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Comparative Economic Analysis of Systemic Therapies for Hepatocellular Carcinoma: A Narrative Review 2015-2025

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 October 2025 and was last updated on 14 October 2025.

INTRODUCTION

Review question / Objective What is the cost-effectiveness of first- and second-line therapies for the treatment of hepatocellular carcinoma?

The overarching research methodology 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. The therapeutic interventions were based on the 2025 version of the EASL guidelines for the treatment of HCC. They were categorized into 1) ablation, 2) intra-arterial therapies, and 3) systemic therapies. Ablation included conventional or drug-enhanced radiofrequency (RFA) or microwave (MW) ablative techniques; selective internal radiotherapy (SIRT) and stereotactic body radiation therapy (SBRT); liver resection (LR), and liver transplantation (LT). Intra-arterial therapies included hepatic artery infusion chemotherapy (HAIC) and transarterial 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 available studies, these treatments were considered either alone or in combination strategies.

Within this overarching research strategy, the current work focuses on first-line or second-line therapies for hepatocellular carcinoma used alone against a drug comparator or placebo or best supportive care.

Rationale The cost-effectiveness of treatments for hepatocellular carcinoma is crucial to guiding the decision-making process in clinical practice. Information on the cost-effectiveness of therapies for hepatocellular carcinoma requires regular updating due to the increasing number of drug agents and treatment strategies being introduced in recent years (5,13,15).

The primary goal of this research project was to gather information on 1) the comparative economic effectiveness, utility, and benefits of treatment strategies for HCC, and 2) the factors influencing treatment costs, including perspectives from clinicians, hospital administrators, policymakers, patients, and stakeholders. It also examines international differences in financial issues related to healthcare providers, payors, and geographic regions.

Condition being studied Treatment strategies for hepatocellular carcinoma.

METHODS

Search strategy The PubMed (PubMed.gov), Google Scholar (https://scholar.google.com/), Cochrane (Wiley Online), Scopus, Web of Science (WoS), and Embase (Embase.com) platforms were searched on July 1, 2025, for this study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines were used for study eligibility criteria, quality assessment, and analysis of results.

Participant or population Patients with hepatocellular carcinoma undergoing first-line or second-line systemic therapies not in combination with non-drug treatment(s), be it surgery, radiology-assisted techniques, or liver transplantation.

Intervention First-line or second-line systemic therapies for hepatocellular carcinoma.

Comparator Systemic therapies or placebo or best supportive care.

Study designs to be included Cost-comparative analyses, be it cost-effectiveness, cost-utility or cost-benefit analyses.

Eligibility criteria Full-length studies published in English between 2015 and June 30, 2025.

Information sources The PubMed (PubMed.gov), Google Scholar (https://scholar.google.com/), Cochrane (Wiley Online), Scopus, Web of Science (WoS), and Embase (Embase.com) platforms were searched on July 1, 2025, for this study.

Main outcome(s) 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, calculating WTP as three times the per capita gross domestic product (GDP).

Data management The artificial intelligence (AI)-based Ryyan platform was used for sorting articles, assessing abstracts, and removing duplicates (https://www.rayyan.ai/). A shared Google Drive repository was used to gather and review articles by all team members.

Quality assessment / Risk of bias analysis Due to the narrative design of the research, we will assess the risk of bias only qualitatively using the Joanna Briggs Institute (JBI) assessment checklist for qualitative research.

Strategy of data synthesis Clinical and demographic data are presented descriptively, including means, standard deviations (SD), medians, and percentages, as reported in the original papers. Means were further adjusted as weighted values from multiple series when appropriate. Medians were combined depending on data availability in the original papers. When raw data were unavailable, medians were pooled using meta-analytic techniques. In this case, 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 as in the original articles included in the analysis. When provided in foreign currencies, intervention costs were converted into 2025 US dollars using a conversion calculator.

Subgroup analysis Due 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; 2) studies comparing simultaneously multiple ICI- and oral-based regimens as first-line; 3) studies on head-to-head comparison of oral agents only as first-line therapy; and 4) studies on first- or second-line therapies versus placebo and/or BSC.

Sensitivity analysis None performed. The review is narrative.

Language restriction English.

Country(ies) involved Italy.

Keywords hepatocellular carcinoma; treatment; systemic therapies; oral agents; immunotherapies; first-line; second-line.

Dissemination plans Publication in a peer-reviewed journal.

Contributions of each author

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