents [SORA, regorafenib (REGO), cabozantinib (CABO)], LEN, and ICIs [pembrolizumab (PEM), a PD-1 inhibitor, and NIV]^[59]. The sequences included SORA - REGO, SORA - CABO; SORA - NIV, SORA - PEM, LEN-REGO, CABO; LEN - LEN-NIV, and LEN-PEM [Table 2]. Data were obtained from randomized

controlled trials (RCTs) of the respective drugs. Although utility outcomes (such as QALYs) were not available, the study indicated that a strategy of TKI/VEGFi followed by ICI upon disease progression is more cost-effective than using TKI/VEGF as both first- and second-line therapies^[59]. The two most cost-effective regimens were SORA - PEM (ICER = US\$227,741.03) and LEN - PEM (US\$230,371.17). However, both regimens were above the WTP national threshold of 150,000 USD^[59].

Multiple comparisons

Nine studies published between 2021 and 2024 compared multiple first-line regimens simultaneously^[60-68]. Detailed information about the authors of the studies, publication years, national health systems examined, QALY/LYS, ICER, WTP, and ICER/WTP are shown in [Table 2](#). Seven of these studies examined the cost-effectiveness of ICI- and TKI/VEGFi-based schedules together^[60,62-65,67,68]; one focused only on TKI/VEGFi^[66], and one included only ICI therapies^[61]. Eight studies included SORA in their comparisons^[60,62-68]. In one study, the most cost-effective regimens were donafenib (DONA)^[67], a deuterium derivative of SORA approved for unresectable HCC in China in 2021^[97,98]; DUR monotherapy^[60]; SIN + BEVA biosimilar^[61]; ATE + BEVA^[62]; CAM + RIV^[61]; LEN^[62], and sunitinib (SUN) [[Table 2](#)]^[65].

Head-to-head comparison of oral agents

Seven studies published between 2019 and 2022 evaluated the cost-effectiveness of oral agents through direct comparisons [[Table 3](#)]^[69-75]. Six of these studies compared LEN to SORA^[70-75], whereas only one Chinese study compared DONA to SORA^[69]. In all cases, data were obtained from published trials, including the ZDGH-3 phase 2 and 3 studies^[98], and the REFLECT trial^[93].

Despite the increased QALY, a Chinese study reported that DONA was less cost-effective than SORA. However, its cost-effectiveness may increase in scenarios with a branded SORA formulation, lower DONA prices, and in high-income regions (ICER/WTP ratio of 0.42)^[69].

All six studies on LEN demonstrated that this drug is a more cost-effective regimen than SORA^[70-75]. In four of them, it was dominant over the comparator due to lower costs and higher utility (QALY) [[Table 3](#)]^[70,71,74,75].

First and second-line therapies versus placebo and/or BSC

A total of 12 studies were included in the final analysis [[Table 4](#)]^[76-87]. Four analyses focused on CABO versus placebo/BSC after failure of first-line TKI/VEGFi therapy, using the CELESTIAL trial as the source dataset^[99]. Two studies^[80,81] involved REGO and were based on the RESORCE trial^[100]. Two studies, each focusing on PEM^[82] and ramucirumab (RAMU)^[83], were based on the KEYNOTE-240^[101] and REACH-2 trials^[102], respectively.

Four studies examined the cost-effectiveness of SORA compared to placebo/BSC as a first-line therapy^[84-87]. Two studies^[84,85] sourced data from the SHARP trial or from its Asia-Pacific population^[103]. One study extracted data from the Surveillance and End Results (SEER) Medicare database^[86], whereas one Chinese study used medical records^[87]. None of the studies demonstrated the cost-effectiveness of the research or active comparators. Detailed information on the study type, year of publication, country of origin, active treatment, QALYs, ICER, and ICER/WTP is reported in [Table 4](#).

Overall

Among the 54 included studies, 35 regimen comparisons were reported: 23 first-line (15 ICI-containing schedules and 8 TKI/VEGFi-based regimens), 4 second-line, and 8 sequencing treatments [[Tables 1-4](#) and [7](#)]. Eighteen active regimens were explored in China, 17 in the USA, and 5 in Europe, while other national markets were only minimally represented [[Tables 1-4](#) and [6-8](#)].

A total of 14 (40.0%) active treatments were shown to be cost-effective. ICI-containing regimens were more frequently cost-effective than other systemic therapies [Tables 1-4 and 8]. Specifically, ATE + BEVA was cost-effective in five studies^[36,38-40,62], SIN + BEVA/BEVA biosimilar in four^[46-48,61], STRIDE in three^[49-51], CAM + RIV in three^[52,53,61], TIS in three^[54-56], and DUR monotherapy in one^[60]. Among oral agents (i.e., TKI/VEGFi), LEN was cost-effective in seven studies^[62,70-75], while DONA and SUN were cost-effective in one study each^[65,67]. SORA was not cost-effective when compared with active comparators or BSC/placebo. The only exception was when a generic SORA formulation was compared with DONA due to the latter's higher price^[69]. The sequencing treatments SORA + PEM and LEN + PEM were cost-effective in one study of patients who failed initial therapy with oral agents^[59].

Qualitative analysis

All 54 studies were initially assessed for eligibility and risk of bias using the JBI assessment grid, which includes 11 items^[88]. The detailed reports of these studies are shown in Table 5. Due to the large number of included studies, responses to the 11 items of the JBI are summarized collectively. Three qualitative items were poorly addressed across the included studies: (1) the comprehensive description of available therapeutic options; (2) the credibility of economic metrics; and (3) the transferability of results. No study evaluated all therapeutic regimens currently available in a specific health market. Cost-effectiveness metrics were not credibly reported in five studies: in four cases, WTPs exceeded those recommended by the WHO^[40,58,82,83], and in one case, WTP was lower than that based on national GDP^[62]. Four studies did not report any WTP^[68,70,71,84]. The transferability of results should be interpreted cautiously for studies exploring only the Chinese market (26 studies) or the Chinese market in combination with the USA (4 studies) or the USA and Europe (1 study), given the different dynamics of drug reimbursement policies [Tables 5-8]. Finally, 14 studies focused on or included drugs and regimens currently approved only in the Chinese market [Tables 5-8]. The Supplementary Table 1 provides a complete list of systemic treatments approved in China, the USA, and Europe at the time of publication.

Further assessments were performed using the ECOBIAS checklist^[89], as shown in Table 6. Metrics of utility, such as QALYs, were reported in nearly all included studies (52 = 96.3%), whereas effectiveness measures, such as LYS, were reported in 15 (27.8%) studies [Table 6]. ICERs were reported in 49 (90.7%) studies, with 2 (3.7%) using ICURs^[43,70]. Three studies (5.5%) employed alternative outcome measures such as cost savings or ICER per month of PFS^[66,68,74]. WTPs were documented in all studies except 4 (92.6%)^[68,70,71,84]. Notably, no CBA has been reported in the international literature on systemic therapies for advanced HCC during the study period.

Almost all studies collected data from published trials on systemic therapies or from network meta-analyses of published trials (51/54, 94.4%)^[90-103]. This limited the ability to accurately count patients included in the review, owing to the risk of double-counting participants from the trials used for cost-comparative assessments. Real-world data were only available from a study in France on ATE + BEVA^[39], a survey of SORA from the USA using SEER program (<https://seer.cancer.gov/registries/>)^[86], and a study from China comparing SORA to placebo/BSC^[87]. Most studies (28/54, 51.8%) used a partitioned survival model, which included PFS, progressive disease (PD), and death, to estimate cost-effectiveness [Tables 1-4]. Twenty-three studies (42.6%) employed a Markov state-transition model, one (1.8%) used a decision analytic approach^[79], one combined propensity score matching with univariate and multivariate survival analysis^[86], and one (1.8%) did not clearly specify the methodology for calculating transitions across health states for patients on systemic therapy [Tables 1-4]^[68]. A lifetime horizon was used to estimate the costs of the therapies in 15 studies (27.8%) [Tables 1-6]. In 21 studies (38.9%), the median [interquartile range (IQR)] timeframe was 10 (9) years [Tables 5 and 6]. However, this was not clearly specified in the remaining 18 studies (33.3%) [Tables 1-4].

A national or regional healthcare system perspective was used in 18 studies (33.3%). A payor's perspective was employed in nine studies (16.7%), whereas a societal perspective was adopted in three studies (5.5%). It was not clearly specified in 24 studies (44.4%) [Tables 1-6].

Tables 7 and 8 provide details on the types and numbers of treatments explored, as well as their distribution across countries. While the overall number of treatments differs only slightly between China and the USA, more treatments were investigated more than once in China [Table 7]. In Chinese studies, among 18 treatments/regimens, LEN was investigated 12 times; ATE + BEVA, 11 times; SIN + BEVA biosimilar, 10 times; DONA, 5 times; and TIS, 4 times. Further treatments were investigated 3 times [Table 7]. Of the 17 treatments investigated in US papers, the most frequently explored were ATE + BEVA (3 times)^[35,43,62]; and STRIDE (2 times)^[49,50]. In Europe, only 5 treatments were explored, with ATE + BEVA being the most frequently investigated regimen (2 times)^[39,68].

DISCUSSION

Although effectiveness is the primary outcome measure for any new therapy, CEAs are crucial for informed decision-making. This is especially true when multiple therapies are available for a specific disease or when several options emerge within a short period^[104]. This situation applies to HCC, for which treatment options have expanded since 2008 with the introduction of systemic therapies^[90-103]. The primary goal of CEAs is to identify strategies that maximize health benefits with available resources or improve the value of money^[104]. In recent years, the number of cost-effectiveness publications related to HCC has increased^[34-87]. This trend mirrors the growing number of publications on the cost-effectiveness of treatment options for stroke, neurological diseases, and cardiovascular conditions^[104]. However, the implications and limitations of this field remain poorly understood by clinicians^[105].

Systemic therapies are transforming the care of patients with HCC^[13], and they are increasingly used in clinical practice not only as first- or second-line treatments but also in combination with radiology-assisted techniques, surgery, and LT^[14]. The current arsenal of systemic therapies includes various drug categories, ranging from oral agents (typically TKIs and VEGFi) to ICIs^[13]. Within each category, differences exist in target molecular mechanisms, pharmacodynamics, pharmacokinetic properties, routes of administration, and side effects^[13]. These characteristics affect not only the drug's effectiveness but also its clinical utility and economic burden.

To assess the cost-effectiveness of systemic therapies for HCC, we conducted a systematic review covering the past decade. Following the PRISMA framework, we used a narrative approach to summarize the findings because international studies varied greatly in research methods, data sources, time horizons, sensitivity analyses, case-scenario simulations, perspectives, and the countries studied [Tables 1-6]^[21,22,34-87].

Main findings

First-line regimens

Overall, the main finding of our review was that 14 (40.0%) of the 35 treatments compared in the literature demonstrated some degree of cost-effectiveness, with only a third of the included studies (18/54) reporting it [Tables 1-4, 7 and 8]. These treatments included 9 first-line ICI-containing regimens, 3 first-line TKI/VEGFi schedules, and 2 sequencing treatments [Table 8]. Among first-line treatments, ICI-containing regimens were more often cost-effective than other active drug regimens^[34-87], and LEN outperformed SORA more frequently than the other targeted oral agents (i.e., DONA, SUN). These results align with the superior clinical effectiveness of these regimens in phase II and III trials [Tables 1-4, 7 and 8].

Finally, despite its widespread use until the introduction of LEN and/or ICI-containing regimens, SORA was not proven to be cost-effective compared to placebo or BSC^[84-87]. However, no study has evaluated the ICER of generic SORA formulations introduced into clinical practice over the past few years. The lack of these studies is likely due to SORA's inferior clinical effectiveness compared to more recent LEN and/or ICIs.

Second-line regimens

Second-line therapies after the failure of initial oral agents have not shown cost-effectiveness for any of the drugs studied (CABO, REGO, PEM, and RAM) when compared to placebo or BSC^[76-83]. This is because the limited improvements in OS and PFS do not justify the high costs of these medications. Only one US study evaluated the cost-effectiveness of eight treatment sequences involving both first- and second-line agents^[59]. Despite limitations from a multiple-comparator analysis using data from randomized clinical trials of six different agents, the study found that two combinations were cost-effective: SORA-PEM and LEN-PEM^[59]. However, these results should be revisited given the proven superiority of ICIs over SORA as first-line options.

Overall, these findings from comparative economic analyses of first- and second-line agents/regimens do not conflict with clinical data but instead underscore the economic burden of introducing new drugs into the healthcare market. Drug prices were the main cost factor in all the included studies, and strategies to reduce these costs may lower the value of ICERs and enhance the ICER/WTP ratios^[42,43,70,71,74,75,81,82].

Limitations

Geographical distribution

An important finding of this research is that most studies were conducted by Chinese authors or focused on the Chinese medical market^[34-87]. Overall, 48.1% (26/54) of the papers examined only the Chinese market, 4 (7.4%) combined China and the USA, and one (1.8%) investigated the Chinese, US, and European markets. This is due to the epidemiological importance of HCC in China, as well as the fact that more first- and second-line agents have been approved for use in China than in other countries or regions [Supplementary Table 1]. To our knowledge, 14 drugs or treatment regimens have been approved for advanced HCC in China as of the publication of this paper, and at least nine targeted agents or combination regimens were recommended by experts in 2024, including SORA, LEN, DONA, ATE + BEVA, SIN + BEVA/BEVA biosimilar, and second-line options such as REGO, CABO, and apatinib.

However, this apparent dominance decreased when comparing the number of treatments studied across different countries or regions, especially for China and the USA [Table 7]. Despite having more publications, the number of regimens examined was nearly the same in Chinese papers ($n = 18$) and studies from the USA ($n = 17$) [Tables 1-4 and 7]. Topic redundancy was observed among Chinese researchers, who studied LEN in 12 publications, ATE + BEVA in 11, SIN + BEVA biosimilar in 10, DONA in 5, and TIS in 3 [Table 7]. A clear reason for this redundancy is hard to determine but may be linked to publication pressure on Chinese researchers, the size of China's healthcare market, the epidemiology of HCC in China^[106], the complex economic factors across different Chinese regions, and the requirements for obtaining marketing approval from Chinese authorities. Lastly, various Chinese pharmaceutical companies have developed and produced a significant portion of systemic drugs for HCC, including CAM, RIV, SIN, various BEVA biosimilars, and DONA, and they obtained marketing approval earlier than in other countries [Supplementary Table 1].

This geographical imbalance in the literature on systemic treatments for HCC calls for caution when applying the review's conclusions to countries outside China and Asia. Macroeconomic factors (such as national GDPs, WTPs, drug reimbursement policies, patient co-payments, drug pricing, discount rates, manufacturer competition, regulation of generic versus brand-name products, etc.) and microeconomic

elements (like access to care and medications, patients' social status, neighborhood deprivation, availability of family support or caregivers, *etc.*) are not always clearly included in comparative economic analyses and continue to affect the benefits and usefulness of systemic drug treatments for advanced HCC.

Methodology of included studies

Several key issues were identified across the studies included in this review, as shown in [Tables 5](#) and [6](#). Only a small number of studies addressed multiple comparators^[59-67], and only a few were based on real-world data^[29,86,87]. This is because nearly all studies relied on phase II/III trials^[90-103], with limited use of post-registration clinical evidence. With the notable exception of SORA, which was approved for use in the USA, Europe, and China between 2007 and 2008, and oxaliplatin-containing regimens approved in China in 2013, all other systemic agents have been approved more recently, from 2017 onward [[Supplementary Table 1](#)]^[106,107].

Post-registration, clinically focused economic analyses are crucial for better linking evidence to real-world practice. This is because initial drug prices typically decrease over time due to annual discounts, contracting, and competition from new therapies. Additionally, as treatments evolve, approved indications often expand to include patient groups not covered in registration trials^[90-103]. Patient selection in randomized clinical trials is usually stricter than in real-world settings, and exclusion criteria - such as bleeding, ascites, and liver decompensation - remain relevant for many patients needing treatment, especially considering their shorter lifespan^[90-103]. Finally, issues like temporary drug withdrawal, dose adjustments due to adverse events, and the use of surgery, radiological procedures, or switching drugs are not addressed in the original trials used for marketing authorization. Therefore, it is not surprising that the societal perspective was considered in only a small percentage of the included studies (5.5%), and that issues of concern to patients (e.g., access to care, work disability, loss of income, *etc.*) were overlooked in the current review.

Review sufficiency

We acknowledge that, since our review relies on the published literature, it may not encompass all relevant economic analyses on the topic. First, financial information on HCC treatments may be shared not only through scientific publications but also via manufacturers' reports, drug leaflets, digital media coverage, and administrative sources. Additionally, economic evaluations of systemic drug treatments might have been communicated only to hospital administrators and/or policymakers, rather than being included in peer-reviewed reports or publications. Furthermore, adjustments are often needed in health economic studies to account for inflation, disparities in resource allocation methods, and differences in pricing and reimbursement policies [such as disease-related group (DRG) tariffs, co-pays, and out-of-pocket systems]. These adjustments are not always reflected in scientific reports and often require experience with a specific national or regional market to incorporate them into comparative economic analyses. Finally, elements of current economic instability - such as increased tariffs on exports to the USA and reduced availability of components from manufacturing countries - can undermine the reliability of analyses and forecasts.

Results transferability

The transferability of the results of this review should therefore be interpreted with caution and considered within the context of each national or regional setting where systemic drugs for advanced HCC are used. Aside from the geographical differences and the methodological limitations previously mentioned, the ultimate cost-effectiveness of systemic treatments depends on the ICER/WTP ratio. The WHO guidelines recommend that the national WTP be set at a level aligned with per capita GDP, ranging from 1 to 3 times that amount^[33]. Since GDPs vary across and within countries, ICER/WTP ratios differ between studies and over time. Furthermore, although ICER/WTP measures access to treatment in a specific scenario, it often

does not fully reflect true cost-effectiveness. National or regional health authorities and administrators may override this ratio for treatments with proven clinical importance, such as those for malignancies or rare diseases, especially when effective options are limited. Policymakers and stakeholders might also implement policies that reallocate financial resources from less effective treatments to more costly ones, thereby increasing access for underserved populations.

Interestingly, the method commonly used to evaluate the cost-effectiveness of systemic therapies for advanced HCC in this review relies on direct comparisons between treatment regimens or schedules, such as ICI-containing regimens versus VEGFi. In nearly all included studies, SORA was used as the standard control against the experimental treatment arm(s). Although this reflects the design of the registration trials used for comparative economic calculations, real-world data suggest a shift from SORA to LEN, a decrease in the use of oral agents as first-line therapies following the advent of ICIs, and an increase in their use as second-line treatments for patients with limited tumor progression^[108,109].

Finally, the comparative approach used in the reviewed papers faces challenges due to the increasing adoption of combination strategies in clinical practice for the treatment of advanced HCC^[14,108,109]. While systemic therapies were initially viewed as alternatives for patients with advanced tumors who were ineligible for surgery (including resection and LT) or radiology-guided procedures, the current clinical landscape shows a growing use of combination approaches. These include systemic therapies, such as neo-adjuvant or adjuvant treatments, or bridging modalities to enhance surgical or radiological outcomes^[108,109]. One example of these innovative approaches is the recent approval by Chinese authorities of PEM in combination with LEN and TACE, emphasizing the need for appropriate methodologies to evaluate their cost-effectiveness in real-world settings.

How can the cost-effectiveness of systemic therapies be improved?

Building on the analysis of accessible comparative economic data, the secondary goal of this review was to raise awareness of strategies to enhance the cost-effectiveness of systemic therapies for advanced HCC. These strategies are shown in [Table 9](#) and are based on Bronfenbrenner's ecological systems theory^[110], which suggests that implementing interventions should involve three levels: the micro-level (the healthcare provider-patient dyad), the meso-level (healthcare organizations), and the macro-level (administrators, policymakers, stakeholders, and society at large). These initiatives should engage all participants involved in caring for patients with advanced HCC, including patients, healthcare providers, healthcare organizations, administrators, policymakers, stakeholders, and scientific societies, and should develop suitable methods to address the complexities of caring for advanced HCC patients.

In conclusion, our systematic review highlights significant variability in comparative economic analyses of systemic therapies for HCC across and within national and international settings. These differences mainly arise from study methodologies, time horizons, drug costs, and the perspectives used (such as societal versus healthcare systems), rather than from the sources of the datasets. However, based on current evidence, ICIs tend to be more cost-effective as first-line agents than any other active comparators studied. Among the oral agents, LEN is more cost-effective than SORA, and both SORA-PEM and LEN-PEM appear to be the most cost-effective sequencing strategies in the single study investigating these drug sequences. Changes in clinical practice, driven by the expansion of systemic therapies beyond their original indications and their combination with radiology-assisted techniques or surgery, necessitate aligning the methodologies of future studies with economic evaluations. A standardized approach to cost-effectiveness research, along with regular updates, is therefore essential given the rapidly evolving clinical landscape and the need to offer patients the highest standard of care.

Table 9. A list of suggested initiatives to increase the cost-effectiveness of systemic therapies for advanced HCC

Level	Initiative(s)	Expected outcome(s)
Micro (patient-healthcare provider interaction)	<ul style="list-style-type: none"> - Integration of multidisciplinary competencies/teams in clinical settings - Education/training of healthcare professionals on systemic therapies with special consideration to ICI-containing schedules and combination approaches - Close monitoring of patients' adverse effects, well-being, quality of life by integration of remote assistance approaches whenever possible - Empowerment of patients and family care givers to increase awareness, preparation and self-management - Prompt treatment of adverse effects - Regular follow-up visits 	<ul style="list-style-type: none"> - Improvement of treatment effectiveness - Reduction of patients' non-adherence - Reduction/mitigation of drug-related adverse effects - Improvement of patients' QoL - Improvement of patients' access to care - Reduction of the economic burden related to the incidence of adverse events, ancillary treatments and referrals - Reduction of physical and work disability - Improvement of LYs, QALYs and ICERs
Meso (healthcare organizations)	<ul style="list-style-type: none"> - Appointment of multidisciplinary teams for the treatment of HCC - Facilitation of competency integration into clinical practice - Facilitation of clinical data collection - Facilitation of interventional pharmacoeconomics, i.e., structured efficiency models to optimize treatment dosages, exposures, and durations - Implementation of real-world clinical studies - Implementation of care pathways within and across healthcare institutions to facilitate patient access to care - Care givers and stakeholders' involvement in the decision-making process 	<ul style="list-style-type: none"> - Improvement of treatment appropriateness - Reduction of unnecessary treatments - Improvement of drug-related side effects management - Integration of individual and societal concerns into clinical data collection
Macro (administrators, policy makers, stakeholders)	<ul style="list-style-type: none"> - Promotion of generic and biosimilar substitution - Shifting of reimbursement models from volume-based to outcome-based strategies - Facilitation of HTA models for advanced HCC - International referencing pricing, i.e., comparing international prices to adjust costs at regional/national levels - Implementation of publicly funded clinical trials to assess cost-effectiveness in real-world settings - Increase administrative efficiency to reduce overhead costs associated with drug contracting - Reduced approval timelines to accelerate drug marketing - Resource shifting according to disease epidemiology - Facilitation of public discourse on the economic metrics to be adopted for treatment of advanced HCC - Involvement of scientific societies and key opinion leaders in designing economic models to capture the economic metrics of cancer treatments 	<ul style="list-style-type: none"> - Reduction of drug prices - Increase of annual drug discount rates - Cost savings from reorganization of administrative models supporting drug delivery - Introduction of more reliable economic metrics to capture the complexities of cancer treatments

HCC: Hepatocellular carcinoma; ICI: immune checkpoint inhibitor; QoL: quality of life; LYs: life-years saved; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HTA: health technology assessment.

DECLARATIONS

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Authors' contributions

Conceived the study: De Simone P, Campani D, Vistoli F

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Drafted the manuscript: De Simone P, Longo D

Assessed the manuscript and addressed critical issues: Giuliani A, Vistoli F

All authors read and approved the final manuscript.

Availability of data and materials

The papers included in this analysis, along with their evaluation of inclusion and exclusion criteria, were stored on the Ryvan platform. Individual credentials secure access to data. Data will be made available upon request.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tools Rayyan and Grammarly were used solely for literature screening/management and language editing, respectively. These tools did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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De Simone P is an Editorial Board Member of *Hepatoma Research*. De Simone P was not involved in any stage of the editorial process, including reviewer selection, manuscript handling, or decision-making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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