RESEARCH ARTICLE

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A Network Meta-Analysis Comparing the Efficacy of Lenvatinib, Atezolizumab plus Bevacizumab, and Sorafenib in the Treatment of Unresectable Hepatocellular Carcinoma

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Abstract

Introduction: Globally, hepatocellular carcinoma (HCC) ranks as the third most common cause of cancer-related death. The five-year overall survival (OS) rate for patients with unresectable HCC is only 12%. Currently, systemic therapies have become the primary treatment options for unresectable hepatocellular carcinoma. Studies comparing the efficacy of first-line treatments including lenvatinib, atezolizumab plus bevacizumab, and sorafenib have shown inconsistent results. There remains a need for updated comparative evidence on cross-mechanism therapy regimens for unresectable disease, as existing findings are still not completely clear. This network meta-analysis aims to provide clearer insights into which treatment offers greater efficacy for patients with unresectable HCC. **Methods:** This study was conducted following the 2022 PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Literature searches were performed using PubMed, ScienceDirect, Google Scholar, the Cochrane Library, SpringerLink, and EBSCO to gather studies comparing lenvatinib, atezolizumab plus bevacizumab, and sorafenib for the management of unresectable HCC. The risk of bias was assessed using the Newcastle–Ottawa Scale (NOS). Overall survival (OS) was analyzed using R statistical software (version 4.4.0). **Results:** Eleven studies reporting overall survival (OS) were included in the OS analysis comparing lenvatinib, atezolizumab plus bevacizumab, and sorafenib in the treatment of unresectable HCC. The network meta-analysis showed no significant OS differences between atezolizumab plus bevacizumab and lenvatinib (HR: 0.98; 95% CI: 0.24–4.10) or sorafenib (HR: 1.4; 95% CI: 0.21–9.87). Furthermore, there was no significant difference in OS between lenvatinib and sorafenib (HR: 1.41; 95% CI: 0.38–5.14). Based on the SUCRA plot in this meta-analysis, atezolizumab plus bevacizumab showed the highest probability of being ranked first among the three therapies. Lenvatinib had the highest probability of being ranked second, while sorafenib was more likely to be ranked third. **Conclusion:** Atezolizumab plus bevacizumab, lenvatinib, and sorafenib demonstrated similar therapeutic efficacy based on overall survival. Although the hazard ratios (HRs) were not statistically significant, the SUCRA ranking suggested a clinical trend favoring atezolizumab plus bevacizumab.

Keywords: Atezolizumab plus bevacizumab- Hepatocellular carcinoma- lenvatinib- sorafenib

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Introduction

Hepatocellular carcinoma (HCC) represents the predominant primary malignancy of the liver in adults, accounting for approximately 75–85% of liver cancer cases worldwide, and remains the third leading cause of cancer-related mortality globally [1–3]. The global incidence of HCC continues to rise, with particularly high burdens observed in East Asia, sub-Saharan Africa, and parts of Southeast Asia, largely due to the endemic prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [4]. In addition to viral hepatitis, other recognized risk factors for HCC include chronic alcohol consumption, non-alcoholic fatty liver disease (NAFLD), diabetes mellitus, obesity, aflatoxin exposure, and genetic disorders such as hemochromatosis. The majority of HCC cases develop on a background of liver cirrhosis, which significantly complicates management due to the dual challenge of tumor progression and underlying hepatic dysfunction [5, 6]. HCC is the sixth most frequent cancer in the world, accounting for 70% of all primary liver malignancies. It is the third biggest cause of cancer-related

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death in the globe [5]. In Indonesia, the age-standard mortality rate for HCC is 7.7 per 100,000 people. This statistic is consistent with a 3-year HCC mortality rate of 94.4% reported in two cancer centres in Indonesia [7].

The prognosis of HCC is strongly influenced by tumor stage, liver function status as assessed by scores such as Child-Pugh and Albumin–Bilirubin score (ALBI) , and the feasibility of curative interventions including surgical resection, liver transplantation, and local ablation. The prognosis of HCC corresponds closely with tumour stage, with early detection associated with more than 70% survival rates at 5 years, whereas advanced stages can entail less than 20% survival rates in the same interval [5]. Unfortunately, a large proportion of patients are diagnosed at advanced stages when curative therapies are no longer feasible, rendering the disease unresectable (uHCC). In this population, the five-year overall survival (OS) rate remains dismal at approximately 12%, underscoring the urgent need for effective systemic therapies [8].

Over the past decade, systemic treatment strategies for uHCC have evolved considerably, moving beyond the historical reliance on sorafenib, a first-generation multi-kinase inhibitor that demonstrated modest survival benefits in the SHARP and Asia-Pacific trials. The therapeutic landscape has expanded to include immune checkpoint inhibitors (ICIs), such as anti–PD-1/PD-L1 antibodies, and combination regimens integrating targeted agents with immunotherapy [9]. Notably, lenvatinib, a potent multi-tyrosine kinase inhibitor targeting VEGFR, FGFR, and other kinases, has emerged as a first-line alternative to sorafenib after demonstrating non-inferiority in OS and superiority in progression-free survival (PFS) and objective response rate (ORR) in the REFLECT trial [10]. Similarly, the combination of atezolizumab, an anti–PD-L1 antibody, with bevacizumab, an anti-VEGF monoclonal antibody, achieved significant survival improvement over sorafenib in the IMbrave150 trial, marking a paradigm shift in first-line therapy for uHCC [11]. Similarly, in Indonesia, according to the HCC Procedures outlined by the Indonesian Ministry of Health, systemic therapy as the first-line treatment for HCC consists of sorafenib, atezolizumab, bevacizumab, and lenvatinib [12].

To achieve an apples-to-apples comparison, meta-analyses assessing the efficacy of lenvatinib, atezolizumab-bevacizumab, and sorafenib in unresectable hepatocellular carcinoma (uHCC) must use a common biological framework. All three regimens share a molecular base in that they target angiogenesis, a critical mechanism in HCC growth. Sorafenib, a groundbreaking systemic treatment for HCC, inhibits RAF kinase and VEGFR/PDGFR receptors, reducing cell proliferation and tumour blood vessel development. Lenvatinib broadens the anti-angiogenesis strategy by blocking VEGFR1-3, FGFR1-4, and additional pro-angiogenic pathways that lead to resistance to first-line treatments. Meanwhile, the atezolizumab-bevacizumab combination combines bevacizumab's VEGF inhibition which not only decreases neovascularisation but also enhances the tumour immunological environment with atezolizumab's stimulation of an antitumor immune response via PD-L1 blockage. These three medicines belong to a same molecular spectrum because they share anti-angiogenic properties and direct and indirect immunomodulatory effects, allowing for parallel, consistent, and relevant comparisons in meta-analyses.

Given the rapid evolution of systemic therapy for uHCC and the absence of conclusive comparative data between lenvatinib, atezolizumab plus bevacizumab, and sorafenib, this study aims to conduct a network meta-analysis to evaluate and compare the efficacy of these regimens. The findings are expected to offer valuable insights into the relative clinical benefits of these agents, guiding optimal treatment selection for patients with unresectable HCC and contributing to improved survival outcomes worldwide.

Materials and Methods

This NMA adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement [13]. This study has been registered in PROSPERO (ID CRD420251102000).

Literature Selection

The search was conducted across databases, including PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco. Additional manual searches of references were performed to prevent any oversights. The search terms utilized were " Unresectable Hepatocellular Carcinoma," "Lenvatinib," "Atezolizumab Plus Bevacizumab," "Sorafenib", and "efficacy". The Boolean operators used are as follows: ("Hepatocellular Carcinoma"[Mesh] OR "hepatocellular carcinoma" OR HCC OR "liver cancer" OR "liver carcinoma" OR hepatoma) AND ("unresectable") AND ("Lenvatinib"[Mesh] OR lenvatinib) OR (("Atezolizumab"[Mesh] OR atezolizumab OR "anti-PD-L1") AND ("Bevacizumab"[Mesh] OR bevacizumab OR "anti-VEGF")) OR ("Sorafenib"[Mesh] OR sorafenib OR nexavar)) AND ("efficacy" OR "treatment outcome" OR survival OR PFS OR OS)). The search period spans from January 10 2025 to July 30 2025. The study selected by I.K.W.A.K and I.G.A.P.S. under the supervisor of I.G.P.S. as investigator.

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were as follows: (1) Studies had to be randomized controlled trials (RCT) with or without blinding, published in English, either domestically or internationally, and observational studies (prospective and retrospective cohorts, case-control, or cross-sectional) were also eligible; (2) Patients aged 18 years or older with Unresectable Hepatocellular Carcinoma; (3) Studies comparing Lenvatinib (LEN) versus atezolizumab plus bevacizumab (ATE/BEV) or Sorafenib (SORA); (4) Outcome indicators included overall survival (OS); (5) Publications were restricted to those in English. The exclusion criteria included: (1) Duplicate publications; (2) Absence of a control group; (3) Conference abstracts and case reports.

Study Quality Assessment

Risk of bias was assessed by two independent investigators (NPSIR and CT.). The modified Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies evaluates three main aspects of study design: selection of study groups, comparability between groups, and outcome assessment. The overall quality score on this scale ranges from 0 to 9.

Data Extraction

The 2 researchers read the title and abstract independently, excluded the irrelevant literature according to the preset inclusion and exclusion criteria, and then read the full text to determine whether it was included. The missing data on the published articles were further completed by personal approach toward contacting the author. EXCEL was used to manage the data, and the extraction content included published information. The following data were extracted from each study: (1) basic information of the clinical trial, including authorship, publication date, and clinical trial registration number, author name, publication year, country, study design, sample size; (2) Basic characteristics of included patients, including gender distribution, age, Child-Pugh class, ECOG score, BCLC stage, etiology, follow-up time number of mortality; (3) Treatments of the experimental and control groups. The primary outcome for this meta-analysis was overall survival (OS). Hazard ratios (HR) and 95% confidence intervals (CI) for OS and PFS were also collected from the selected studies. A 95% confidence interval was included as one of the components in this analysis. When the data are presented as a survival plot using a Kaplan-Meier curve, the HR is calculated from the reconstructed data.

Statistical Analysis

Network meta-analysis was carried out based on the Bayesian model of Markov chain Monte Carlo method and R 4.1.3 was used for statistical analysis and graphics plotting, applying mvmeta, gemtc, and its packages.

When calculating effect size, the data of binary classification variables were expressed as hazard ratio (HR) were calculated with 95% confidence intervals (95%CI). Heterogeneity of comparisons was evaluated using I2. I2 > 30%, >50%, and >70% were considered as moderate, substantial and considerable heterogeneity. A fixed-effects model was employed to establish three independent Markov chains, each running 20,000 burn-in iterations followed by 50,000 sampling iterations. In this study, taking into account the potential heterogeneity between studies, a random-effect model was used. The iteration results of the Markov chains, represented as HRs and ORs, were used to rank the efficacy of the different treatment regimens, with the findings visualized through graphical representations.

The efficacy of different interventions was ranked according to surface under the cumulative ranking curve (SUCRA), The closer the SUCRA value is to 100, the more effective the drug is. For heterogeneity in the study meta-regression analysis were used to explore the source of heterogeneity. Lenvatinib was the drug that had the most direct comparison with other drugs in 11 included studies, and its effectiveness and safety had been verified by many clinical trials. Therefore, In the process of statistical analysis, Lenvatinib was used as the control of all drugs in this study for network meta-analysis. Publication bias was assessed using funnel plots.

Results

Literature Selection and Study Selection

A total of 1336 records were identified through the initial search from online databases (PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco). As many as 37 articles were removed for duplication, and 1122 studies were discarded after scanning the titles and abstracts. After a detailed reading and full text assessment, 157 articles were excluded cause by unmatched with the inclusion and exclusion criteria. As many as 9 studies lacked the related data. Finally, 11 articles were included in this analysis. The entire literature search process follows the PRISMA Guideline 2022 and is summarized through a flowchart as follows (Figure 1).

Characteristics of Included Studies

All eligible studies included a total of 3222 participants: 1453 in the lenvatinib group, 1225 in the sorafenib

Table 1. Newcastle Ottawa Scale Assessment of Bias

Study, Year	Selection				Comparability	Outcome			Total	Quality
Burgio, 2021 [14]	1	1	1	1	1	1	1	1	8	Good
Casadei-Gardin, 2020 [15]	1	1	0	1	1	1	1	1	7	Good
Tomonari, 2020 [16]	1	1	1	1	1	1	1	1	8	Good
Kim, 2020 [17]	1	0	1	1	2	1	1	1	8	Good
Rimini, 2021 [18]	1	1	1	0	1	1	1	1	7	Good
Kimura, 2024 [19]	1	1	1	1	1	1	1	1	8	Good
Su, 2022 [20]	1	1	1	1	1	1	0	1	7	Good
Hiraoka, 2022 [21]	1	1	1	1	1	1	1	0	7	Good
Kim, 2022 [22]	1	1	1	1	0	1	1	1	7	Good
Niizeki, 2022 [23]	1	1	1	1	1	1	1	1	8	Good
Hatanaka, 2023 [24]	1	1	1	1	1	1	1	1	8	Good

Table 2. Baseline Characteristic Studies

Study, Year	Study Design	Country	Drug	Number of Sample	Male (N)	Female (N)	Age		Child-Pugh class: A/B		ECOG score: 0–1/2		BCLC		Etiology		Follow up time	Number of Mortality	HR
							Range Age	Mean	A	B	0	>0	B	C	Viral	Non-viral			
Burgio, 2021[14]	Prospective	Italy	LEN	144	111	33	N/A	N/A	137	7	114	30	36	108	101	43	11 months	142	0.54 (0.27 - 0.73; p = 0.0115)
			SORA	144	119	25	N/A	N/A	134	10	114	30	36	108	89	55		98	
Casadei-Gardin, 2020[15]	Prospective	Italy	LEN	385	314	71	62.1-82-1	72.1	347	38	318	67	210	175	222	163	24 months	161	0.82 (0.62-1.08)
			SORA	552	42	510	51.1-74.1	62.6	489	63	266	286	69	483	405	147		397	
Tomonari, 2020[16]	Retrospective	Japan	LEN	52	36	16	53–88	70	27	25	38	14	27	25	33	19	20 months	46	0.92 (0.79 - 1.06)
			SORA	52	35	17	43-85	71	27	25	37	15	29	23	29	23		42	
Kim, 2020[17]	Retrospective	Korea	LEN	44	39	5	N/A	51.0-66.3	36	8	41	3	N/A	N/A	N/A	N/A	12 months	11	0.46 (0.26 - 0.80; p = 0.006)
			SORA	61	51	10	N/A	58.0-70.5	56	5	59	2	N/A	N/A	N/A	N/A		9	
Rimini, 2021[18]	Prospective	Italy	LEN	92	75	17	N/A	N/A	87	5	70	22	36	56	56	36	20 months	75	0.64 (0.45 - 0.91; p = 0.015)
			SORA	92	81	11	N/A	N/A	85	7	65	27	36	56	56	36		72	
Kimura, 2024[19]	Retrospective	Japan	LEN	41	35	6	58-86		N/A	N/A	29	7	N/A	N/A			46 month	30	0,63 (0,41-0,97)
			ATE/BEV	36	22	14	57-85		N/A	N/A	28	13	N/A	N/A				36	
Su, 2022[20]	Retrospective	China	LEN	46	38	8	39.8–86.9		41	5	24	22	16	30			12 month	17	0.812, 95%CI: 0.495–1.331; P= 0.812)
			ATE/BEV	46	38	8	38.4–83.9		40	6	18	28	14	32				16	
Hiraoka, 2022[21]	Retrospective	Japan	LEN	57	41	16	69-79		39	18	47	10	34	23			25 month	19	0.573 (95% CI: 0.341–0.963, p = 0.035)
			ATE/BEV	194	148	46	68-79		133	61	148	46	93	101				43	
Kim, 2022[22]	Retrospective	Korea	LEN	146	124	22	55-70		127	19	105	41	14	18			15 month	39	0.79; 95% CI, 0.44–1.41; p = 0.417
			ATE/BEV	86	70	16	56-71		82	4	36	50	132	68				19	
Niizeki, 2022[23]	Retrospective	Japan	LEN	152	127	25	31-93		N/A	N/A	N/A	N/A	78	68			54 month	48	p = 0.039
			ATE/BEV	152	118	34	51-93		N/A	N/A	N/A	N/A	81	67				36	
Hatanaka, 2023[24]	Retrospective	Japan	LEN	324	276	48	69-79		310	14	262	52	115	172	35	21	84 month	19	N/A
			SORA	324	276	48	70-80		310	14	274	50	122	172	264	112		274	

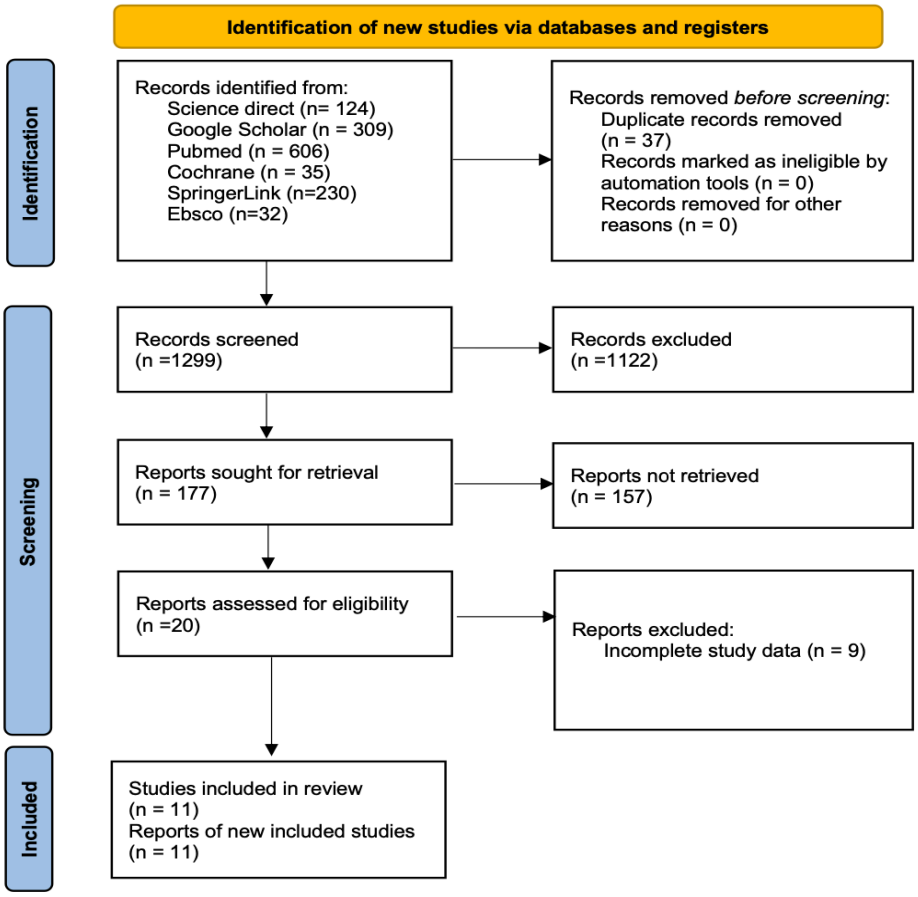

Figure 1. PRISMA Flowchart

group, and 514 in the atezolizumab plus bevacizumab. The published year ranged from 2020 to 2024. Based on study design, most of them are cohort study designs consisting of 3 prospective studies and 8 retrospective studies. The regions studied included Asia and Europe, with the majority (5 studies) from Japan, 3 studies from Italy, 2 study from Korea, and 1 study from China. The characteristics of the included studies are summarized in Table 2. Besides, the 11 cohort studies had NOS scores ranging from 7 to 8, indicating a high quality of data in all included studies (Table 1).

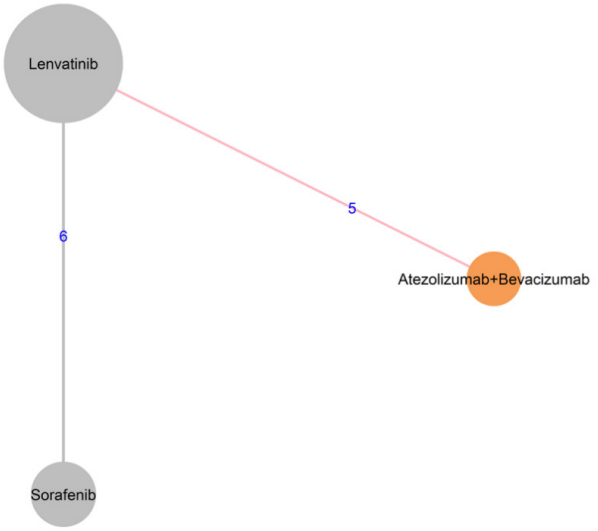

Figure 2. Network Diagram comparing the Overall Survival of lenvatinib, atezolizumab plus bevacizumab, and sorafenib in the treatment of unresectable hepatocellular carcinoma. All interventions were evaluated in their standard monotherapy or immunotherapy anti-VEGF combination forms without concomitant cytotoxic chemotherapy, and no chemotherapy backbone was included in any of the contributing studies. Comparisons were generated using the Bayesian framework.

Efficacy Analysis

Overall Survival (OS)

Eleven studies that reported OS were included in the OS analysis of lenvatinib versus atezolizumab+bevacizumab and sorafenib in the treatment of unresectable HCC (Figure 2, Table 3). The network meta-analysis showed no significant OS differences between Atezolizumab+Bevacizumab and Levatinib (HR: 0.98; 95%CI: 0.24-4.10) or Sorafenib (HR: 1.4 (CI: 0.21-9.87). Furthermore, there was no significant difference in overall survival between Lenvatinib and sorafenib (HR: 1.41; 95%CI: 0.38-5.14) (Figures 3, 4).

Although no strict cutoff exists, SUCRA is interpreted using relative, not absolute, thresholds: High SUCRA (>80%) means strong probability that the treatment is among the top performers and suggests best or near-best option in the network. Moderate SUCRA (50–80%) means treatment has a balanced probability of being in the upper-middle ranks. Low SUCRA (<50%) means the treatment tends to rank lower, but a low SUCRA does not

Table 3. League Table of the Overall Survival of Lenvatinib versus Atezolizumab+bevacizumab and Sorafenib in the Treatment of UnresectableHepatocellular Carcinoma based on Bayesian Network Meta-Analysis. An HR < 1.00 indicates better survival benefits

Comparison	Hazard Ratio (HR)	95% Confidence Interval
Lenvatinib vs Atezolizumab + Bevacizumab	0.98	0.24 – 4.10
Lenvatinib vs Sorafenib	1.41	0.38 – 5.14
Atezolizumab + Bevacizumab vs Lenvatinib	1.02	0.24 – 4.25
Atezolizumab + Bevacizumab vs Sorafenib	1.44	0.21 – 9.87
Sorafenib vs Lenvatinib	0.71	0.19 – 2.61
Sorafenib vs Atezolizumab + Bevacizumab	0.69	0.10 – 4.83

mean "ineffective", only that the treatment is less likely to be the best compared with others in the same network [25] (Figure 6).

Based on network meta-analysis data, the SUCRA graphic below shows the relative ranking probability of overall survival for three therapies for unresectable hepatocellular carcinoma: atezolizumab + bevacizumab, lenvatinib, and sorafenib. Each line reflects the cumulative probability that a therapy will rank among the top spots, with bigger curves signifying superior overall performance. Atezolizumab + bevacizumab had the highest SUCRA values across ranks, implying that it has the best chance of becoming the most successful treatment for OS. Lenvatinib has an intermediate but consistently favourable probability profile, implying a moderate-to-high chance of placing at the top. Sorafenib has the lowest cumulative ranking probability, indicating a lesser likelihood of being among the top-performing medicines. Overall, Atezolizumab+Bevacizumab showed the highest probability of being ranked first compared to the other two therapies. Lenvatinib had the most probability of being ranked second. Sorafenib actually had a higher probability of being ranked third (Figure 5).

Discussion

Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide, particularly in patients with chronic liver disease and cirrhosis. In advanced stages or when unresectable, systemic therapy becomes the primary treatment option [26–28]. Despite being a long-standing first-line therapy, sorafenib has shown limited clinical response, owing to its relatively weak anti-angiogenic effects and the rapid emergence of resistance via activation of alternative pro-angiogenic pathways such as FGF, PDGF, and MET. Lenvatinib is intended to target a larger spectrum of angiogenesis and tumour growth pathways, notably by inhibiting VEGFR1-3 and FGFR1-4, hence circumventing sorafenib's common escape mechanism. Meanwhile, the combination of atezolizumab and bevacizumab was pushed since new findings in HCC biology suggest that angiogenesis not only promotes tumour growth but also produces an immunosuppressive immunological milieu. Bevacizumab inhibits VEGF, which increases T lymphocyte infiltration and activation, hence boosting the benefits of atezolizumab's PD-L1 blocking treatment. The development of lenvatinib and combined immunotherapy-anti-VEGF reflects the need to

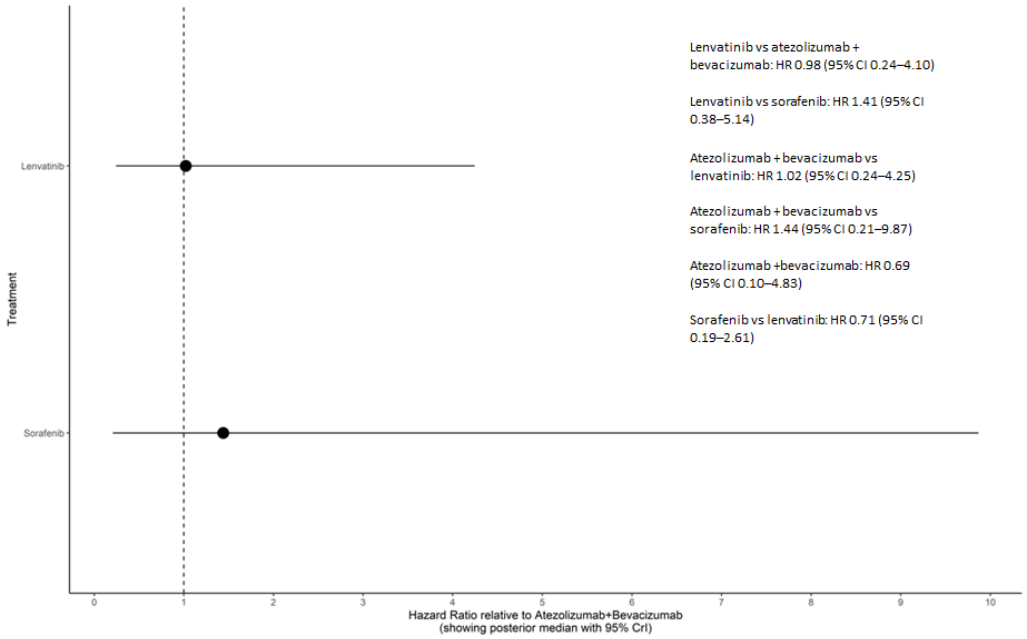

Figure 3. Quantitative Pairwise Hazard Ratios (HR) and 95% Confidence Intervals from the Bayesian Network Meta-Analysis Comparing Lenvatinib, Atezolizumab + Bevacizumab, and Sorafenib for Overall Survival

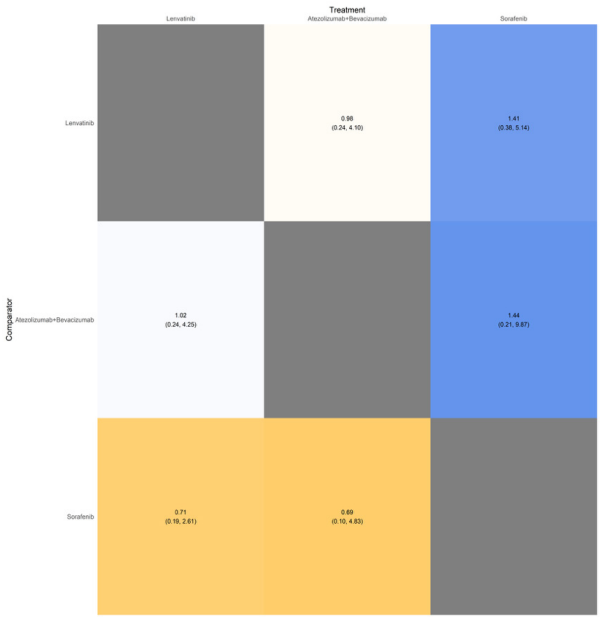

Figure 4. Heat Plot of the OS Analysis of Lenvatinib versus Atezolizumab+Bevacizumab and Sorafenib in the Treatment of Unresectable HCC

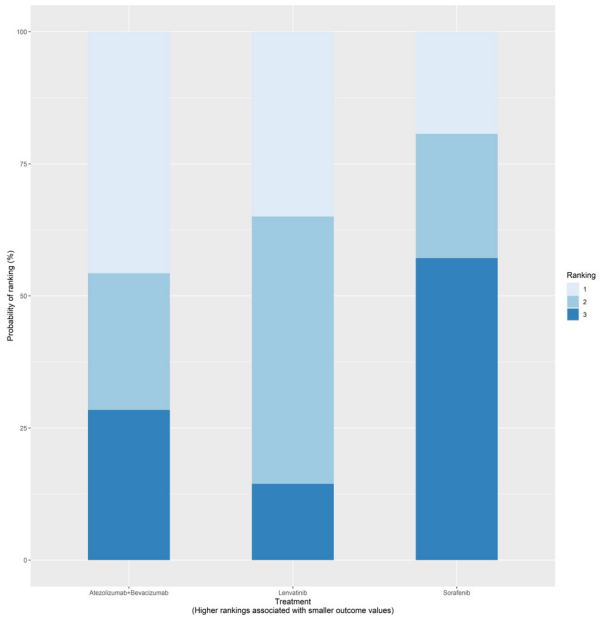

Figure 5. Rankogram of the OS Analysis Lenvatinib Versus Atezolizumab+Bevacizumab and Sorafenib in the Treatment of Unresectable HCC

overcome sorafenib's limitations, increase angiogenesis control, penetrate tumour biological resistance, and restore anticancer immune responses. Sorafenib, since its approval in 2007, has long been the first-line standard. However, its development was followed by the emergence of lenvatinib and the combination immunotherapy atezolizumab with bevacizumab, which has changed the treatment paradigm. Comparing the efficacy of these three therapeutic options is highly relevant for determining the optimal treatment strategy in patients with unresectable HCC [29, 30].

The results of this network meta-analysis showed no significant difference in overall survival (OS) between the combination of atezolizumab+bevacizumab and lenvatinib. Similarly, lenvatinib and sorafenib showed no significant difference. However, a ranking analysis based on SUCRA placed atezolizumab+bevacizumab as the therapy with the highest probability of providing the best OS, followed by lenvatinib, while sorafenib was in last place.

This finding is in line with evidence from the IMbrave150 clinical trial written by Finn et al. [31], which

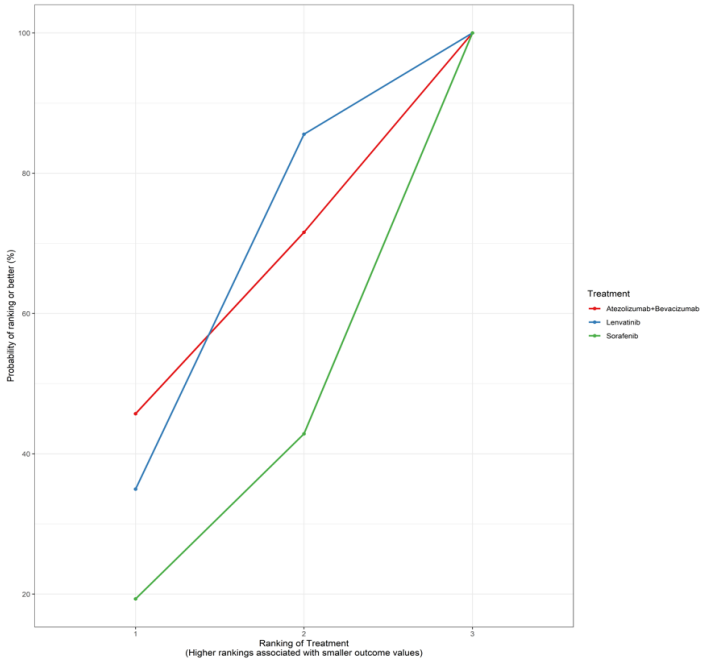

Figure 6. Sucraplot of the OS Analysis of Lenvatinib versus Atezolizumab+Bevacizumab and Sorafenib in the Treatment of Unresectable HCC

is a landmark study in HCC therapy. The study showed that over a follow-up period of 8.6 months, 28.6% of patients with atezolizumab–bevacizumab died, while this figure was 39.4% in the sorafenib group, with a hazard ratio for death reaching 0.58 (95%CI: 0.42–0.79; p <0.001). These results are supported by the 12-month overall survival rate in the atezolizumab–bevacizumab group, which was 67.2% (95% CI, 61.3 to 73.1) and 54.6% (95% CI, 45.2 to 64.0) in the sorafenib group [31]. The meta-analysis and the Finn study found similar results on the superiority of atezolizumab-bevacizumab over sorafenib, but they differed significantly in design and population characteristics, which could introduce bias. The Finn study was a phase 3 clinical trial with a 2:1 randomised design, a more homogeneous population, and strict inclusion-exclusion criteria, including a Child-Pugh A liver function test and varicose vein screening prior to bevacizumab therapy, which resulted in improved variable control and bias minimisation. Furthermore, the clinical trial standardised the regimen and timing of atezolizumab-bevacizumab and sorafenib, but variability in dose, adherence, and combination of supportive treatments may have influenced the cohort study's results [31].

Furthermore, the median PFS was also higher with the atezolizumab–bevacizumab combination. Our previous meta-analysis by Remitha et al. [32] also confirms that atezolizumab+bevacizumab is non-inferior than lenvatinib with no significant different on OS and PFS with hazard ratio of 0.72 (p = 0.20) and 0.90 (p = 0.23) respectively. The consistency of non-inferiority, even the superiority in the primary outcome, confirms that combination immunotherapy provides a superior survival benefit compared to tyrosine kinase inhibitors alone. Our analysis, which found no statistically significant difference between atezolizumab+bevacizumab and lenvatinib or sorafenib, may be explained by inter-study heterogeneity, limited study size, and design differences that make the results less robust than in head-to-head trials [32].

Meanwhile, the results of the analysis related to lenvatinib were consistent with the REFLECT trial, which demonstrated non-inferiority of lenvatinib to sorafenib. In that trial, the median OS was 13.6 months with lenvatinib versus 12.3 months with sorafenib, with a hazard ratio of 0.92 (95%CI: 0.79 – 1.06). Although not superior in OS, lenvatinib provided a significantly higher ORR, with an objective response rate of 18.8% (95%CI: 15.3 – 22.3) compared to 6.5% (95%CI: 4.3 – 8.7) in the sorafenib group (p<0.001). Furthermore, the median PFS in the lenvatinib group was 7.4 (7.3–9.1) months compared to 3.7 (3.6–5.4) months in the sorafenib group (HR: 0.61, 95%CI: 0.51–0.72; p < 0.001) [33]. This indicates that lenvatinib was able to control disease progression better, although the difference in OS was not significant, likely due to the influence of second-line therapy after progression [34].

Theoretical pharmacological considerations generally support the discovery that lenvatinib's VEGFR/FGFR-targeted anti-angiogenic mechanisms are highly effective in highly vascularised tumours, a common phenotype in HBV-associated and early-intermediate-stage BCLC C disease, which account for a sizable proportion of both datasets. The clinical character of the included populations may influence differences in the importance of the results obtained, particularly in terms of major factors of systemic medication response such as tumour stage, liver function reserve, and underlying aetiology. The heterogeneity among the included cohorts shows that subgroup variations must be examined. Patients with HCV-associated HCC, high AFP levels, or a substantial tumour load, for example, may have distinct angiogenic signalling pathways and immunological microenvironments, which could affect therapy response [34].

Systemic treatments for unresectable HCC differ in efficacy due to their varied modes of action and the various biological pathways that drive tumour growth in this extremely heterogeneous illness [8, 9]. Multikinase inhibitors, such as sorafenib and lenvatinib, primarily target angiogenesis by blocking VEGFR and other pro-vascular signals, delaying tumour growth in malignancies that rely heavily on neoangiogenesis [7, 9]. However, they do not directly engage the immune system. Immunotherapies, such as atezolizumab (anti-PD-L1) combined with bevacizumab (anti-VEGF), on the other hand, improve antitumor immunity while also normalising aberrant tumour vasculature, resulting in a more favourable microenvironment for immune cell infiltration [9]. This pathway has the potential to induce deeper and more persistent responses in tumours with significant immunogenic properties. The biological course of HCC itself, defined by underlying liver disease, aetiology, inflammation, fibrosis, and tumour genetics, also determines how these treatments operate [8, 9]. Sorafenib is a multi-kinase inhibitor that works by inhibiting RAF kinase and VEGFR [35, 36]. However, its inhibitory scope is relatively limited, so its antitumor effects primarily suppress angiogenesis and certain proliferation pathways. Lenvatinib, on the other hand, has a broader inhibitory profile, including VEGFR1-3 and FGFR1-4 [37, 38]. This FGFR targeting is important, as the FGF/FGFR pathway is known to play a major role in VEGF-resistant angiogenesis and HCC progression [39]. This may explain why lenvatinib often shows a higher objective response rate (ORR) than sorafenib, although this superiority does not always translate directly into a significant difference in overall survival (OS), as OS is also influenced by subsequent therapy and patient factors [29].

Several clinical and molecular factors can influence overall survival (OS) in HCC patients, explaining why medications such as lenvatinib may appear superior to other medicines in specific populations. From the standpoint of the patient, liver function (Child-Pugh/ALBI) is an important predictor of therapy duration and tolerability; patients with high liver reserve (Child-Pugh A) have a longer OS because they can maintain systemic therapy intensity for a longer period of time. Performance and fitness, as well as comorbidities, sarcopenia, and portal hypertension, all have an impact on therapy success and the likelihood of premature cessation [29].

The combination of atezolizumab and bevacizumab introduces a new paradigm by combining immunotherapy and anti-angiogenesis. Atezolizumab, as an anti-PD-L1

antibody, restores effector T cell function previously inhibited by the PD-1/PD-L1 checkpoint pathway [40, 41]. Bevacizumab's VEGF inhibition was thought to normalise tumour vascularization, diminish immunosuppressive signalling, and improve lymphocyte trafficking into the tumour. Atezolizumab, a PD-L1 inhibitor, then targets this more permissive environment, releasing inhibitory checkpoints that allow cytotoxic T cells to produce a more effective antitumor response. The atezolizumab-bevacizumab regimen advanced our understanding of immune escape mechanisms and suggested that targeting the VEGF-PD-L1 axis could overcome resistance to systemic treatments in HCC [40, 41]. However, this immune activity is often limited by the hypoxic and immunosuppressive tumor environment, in part due to VEGF activity. This is where bevacizumab plays a role, by normalizing tumor vasculature, reducing interstitial pressure, decreasing regulatory T cell infiltration, and increasing T lymphocyte homing into the tumor microenvironment. This synergistic interaction results in more effective antitumor immune activation than tyrosine kinase inhibitor monotherapy [42, 43].

The clinical implication of these findings underscores the growing necessity for highly individualized therapy in unresectable HCC, where treatment decisions should not rely solely on clinical eligibility or a clinician's empirical judgment. A biologically informed framework is required, in which several molecular and immunologic factors are systematically evaluated in the context of the immune microenvironment including PD-L1 expression, intratumoral CD8+ T-cell density, regulatory-to-effector T-cell ratios, interferon-γ–related transcriptomic signatures, and the microenvironment before determining the therapeutic regimen. Mutation profiling particularly alterations such as TP53, CTNNB1, TERT, and FGF-related pathways has been shown to correlate with tumor behavior and may identify clinically actionable variants that guide the selection of targeted or immunotherapeutic agents. Approximately half of patients with advanced HCC harbor molecular alterations that are potentially actionable and thus relevant for therapeutic stratification [44]. Similarly, assessment of drug-target protein expression, such as VEGF/VEGFR and FGFR signaling components, provides an important basis for predicting response to VEGF-directed agents or tyrosine kinase inhibitors for example, overexpression of FGF19 or its surrogate biomarkers has been associated with enhanced responsiveness to lenvatinib [45, 46]. In the context of immunotherapy, evaluation of immune-microenvironment characteristics including PD-L1 expression, intratumoral CD8+ T-cell density, regulatory-to-effector T-cell ratios, interferon-γ–related transcriptomic signatures, and spatial organization of immune infiltrates offers additional predictive insights beyond conventional clinical assessment. Advances in liquid biopsy, circulating tumor DNA, spatial transcriptomics, and multimodal biomarker integration further strengthen precision-based decision-making, ensuring that treatment selection is rooted in tumor biology rather than clinical guessing [47].

Within this precision-medicine framework, the combination of atezolizumab and bevacizumab should remain the primary therapeutic choice for patients with intact liver function, no contraindications to immunotherapy, and low risk of gastrointestinal bleeding. Lenvatinib stands as a rational alternative for patients who are not eligible for immunotherapy such as those with active autoimmune disease, prior organ transplantation, or constrained access and can be prioritized when molecular predictors indicate favorable response to FGFR- or VEGF-pathway inhibition. Sorafenib, although ranking lower in probability estimates compared with newer regimens, continues to hold clinical relevance in resource limited settings where drug availability and healthcare infrastructure may restrict access to more advanced therapeutic options, thereby ensuring equitable treatment pathways across diverse clinical environments [48]. The statistical insignificance of the OS comparison in this analysis must be understood in a methodological context. The wide range of confidence intervals reflects the limited number of studies, heterogeneity of study designs, and population variation. Factors such as liver function, etiology of liver disease (hepatitis B, hepatitis C, or non-viral), and history of variceal bleeding significantly influence both treatment choice and OS outcomes.

Furthermore, the use of post-progression salvage therapy differed across studies, potentially obscuring any real differences between regimens. This network meta-analysis's non-significant OS findings are most likely influenced by a number of major and minor limitations inherent in the included cohort studies. All of the included studies were observational rather than randomised, which introduced baseline imbalances in liver function, performance status, tumour burden, and patterns of subsequent therapy, all of which have a significant impact on survival and can dilute comparative effects. Significant clinical heterogeneity, caused by differences in aetiology (HBV, HCV, MASLD), BCLC stage distribution, ALBI grade, and regional treatment practices, complicates indirect comparisons, especially when the atezolizumab-bevacizumab arm has a much smaller sample size (n=514) than the larger lenvatinib and sorafenib cohorts, reducing statistical power. Variability in treatment regimens, dosing adjustments, and real-world adherence (especially for TKIs) all contribute to noise that can obscure true survival differences. Therefore, although the statistical data do not support absolute superiority, the direction of the SUCRA trend is consistent with biological understanding and data from large clinical trials [49–51].

The strength of this network meta-analysis lies not merely in the inclusion of eleven eligible studies, but in the ability of the analysis to generate a coherent comparative conclusion regarding the relative efficacy of atezolizumab+bevacizumab, lenvatinib, and sorafenib for unresectable HCC. By integrating direct and indirect evidence, this study provides a structured synthesis that clarifies the therapeutic hierarchy suggested by SUCRA ranking while simultaneously identifying areas in which statistical differences remain inconclusive. The analysis offers a comprehensive interpretation of survival outcomes, mechanistic plausibility, and the contextual factors that may influence treatment performance across heterogeneous populations. More importantly, the strength

of this work resides in its capacity to translate aggregated evidence into clinically meaningful recommendations while highlighting the biological rationale, methodological considerations, and implications for individualized therapy thereby contributing not only to evidence consolidation but also to improved decision-making frameworks in the management of unresectable HCC.

The absence of statistical significance and the breadth of the confidence intervals in this analysis are more appropriately understood as manifestations of methodological intricacies and biological heterogeneity rather than as deficiencies of the study. These patterns likely arise from substantial inter-study variability, encompassing differences in study design, underlying population characteristics, liver function reserve, tumor burden, disease etiology, and the use of subsequent lines of therapy, all of which can meaningfully influence comparative estimates within a network meta-analytic framework. From a theoretical standpoint, the complex biological diversity of HCC with its markedly variable angiogenic and immunologic profiles may further attenuate measurable differences across therapeutic regimens, particularly in analyses reliant on indirect comparisons. Taken together, these methodological and biological considerations underscore the need for cautious contextual interpretation and affirm that statistically non-significant outcomes should not be viewed as undermining the validity of the analysis, but rather as reflective of the inherent complexity of real-world HCC populations.

Although quality of life, toxicity, and etiology or liver function based subgroup analyses are clinically important, their absence in this study reflects the predefined scope of the analysis rather than a methodological limitation.

In conclusion, although atezolizumab + bevacizumab, lenvatinib, and sorafenib demonstrated comparable OS, Bayesian ranking suggested atezolizumab + bevacizumab had the highest probability of superior efficacy. Future large-scale randomized head-to-head trials and real-world studies are warranted to confirm these findings and assess safety and cost-effectiveness.

Author Contribution Statement

All authors contributed equally in the study processes. N.P.S.I.R. (Conceptualization, Formal Analysis, Data Curation, Investigation, Methodology, Project Administration, Validation); I.G.A.P.S (Data Curation, Investigation, Resources, Validation); I.K.W.A.K (Data Curation, Investigation, Resources, Validation); C.T.M (Software, Methodology, Formal Analysis); I.G.P.S (Formal Analysis, Methodology; Supervision, Validation); D.A.S (Formal Analysis, Methodology; Supervision, Validation); I.K.M (Supervision, Project Administration, Funding Acquisition, Validation).

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Ethical Declaration

This meta-analysis is a review article that do not have any ethical declaration file. Our systematic review and meta-analysis have registered on PROSPERO database with registration number of CRD420251102000.

Data Availability

The search was conducted across databases, including PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco. The data available based on the methods.

Study Registration

This study has been registered in PROSPERO (ID CRD420251102000).

Conflict of Interest

There is no conflict of interest on this systematic review and meta-analysis

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