

COMPARATIVE ECONOMIC ANALYSIS OF LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: A NARRATIVE REVIEW

Paolo De Simone^{1,2}, Daniela Peritore³, Juri Ducci⁴, Donato Longo⁵,
Daniela Campani^{2,6}, Raffaele Donadio³, Quirino Lai⁷

¹ Liver Transplant Program, University of Pisa Medical School Hospital, Pisa, Italy; ² Department of Surgical, Medical, Biomolecular Pathology and Intensive Care, University of Pisa, Pisa, Italy; ³ The Italian National Center for Transplantation, Rome, Italy; ⁴ Pisa University Hospital, Pisa, Italy; ⁵ Intensive Care Unit, Vito Fazzi Hospital, Lecce, Italy; ⁶ Pathology Department, Pisa University Hospital, Pisa, Italy; ⁷ Department of General and Transplant Surgery, La Sapienza University of Rome, Rome, Italy

Summary

We conducted a systematic review of comparative economic studies on liver transplantation (LT) for hepatocellular carcinoma (HCC). Outcomes included the types and number of cost-effective treatments, utility measures (such as quality-adjusted life years (QALYs) or life-years saved (LYS)), the incremental cost-effectiveness ratio (ICER), and the ratio of the ICER to the willingness-to-pay (WTP) threshold. The risk of bias was assessed using the ECOBIAS checklist. A total of ten references were included, comprising six studies based on real-world data involving 14,911 patients (1,741 patients who received LT; 13,170 patients who received alternative treatments). Four studies used simulated populations derived from international data. QALYs were reported in four studies; LYS in three, while three studies did not report utility measures. ICERs were provided in seven studies, and costs in three. WTP thresholds were reported in only five studies. Three studies compared LT to resection; two compared LT to both resection and radiofrequency ablation (RFA); two used multiple comparators, two examined downstaging procedures combined with LT *versus* LT alone, and one compared LT for HCC within to HCC beyond Milan criteria. In all studies with reported utility indicators (7/10), LT was associated with improved QALYs or LYSs, due to more prolonged survival and lower recurrence rates. Due to its upfront burden, LT was cost-effective for younger patients, those with lower alpha-fetoprotein levels, and those with shorter waiting times. Downstaging procedures improve LT cost-effectiveness, and trans-arterial radio-embolization (TARE) is superior to trans-arterial chemoembolization (TACE). Several methodological limitations were identified in the model structures and internal consistency. Due to the increased use of LT and the introduction of new comparators in clinical practice, a standardized methodology is necessary to align economic analyses with real-world practice (INPLASY registration number: 2025100049).

Key words: hepatocellular carcinoma, treatment; liver transplantation, cost, cost-effectiveness

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Correspondence

Paolo De Simone
E-mail: paolo.desimone@unipi.it

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Abbreviations

AFP: alpha-fetoprotein
 BCLC: Barcelona Clinic Liver Cancer
 BSC: best supportive care
 CA: cost-analysis
 CBA: cost-benefit analysis
 CEA: cost-effectiveness analysis
 CIT: carbon-ion therapy
 CMA: cost-minimization analysis
 COIA: cost-of-illness analysis
 CP: Child-Pugh
 CUA: cost-utility analysis
 DCD: donation after cardiocirculatory death
 ECD: extended criteria donors
 GDP: gross domestic product
 HAIC, hepatic artery infusion chemotherapy
 HBV: hepatitis B virus
 HCC: hepatocellular carcinoma
 HCV: hepatitis C virus
 ICER: incremental cost-effectiveness ratio
 ICI: immune checkpoint inhibitors
 INPLASY: International Platform of Systematic Review and Meta-Analysis Protocols
 LDLT: living donor liver transplantation
 LT: liver transplantation
 LYS: life years saved
 MP: machine perfusion
 MW: microwave
 OS: overall survival
 PFS: progression-free survival
 PSM: propensity score matching
 QALY: quality-adjusted life year
 RFA: radio-frequency ablation
 RWD: real-world data
 SBRT: stereotactic body radiation therapy
 SEER: Surveillance and End Results Medicare Registry
 SIRT: selective internal radiation therapy
 TACE: transarterial chemoembolization
 TARE: trans-arterial radio-embolization
 WHO: World Health Organization
 WTP: willingness-to-pay

INTRODUCTION

Liver transplantation (LT) is a resource-intensive procedure, with its economic burden depending on the initial surgery, intensive care resources, and long-term follow-up care ¹. The overall improvement in patient survival and transplant outcomes has come with a trade-off of significantly increased costs and questions about the cost-effectiveness of LT ^{2,3}. Several studies have confirmed the rising cost of LT ⁴⁻⁶. Factors contributing to increased

costs include the use of organs from extended-criteria donors (ECD) and broader organ distribution, which result in significant logistical expenses ⁴. Advanced technologies, such as machine perfusion (MP) devices, have further increased costs due to their high prices, proven benefits, and market monopolization ⁷. Moreover, living donor liver transplants (LDLT) and the use of donation after cardiac death (DCD) organs involve higher initial expenses but may offer long-term savings ^{4,7,8}.

The ability of modern healthcare systems to survive in today's cost-conscious environment relies on a better understanding of the costs and factors influencing therapeutic intervention expenses ⁹. This is especially crucial in cancer treatment, where increasingly expensive methods do not always result in significant improvements in quality or length of life ^{10,11}. Unfortunately, the failure to effectively control costs remains a major weakness of healthcare systems, and the rise in healthcare expenses is expected to continue unabated ¹².

Within the landscape of hepatocellular carcinoma (HCC), LT is a well-established treatment option ¹³, although alternatives include radiology-assisted interventions, surgery, systemic therapies, or combinations of these ¹⁴⁻¹⁸, with a steadily increasing cost ^{19,20}. Although their importance in clinical practice is widely recognized, economic factors have largely been overlooked in HCC management guidelines. The current global recommendations for HCC, such as the Barcelona Clinic Liver Cancer (BCLC) staging system ¹⁴, have not incorporated economic considerations into their frameworks. This is because there are significant variations in cost estimation methods across studies, countries, and healthcare systems, making it difficult to include economic factors in the literature on treatment effectiveness.

To address this gap, we have reviewed comparative economic studies of LT for HCC and examined their variations based on patient characteristics, tumor stages, institutions, and countries involved in the studies.

MATERIALS AND METHODS

Research design

This is a narrative review of comparative economic studies on LT for HCC, based on a review of the literature. The current review methodology follows the principles outlined by Sukhera in 2022 ²¹. This format was selected due to the wide range of study methodologies employed in the international literature on HCC treatment costs, aiming to offer a subjective critique of the available evidence and provide insights into how to advance the field from various or unconventional perspectives ^{21,22}. There is a consensus that narrative reviews are well-suited for

exploring controversial topics and offering new insights or perspectives in extensively researched areas²². Thus, we followed the five foundational steps described in previous publications²¹⁻²³.

Rationale for the review

The cost-effectiveness of treatments for HCC is vital for guiding clinical decisions. It requires regular updates due to the increasing number of treatment options introduced in recent years¹³⁻¹⁸.

The main goal of this research was to gather information on 1) the comparative economic effectiveness, utility, and benefits of treatment strategies for HCC; and 2) the factors affecting treatment costs, including insights from clinicians, hospital administrators, policymakers, patients, and stakeholders. It also examines international differences in financial issues related to healthcare providers, payers, and geographic regions. Within this broad context, this study focused on the cost-effectiveness of LT.

Research question

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

Within this framework, the current study's research question was: Is LT for HCC as cost-effective as alternative therapies?

Boundaries and definitions

The research methodology used the P (patients/disease), I (interventions), C (comparators), and O (outcomes) frameworks, in which patients were 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 version of the EASL (European Association for the Study of the Liver) guidelines for the treatment of HCC. These were categorized into 1) ablation; 2) intra-arterial therapies; and 3) systemic therapies²⁴. Ablation includes conventional or drug-enhanced radiofrequency (RFA) or microwave (MW) ablation techniques, selective internal radiotherapy (SIRT) or trans-arterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), liver resection (LR), and liver transplantation (LT). Intra-arterial therapies included hepatic artery infusion chemotherapy (HAIC) and trans-arterial chemoembolization (TACE). We also expanded the research strategies 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.

In line with internationally accepted definitions, comparative economic evaluations were classified as

cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-of-illness analysis (COIA)²⁵. COIA studies were excluded from this analysis because they did not include a treatment or disease population comparator²⁵. Notably, there is a significant overlap between these evaluations, especially between CEA and CUA^{25,26}. Some authors do not differentiate between CEA and CUA, whereas others view CUA as a subset of CEA²⁷⁻²⁹.

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) were used for the study eligibility criteria, quality assessment, and analysis of results³⁰. A PRISMA checklist for the abstract and paper is provided as supplementary material.

Comparative economic studies were retrieved using the following search terms: patient/disease, i.e., "hepatocarcinoma", "hepatoma", "hepatocellular carcinoma", "HCC", AND intervention comparators, i.e., "treatment", "management", "ablation", "radiofrequency", "thermal", "microwave", "surgery", "resection", "liver resection", "transplantation", "liver transplantation", "embolization", "chemoembolization", "transarterial therapy", "TACE", "transarterial chemoembolization", "HAIC", "systemic therapy", "VEGF", "VEGF inhibitors", "sorafenib", "lenvatinib", "regorafenib", "cabozantinib", "donafenib", "immunotherapy", "immune checkpoint inhibitors", "atezolizumab", "bevacizumab", "nivolumab", "durvalumab", "tremelimumab", "pembrolizumab", "ipilimumab", "toripalimab", "camrelizumab", "rivoceranib", "tislelizumab", "sintilimab", "sunitinib", "brivanib", "STRIDE", AND outcome, "cost", "economic", "resources", "financial", "cost analysis", "cost-effectiveness", "cost-utility", "cost-benefit", "saving", "acceptability".

Only full-length articles written in English or available in English translations were included. Systematic reviews, commentaries, empirical studies, gray literature, trade publications, and digital media communications were excluded and used solely to identify additional references not captured in the initial search. Due to multiple factors such as rising healthcare costs for HCC treatment³⁻⁵, recent advancements in medical technologies for HCC⁷, shifts in liver disease epidemiology with the emergence of metabolic dysfunction-associated liver disease (MASLD)³, and the increasing volume of publications on HCC, the literature review was initially limited to studies published between 2015 and June 30, 2025. However, if the thematic coverage was inadequate, a second search was performed without date restrictions, and key or seminal papers on the topic, along with other relevant manuscripts, were considered regardless of their publication date.

The references were first assessed independently by three investigators (PDS, DL, JD) based on the face value of their abstracts, with any disagreements resolved by a fourth reviewer (DP). The reference lists of the articles were also checked for additional literature (i.e., snowballing). An AI-based Ryyan platform was used to sort articles, evaluate abstracts and texts, and eliminate duplicates (<https://www.rayyan.ai/>). A shared Google Drive repository was utilized to gather and review articles from all team members.

After the papers were collected, at least three investigators from the study team independently reviewed them. The risk of bias for the included papers was assessed using the ECOBIAS tool, which comprises 23 items that explore overall and model-specific (data, structure, and consistency) biases in economic studies ³¹.

Sufficiency statement

Due to its narrative structure, we acknowledge that our review does not encompass all relevant literature on the topic. Several factors contribute to this limitation: 1) financial information on HCC treatments may have been shared not only through scientific publications but also via manufacturers' reports, leaflets, digital media coverage, and other sources; 2) economic evaluations of treatment procedures might have been provided to hospital administrators and/or policymakers only, rather than as part of peer-reviewed reports or publications; 3) adjustments are often necessary in health economic studies to account for inflation, disparities in resource provision methods, and differences in pricing and reimbursement policies (such as disease-related group (DRG) tariffs, co-pays, and out-of-pocket systems); 4) financial data may be available for all types of diseases treated by the interventions included in this analysis, meaning costs of LT and liver surgery may be reported for various indications (such as alcohol, liver steatosis, HCC, cholangiocarcinoma, colorectal liver metastases, etc.), but are not easily distinguished across these indications; 5) finally, elements of economic instability – such as increased tariffs on exported goods to the U.S. and reduced availability of components from producing countries – can undermine the reliability of future predictions. If thematic sufficiency or saturation was poor for a specific procedure, the research strategy was repeated to include previous eras and gray literature whenever feasible.

Data extraction and interpretation

Data extraction included the following variables: article year, author, title, study type, country, population description, intervention and comparators, and measures of effectiveness, specifically quality-adjusted life years (QALYs) or life-years saved (LYS). It also covers descriptions of costing methods, time horizon, discount rate (if any), currency, sensitivity analysis details, reported costs,

and economic metrics. The HCC stage was determined using the BCLC staging system, along with the type of intervention (curative or non-curative) ⁵. International currencies were converted to US dollars (US\$) using a currency conversion calculator ³². Owing to the narrative design of the current research, no inflation adjustment was made to the values reported in the original papers.

We used three main measures to evaluate the outcome of the retrieved economic comparisons: 1) QALYs and LYSs as indicators of clinical utility and effectiveness; 2) the incremental cost-effectiveness ratio (ICER) per QALYs/LYSs gained (or the incremental cost-utility ratio (ICUR)) as a measure of the additional costs associated with improved clinical outcomes; and 3) the ratio of ICER to willingness-to-pay (WTP) as an indicator of the intervention's cost-effectiveness. The WTP thresholds were based on those reported in the original papers. When these were not provided, we followed the World Health Organization (WHO) guidelines to calculate WTP as one to three times the per capita gross domestic product (GDP) ³³.

Data description and analysis

Clinical and demographic data were presented descriptively, including means, standard deviations (SD), medians, and percentages, as reported in the original papers. The missing data were not replaced. Means were further adjusted as weighted values from multiple series when appropriate. The medians were combined depending on data availability in the original papers. When raw data were unavailable, the medians were pooled using meta-analysis techniques. A random-effects model with inverse variance weighting was employed to combine medians from individual studies, accounting for expected variability and enabling generalization to broader populations. Monetary data are displayed in the original articles included in the analysis. When provided in foreign currencies, intervention costs were converted to 2025 US dollars using a conversion calculator ³². Data were tabulated, including the first author, year of publication, country explored (because the authors' nationality did not always correspond to the healthcare system analyzed), treatments and comparators, QALYs/LYSs, WTPs, and methodological considerations of interest (Tab. I). Finally, a summary of methodological differences was tabulated based on the ECOBIAS inputs (Tab. II).

Ethic issues

The current study was exempt from review by the investigators' ethics committee in accordance with current Italian national regulations. This study was registered with the International Platform of Systematic Review and Meta-Analysis Protocols (INPLASY) at www.inplasy.com (#INPLASY2025100049; <https://doi.org/10.37766/inplasy2025.10.0049>).

RESULTS

The outcomes of the search strategy

The article-sorting algorithm is illustrated in Figure 1. Starting with 30,500 references from the databases, 842 (100%) were screened based on abstracts because they potentially matched the study framework's objectives owing to general hints at economic considerations, and 164 (19.5%) 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 comparator, 9 (5.5%) involved wrong populations, 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.

Out of these 126 studies (100%), 54 (42.8%) focused exclusively on systemic therapies and were analyzed in a separate survey, while 72 (57.2%) centered on non-drug treatments. Specifically, 16 studies (12.6%) examined SIRT, 11 (8.7%) focused 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 treatments, 4 (3.2%) on different treatment modalities, and 2 (1.6%) on the combination of HAIC and systemic chemotherapy. Due to the limited number of retrieved studies, the research strategy was further expanded before 2015 by utilizing snowball sampling and database inquiry, as literature databases became established. This search found an additional five studies.

Among the 12 studies retrieved³⁴⁻⁴⁵, one was an umbrella review of previous studies on HCC in HCV patients by Chinese authors but did not include cost-comparison data³⁴. One study from the USA compared TARE to TACE as a downstaging method before LT³⁵. A German study examined the costs of LT among Milan-in and Milan-out HCC patients³⁶. Two studies from the USA compared LT to liver resection^{37,38}. One study compared LT to resection and RFA in the USA and France³⁹. One study compared LT to non-LT therapies in Italy and the USA⁴⁰. Another comparison was made between LT and transplantation preceded by adjuvant procedures in the USA and Italy⁴¹. A Singaporean study compared LT to resection for early HCC⁴². One US study used real-world data from the SEER database to compare outcomes of transplant, resection, liver-directed therapies, radiation, chemotherapy, or no treatment⁴³. A Canadian study utilized data from the Ontario Cancer Registry to compare the costs of illness associated with HCC *versus* non-HCC patients⁴⁴. In contrast, a study from Spain explored the cost-effectiveness of adjuvant therapies for HCC before LT⁴⁵. Based on the

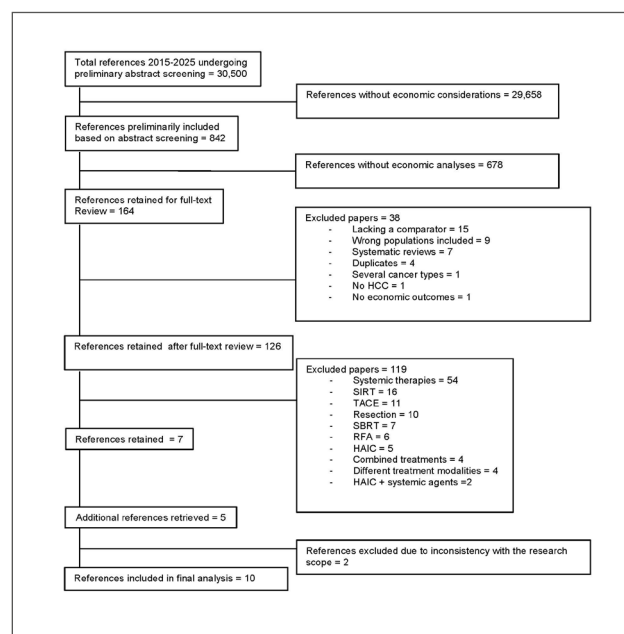


Figure 1. The search strategy algorithm.

current research scope, the Chinese study by Yan Y et al.³⁴ and the Canadian study by Thein HH et al.⁴⁴ were deemed inconsistent, and a final set of 10 papers^{35-43, 45} was selected. These studies were published between 2002 and 2024, including one in 2024³⁵, one in 2022³⁶, two in 2019^{37,38}, one in 2017³⁹, three in 2015⁴⁰⁻⁴², and another in 2015⁴³, as well as one in 2002⁴⁵. Table I illustrates the studies retained in the current analysis, while Table II shows the results of the ECOBIAS tool.

Population and treatments

Out of the 10 studies, 6 were based on real-world data (RWD) or registries involving a total of 14,911 patients^{35-38,40,43}. Of these, 1,741 (11.7%) were treated with LT, and 13,170 (82.3%) with non-LT therapies or best supportive care (BSC). The remaining 4 studies used simulated populations of patients derived from international studies^{39,41,42,45}.

Three studies examined the cost-effectiveness of LT compared to resection^{37,38,42}. Resection, RFA, and LT were explored in two studies^{39,41}. Multiple comparators were used in two studies^{40,43}. Two studies investigated adjuvant or downstaging strategies before LT using data from a real-world population in the United Network for Organ Sharing (UNOS) database³⁵ and a simulated cohort based on international data⁴⁵. One study assessed the cost-effectiveness of LT within and beyond the Milan criteria³⁶.

Perspective

A payor's perspective was used in four studies^{35,36,43,45}. A national/regional healthcare system perspective was

Table I. Results of comparative economic studies on LT for HCC.

#	First author (Ref)	Year	Country	Indication	Treatments	QALY ^a		ICER ^b	WTP ^c	ICER/WTP ^d	Methods/results interpretation
1	Wu X ³⁵	2024	USA	HCC downstaging before LT	TARE (#466) vs TACE (#649)	TARE = 2.51 TACE = 2.29		TARE vs TACE = US \$55,964	US \$100,000	0.55	• Data extracted from the UNOS database 2016-2021 • Payor's perspective • 5-year horizon • Markov model • Monte Carlo simulation for sensitive scenario analyses • TARE was more cost-effective than TACE. Namely TARE was more cost-effective in 89.24% of cases, for patients requiring 1 fewer loco-regional therapy before LT, and either before or after 2019 • TARE cost-effectiveness was stable across CP groups and AFP values • TACE was more cost-effective than TARE if 48.3% of patients received a transplant within 3 months after the procedure • TARE was more cost-effective than TACE when cost of TACE exceeded US\$4,831 or when the cost of TARE was lower than US \$43,542,023
2	Gundlach JP ³⁶	2022	Germany	HCC within and outside the Milan criteria undergoing LT	LT in Milan out (#56) vs Milan in (#46) HCC patients	Not provided		Not provided The authors described cost only, with median cost for Milan out (Euros 43,500) patients not statistically different from those of Milan in patients (Euros 30,300)	Not provided	Cannot be calculated	• Data extracted from an institutional database • The perspective was that of a German insurance provider • Costs were based on reimbursement policies • No time horizon was defined • No model structure was described • No sensitivity analysis performed • Costs of LT were not different in patients within and beyond Milan criteria • Cost drivers were lab-MELD points, multidrug resistant infections, dialysis, operation times, and transfusions, but not HCC stage
3	Skill N ³⁷	2019	USA	HCC in HCV positive patients (HCC stage was not clearly stated)	Resection (#20) vs LT (#24)	Not provided		Not provided The authors described costs only, with median cost of LT (US \$740,714) significantly higher than that of resection (US \$316,873) Annual cost of LT decreases for patients surviving > 5 years to a mean (SD) of US \$123,047 (11,670) Patients who received resection and survived > 2 years had a mean annual cost of US \$198,185 (87,642)	Not provided	Cannot be calculated	• Patients were identified through clinico-pathological records • No clear perspective was identified • Lifetime horizon • The analysis was based on billable encounters from date of diagnosis to death, last encounter or censor date • No model structure was described • No sensitivity analysis performed • Costs of LT were higher than for resection • The major cost driver was surgery for both treatment modalities • The value of each treatment was dependent on length of survival • Extended survival after LT (i.e., >2 years) dilutes the up-front load of surgery and costs per year decrease as the survival increases
4	Mickelakos T ³⁸	2019	USA	HCC in CPA cirrhosis (within Milan)	Resection (#95) vs LT (#89)	Not provided		Not provided Mean cost was lower for resection (US \$37,391) than for LT (US \$137,996)	Not provided	Cannot be calculated	• Patients were identified through institutional databases between 1992 and 2015 • Societal perspective used • Lifetime horizon • Cost data were derived from the Agency for Healthcare Research and Quality (AHRQ)/Healthcare Cost and Utilization Project (HCUP) database • ICD-9 codes were used to identify procedures and their respective costs • No model structure was described • No sensitivity analysis performed • Costs of LT were higher than for resection • The major cost driver was surgery for both treatment modalities

Table I. continues.

#	First author (Ref)	Year	Country	Indication	Treatments	QALY ^a		ICER ^b	WTP ^c	ICER/WTP ^d	Methods/results interpretation
5	Cadier B ³⁹	2017	France, USA	Surveillance and treatment for HCC	Resection vs. RFA vs LT in a fictive cohort of 1,000 patients	0.37 LYS for gold-standard monitoring vs real-life monitoring		France US \$1,754 for gold-standard monitoring US \$3,022 for RFA US \$6,387 for resection US \$23,594 for LT USA US \$32,415 for gold-standard monitoring US \$39,165 for RFA US \$38,776 for resection US \$164,557 for LT	Not provided	Cannot be calculated	• Only patients with compensated cirrhosis were considered • Data were extracted from the ANRS C012 CirVir and CHANGH cohorts. LT survival was derived from the Biomedicine Agency Report and RFA outcomes from case series • The perspectives used were those of the French and US healthcare systems • Markov model comparing gold-standard surveillance programs vs real-life practice • 10-year horizon • Annual discount rate 4% Implementing gold-standard surveillance programs for cirrhotic patients increases the cost-effectiveness of RFA over resection and LT
6	Vitale A ⁴⁰	2015	Italy, USA	HCC	LT vs non-LT therapies (RFA, TACE, resection or BSC) in a cohort of 2,419 patients not treated with LT	Italy: QALY of LT ranged from 6.5 to 1.8 according to the AFP model score (higher QALYs for lower AFP model scores) USA: QALY of LT ranged from 6.7 to 1.7 according to the AFP model score (higher QALYs for lower AFP model scores)		Italy: ICER LT ranged from US \$19,314 to US \$ 77,575 according to the AFP model score (higher ICER for higher AFP model scores) USA: ICER LT ranged from US \$32.941 to US \$115,933 according to the AFP model score (higher ICER for higher AFP model scores)	US \$50,000	Italy: NHB ranged from 3.0 to -2.0 according to the AFP model score (i.e., NHB was higher for lower scores) USA: NHB ranged from 2.5 to -2.0 according to the AFP model score (i.e., NHB was higher for lower scores)	• Data were extracted from the ITA.LI.CA database from 1988 to 2012 • A Markov model was constructed to calculate the utility of LT in patients not assigned to LT and using the AFP model as a framework for the analysis • The primary endpoint was the NHB (QALY-incremental costs/WTP) • Lifetime horizon • Costs were calculated in the Italian and US healthcare scenarios Both in Italy and the USA, LT was cost-effective for lower AFP model scores Cost-effectiveness of LT was sensitive to tumor features, patient age (< 60 years), liver decompensation (CPB, CPC) and lack of effective alternative treatments
7	Spolverato G ⁴¹	2015	USA, Italy	Early HCC in compensated cirrhosis	LT vs RFA or resection [strategy A] or LT after RFA/resection [strategy B])	Both in the USA and Italy, LT QALY was 0.2 and 1.0 over resection and RFA, respectively		Italy: LT vs resection US \$471,985 LT vs RFA US \$113,530 USA: LT vs resection US \$346,535 LT vs RFA US \$92,282	US \$50,000	NHB Italy: LT vs resection -1.7 LT vs RFA -1.3 USA: LT vs resection -1.2 LT vs RFA -0.8	• A Markov transition model was constructed from a case base of compensated patients within Milan criteria (55 years) • Transition probabilities were derived from published evidence • A lifetime horizon was adopted • Health-care provider's perspectives • The primary objective was NHB LT is not cost-effective except for younger patients, multinodular disease and shorter waiting times Salvage LT is not cost-effective

Table I. continues.

#	First author (Ref)	Year	Country	Indication	Treatments	QALY ^a		ICER ^b	WTP ^c	ICER/WTP ^d	Methods/results interpretation
8	Lim KC ⁴²	2015	Singapore, USA, Switzerland	Early HCC in CPA/CPB cirrhosis	LT vs resection	Resection = 3.9 LT = 5.3		USA: US \$115,743 Singapore: US \$111,821 Switzerland: US \$156,300	USA: US \$50,000 Singapore: US \$50,123 Switzerland: US \$51,507	USA: 2.3 Singapore: 2.2 Switzerland: 3.0	• A Markov transition model was constructed from a case base of compensated patients within Milan criteria (55 years) • Resection was the routine alternative against which deceased donor LT was evaluated • Transition probabilities were obtained from international reviews and the US and Singapore Organ Procurement Agencies • Lifetime horizon • Healthcare perspective • Annual discount rate 3%
											• LT is not cost-effective in any of the 3 countries • Cost-effectiveness of LT is sensitive to 5-year cumulative survival, one-time cost for LT, utility, per-month cost in year 2 and onwards, and the post-resection recurrence rate
9	Fadya S ⁴³	2013	USA	HCC stages I to IV	LT (#411) vs. resection (#829) vs liver directed (#1817) vs radiation (#483) vs chemotherapy (#924) vs no treatment (#6583)	LT had greater LYS for stage I, II, and unstaged patients Resection had greater LYS for stage III patients Liver directed therapies had greater LYS for stage IV patients		LT ICERs were US \$55,066, US \$38,337 and US \$93,351 for stage I, II and unstaged patients, respectively Resection ICER was US \$37,366 for stage III patients Liver directed therapies ICER was US \$33,940 for stage IV patients	Not provided	Not provided	• Data were retrieved from the SEER and Medicare registries for patients treated between 2000 and 2007 • Costs were assessed from Medicare's perspective • A partitioned survival analysis was adopted
											• LT was more cost-effective for stage I, II and unstaged patients due to higher survival benefit. • Resection was more cost-effective for stage III patients • Liver directed therapies were more cost-effective for stage IV patients
10	Llovet JM ⁴⁵	2002	Spain	Early HCC undergoing LT	1) adjuvant treatment (resection or percutaneous treatment (PEI) vs 2) standard management	The net gain in life expectancy (LE) in months was used Pre-transplant resection was associated with a net gain in LE of 4.8-6.1 months PEI was associated with a net gain in LE of 5.2 to 6.7 months and increased according to waiting list times		Marginal costs per life years gained was US \$40,000 for resection and US \$23,000 for PEI	US \$50,000	Resection = 0.8 PEI = 0.46	• Hypothetical cohort of patients with early HCC divided into 2 categories (resection vs PEI) • RFA was not considered due to unavailability of data on antitumoral activity at the time of publication • Markov model. Transition probabilities were derived from literature data • Payer's perspective • Lifetime horizon • Annual discount rate 3% • Quality of life estimates were not used, and effectiveness was based on survival only
											• Adjuvant treatments (resection or PEI) were cost-effective before LT vs LT alone • Cost-effectiveness was sensitive to waiting list times, risk of drop out and post-transplant survival • However, resection was particularly cost-effective for waiting times exceeding 2 years, while PEI retained cost-effectiveness for all waiting times

^a QALY is expressed as an increase or decrease versus the comparator; ^b ICER is expressed per QALY unit; ^c WTP is expressed per QALY unit; ^d If ICER/WTP > 1, the treatment is not cost-effective in the context explored.

AFP: alpha-fetoprotein; BSC: best supportive care; CP: Child-Pugh; CPA: Child-Pugh A; CPB: Child-Pugh B; CPC: Child-Pugh C; GDP: gross domestic product; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; ICD: international classification of diseases; ICER: incremental cost-effectiveness ratio; LE: life expectancy; LT: liver transplantation; LYS: life-years saved; MELD: model for end-stage liver disease; NHB: net health benefit; OS: overall survival; PEI: percutaneous ethanol injection; PFS: progression-free survival; QALY: quality-adjusted life years; RFA: radiofrequency ablation; RWD: real-world data; SD: standard deviation; SEER: Surveillance and End Results Medicare database; TACE: trans-arterial chemoembolization; TARE: trans-arterial radioembolization; WTP: willingness to pay.

Table II. The ECOBIAS checklist.

Part A: overall checklist for bias in economic evaluation			References									
			35	36	37	38	39	40	41	42	43	45
1	Narrow perspective bias	Was a societal perspective adopted? If not, has a different perspective been justified?	N/N	N/N	N/N	Y	N/Y	N/N	N/N	N/N	N/N	N/Y
2	Inefficient comparator bias*	Were the best alternatives chosen as comparator? Was current practice chosen as a comparator? Have all comparators been described in sufficient detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/N
3	Cost measurement omission bias	Were all costs relevant to the disease and intervention identified and considered?	Y	N	N	N	Y	Y	Y	Y	Y	Y
4	Intermittent data collection bias	Was the resource use measured continuously?	Y	U	U	U	Y	Y	Y	Y	Y	Y
5	Invalid valuation bias	Is the price calculation presented in a detailed manner? Have reference prices been used?	Y	Y	N	N	Y	Y	Y	Y	Y	Y
6	Ordinal ICER bias	Have cardinal scales for the outcomes measure in a CEA been used?	Y	N	N	Y	Y	Y	Y	Y	Y	Y
7	Double-counting bias	Are variables adequately checked for double-counting?	U	U	U	U	U	U	U	U	U	U
8	Inappropriate discounting bias	Have discounting rates from guidelines been applied?	Y	U	U	U	Y	U	U	Y	U	Y
9	Limited sensitivity analysis bias§	Have the four principles of uncertainty (methodological, structural, heterogeneity, parameter) been considered in sufficient data	N	N	N	N	Y	N	N	Y	N	Y
10	Sponsor bias	Have sponsorships been disclosed? Is the study protocol freely accessible?	Y/N	N/N	N/N	N/N	Y/N	N/N	N/N	N/N	N/N	Y/N
11	Reporting and dissemination bias	Has the study/trial been listed in a trial register? Have all results been reported according to the study protocol	N/U	N/U	N/U	N/U	N/U	N/U	N/U	N/U	N/N	N/U
Part B: Model-specific bias in economic evaluation												
I Bias related to structure												
12	Structural assumptions bias	Is the model structure in line with coherent theory? Do treatment pathways reflect the nature of disease?	Y	N	N	N	Y	Y	Y	Y	Y	N
13	No treatment comparator bias*	Is there an adequate comparator, i.e. care as usual?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
14	Wrong model bias	Is the model chosen adequate regarding the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	Limited time horizon bias	Was a lifetime horizon chosen? Were shorter time horizons adequately justified?	N	N	Y	U	Y/NA	Y/NA	N/Y	Y/NA	N/N	Y
II Bias related to data												
17	Bias related to data identification	Are the methods of data identification transparent? Are all choices justified adequately? Do the input parameters come from high-quality and well-designed studies?	Y/Y	N	N	N	Y/Y	Y/Y	Y/Y	Y	Y	Y

Table II. *continues.*

Part A: overall checklist for bias in economic evaluation			References									
18	Bias related to baseline data	Are probabilities, for example, based on natural history data? Is transformation of rates into transition probabilities done accurately?	Y/Y	N	N	N	Y/Y	Y/Y	Y/Y	Y	Y	Y
19	Bias related to treatment effects	Are relative treatment effects synthesized using appropriate metanalytic techniques? Are extrapolations documented and well justified? Are alternative assumptions explored regarding extrapolation?	Y	N	N	N	Y	Y	Y	Y	Y	Y
20	Bias related to quality-of-life weights (utilities)	Are the utilities incorporated appropriate for the specific decision problem?	Y	N	N	N	Y	Y	Y	Y	Y	N
21	Non-transparent data incorporation bias	Is the process of data incorporation transparent? Are all data and their sources described in detail?	Y	N	N	N	Y	Y	Y	Y	Y	Y
22	Limited scope bias§	Have the four principles of uncertainty (methodological, structural, heterogeneity, parameter) been considered?	Y	N	N	N	Y	Y	Y	Y	N	Y
III Bias related to consistency												
23	Bias related to internal consistency	Has internal consistency in terms of mathematical logic been evaluated?	Y	N	N	N	Y	N	N	N	N	N

* These biases are overlapping regarding their content; § These biases are overlapping regarding their content; N: no; NA: not applicable; U: unknown; Y: yes.

used in four studies³⁹⁻⁴². A societal perspective was used only once³⁸. No clear perspective was identified in one study³⁷.

Time horizons

A lifetime horizon was used in 6 studies^{37,38,40-42,45}. One study used a 5-year horizon³⁵. One study used a 10-year horizon³⁹. Two studies did not clearly specify the time horizon adopted^{36,43}.

Outcome measures

QALYs were provided in 4 studies^{35,40-42}. Three studies used LYS as measures of utility^{39,43,45}, while no utility or benefit measures were reported in 3 studies³⁶⁻³⁸. ICERs or marginal cost increments per utility measures were reported in 7 studies^{35,39-43,45}, while costs only were reported in 3 studies³⁶⁻³⁸. WTPs were provided in 5 studies only^{35-40-42,45}. A detailed illustration of the economic and utility items evaluated by each study is reported in Table II.

Treatment comparison

LT versus resection

Three studies compared LT to resection using real-world patient cohorts in two reports^{37,38} and a simulated population in one⁴². The two real-world studies focused solely on

costs, whereas the study from Singapore⁴² also provided utility measures. The survey by Skill et al used a cohort of hepatitis C virus (HCV) patients but did not include information on HCC stage³⁸; the study by Mickelkakos et al examined HCC within the Milan criteria in Child-Pugh (CP) A patients, while the study by Lim et al used a simulated population of patients with Milan-in-HCC in compensated cirrhosis⁴². LT was associated with higher costs than resection in all three studies, primarily due to the upfront surgical burden in transplantation compared to resection. In the only study that included utility measures, LT was not more cost-effective than surgery; however, its cost-effectiveness was sensitive to variables such as 5-year cumulative survival, one-time LT cost, utility, monthly costs in years 2 and beyond, and the post-resection recurrence rate⁴².

LT versus resection and RFA

Two studies compared LT with both resection and RFA^{39,41}. Both studies used simulated populations derived from international data or registries. The study by Cadier et al. examined the impact of surveillance programs for HCC on the cost-effectiveness of subsequent treatments in France and the USA³⁹, while Spolverato et al. explored two strategies: LT alone and LT after RFA or resection for patients

within Milan criteria and with compensated cirrhosis⁴¹. Cadier et al. found that implementing a guideline-based screening program for HCC in patients with cirrhosis results in cost savings and improved utility measures for HCC treatments in both France and the USA, with a greater benefit observed with RFA³⁹. Despite higher costs for resection and transplantation compared to RFA, all three procedures were cost-effective at a WTP threshold of US\$50,000 in France. In contrast, transplantation had a cost of US\$164,557 in the USA, well above this threshold³⁹. Using the net health benefit (NHB, calculated as incremental health gain minus incremental costs divided by WTP) as the primary measure of cost-effectiveness, Spolverato et al. demonstrated that transplantation provides better utility measures (i.e., increased QALYs) than both resection and RFA, but it is not cost-effective even in the salvage scenario. Its cost-effectiveness improves, however, for younger patients, shorter waiting times, and multinodular HCC⁴¹.

Multiple comparators

Two studies used multiple treatment comparators^{40,43}. Vitale et al.'s study modeled liver transplantation (LT) in a population of patients from a nationwide Italian registry, who had compensated cirrhosis and hepatocellular carcinoma (HCC) within Milan criteria, with a median age of 55, as the reference scenario⁴⁰. They calculated recurrence-free survival (RFS) and overall survival (OS) rates based on the AFP model⁴⁶. Their analysis employed utility measures from Italian and US databases, with NHB as the primary outcome measure⁴⁰. Despite the utility of LT being dominant over no-LT therapies under these conditions, its cost-effectiveness was not confirmed because LT incurred higher costs, and ICERs exceeded WTP threshold. However, LT's cost-effectiveness improved at lower AFP levels (indicating lower risk of post-transplant recurrence), in younger recipients, those with decompensated cirrhosis, and when no alternative therapies were available⁴⁰.

The paper by Fadya et al. retrieved data from the SEER registry between 2000 and 2007 and compared LT (411 patients), resection (829 patients), liver-directed therapies (1817 patients), radiation (483 patients), chemotherapy (924 patients), and no treatment (6583 patients)⁴³. Their study demonstrated that LT was more cost-effective for stage I, II, and unstaged patients due to higher survival benefit⁴³. Resection was more cost-effective for stage III patients, while liver-directed therapies were more cost-effective for stage IV patients⁴³.

Downstaging treatments before LT

Two studies examined the cost-effectiveness of pre-transplant downstaging therapies^{35,45}. A recent study from the USA compared the cost-effectiveness of TARE

(466 patients) with that of TACE (649 patients), using data from the UNOS database from 2016 to 2021³⁵. Despite the utility of both procedures in improving post-transplant survival rates, TARE was more cost-effective than TACE, especially for patients requiring one fewer loco-regional therapy before transplantation and regardless of the era considered³⁵. TACE was more cost-effective for patients receiving a transplant within 3 months after the procedure³⁵.

A Spanish study by Llovet et al examined the cost-effectiveness of resection or percutaneous ethanol injection (PEI) in a simulated group of patients with Milan criteria-in-HCC and compensated cirrhosis. Although the study's assumptions no longer accurately reflect current clinical practice, due to the limited use of PEI, both procedures were associated with improved utility of LT, resulting in increased post-transplant survival rates and reduced recurrence risk⁴⁵. Both procedures were cost-effective, but resection proved superior to PEI⁴⁵.

DISCUSSION

Although effectiveness is the primary outcome measure of 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 period⁴⁷. This applies to HCC, where treatment options have expanded over time, particularly after improvements in transplant, surgical, and systemic therapies¹³⁻¹⁸. The main goal of CEAs is to identify strategies that maximize health benefits within available resources or improve the value of money⁴⁷. However, the implications and limitations of this field are still not fully understood by clinicians⁴⁸. To evaluate the cost-effectiveness of LT in treating HCC, we conducted a narrative review of cost-comparative studies. This approach has been chosen due to the significant differences among the studies in research methods, data sources, time horizons, sensitivity analyses, case scenario simulations, perspectives, and countries studied³⁴⁻⁴⁵. A narrative review also serves as an ideal tool for highlighting innovative or unique pathways in the scientific field^{21,22}.

Overall, the most significant finding of our review was that the cost-effectiveness of LT for treating HCC has been minimally studied, particularly when compared to the numerous economic analyses examining the financial, human, and environmental resources utilized by LT¹⁻³. Our systematic review identified only 10 studies meeting the criteria for CEAs comparing LT with other treatment options, and their publication has been sporadic over the past 20 years^{35-43,45}. This may be due to the perceived difficulty in accounting for all direct and indirect costs involved in LT, particularly given the lifetime horizon

necessary to align economic analyses with clinical practice and societal interests, as well as the variation in clinical patterns across institutions and countries. Additionally, a lack of interest from clinicians may contribute to this scarcity of information, since the available literature on LT for HCC primarily focuses on optimizing patient selection criteria, improving pre- and post-transplant management strategies, minimizing tumor recurrence, and expanding the donor pool to maximize survival outcomes⁴⁹. In this regard, the new scenarios of LT involving immune checkpoint inhibitors (ICI)-based pre-transplant downstaging and MP technology await proper comparative economic evaluations versus no-LT treatments.

As a result, the available evidence does not fully align with the evolving clinical practices for HCC. Besides some outdated studies examining PEI as a downstaging technique before transplantation⁴⁵, most published research mainly compares LT, resection, and RFA for patients with early-stage HCC (i.e., within the Milan criteria)³⁵⁻⁴³. Even simulated study populations focus on case-based clinical scenarios from middle-aged, compensated cirrhotic patients, 55 years old, with early HCC⁴⁰⁻⁴². However, clinical practice is expanding its criteria for selecting HCC patients for LT⁵⁰, shifting from virus-related to MASLD-related cirrhosis⁵¹, and managing increasingly complex patients referred for LT². Even pre-transplant downstaging, bridging, and neo-adjuvant treatments often involve a combination of techniques to keep patients on the transplant waiting list⁵². These factors further increase the complexity of economic data needed for comparative analyses of LT for HCC patients.

The main finding of this review is that, although all studies with available utility measures have confirmed the clinical effectiveness of LT for HCC, its cost-effectiveness was demonstrated to a limited extent^{35-43,45}. This is due to the high cost of LT, especially regarding the upfront burden of surgery and the additional costs of medication required during long-term follow-up of recipients. This explains why LT is not considered superior to resection, particularly for early-stage HCC in compensated patients, where the curative potential of surgery is more easily achieved than for patients with advanced disease. Conversely, with extended follow-up, LT appears superior to surgery or loco-regional therapies, especially for younger patients, those with multinodular disease, lower alpha-fetoprotein (AFP) levels, more severe liver disease, and shorter waiting list times^{35-43,45}. In other words, the cost-effectiveness of LT for HCC is especially sensitive to factors that influence progression-free survival (PFS) and overall survival (OS), and case-specific analyses are necessary to identify patients with better cost-effectiveness margins.

Our review has inherent limitations, as indicated by the bias risk of the included studies, reported according to

the ECOBIAS checklist. Specifically, these risks stem from a frequently narrow economic perspective in data analysis, insufficient consideration of uncertainty principles in economic evaluations, underreporting of sponsor biases, inconsistent inclusion of utility parameters across studies, and frequent neglect of internal consistency assessments of the proposed models (Tab. II). A standardized methodology is highly favored for addressing these issues in future cost-comparative evaluations.

In conclusion, our narrative review highlights the limited availability and high risk of bias in the cost-comparative studies of LT for HCC patients identified in the international literature. Based on current methodologies, LT is cost-effective for patients with higher overall and recurrence-free survival rates post-transplant. However, the available evidence does not always reflect evolving clinical scenarios, and shared methodologies are necessary for future studies that include economic evaluations. A standardized approach to cost-effectiveness research, along with regular updates, is therefore crucial given the rapidly changing clinical landscape and the goal of providing patients with the highest quality of care.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

PDS, DL, QL: study design; DP, JD, DL, RD: data collection; PDS, DP, DL: drafting the manuscript; DP, JD, DL, RD, DC, QL: final manuscript review.

Data availability

The papers included in this analysis, along with their inclusion and exclusion criteria evaluations, were stored on the Rryan platform (www.rryan.ai). Individual credentials secure access to data. Availability of data will be granted upon request.

Ethical consideration

Not applicable.

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