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Original Article

Lenvatinib plus Immune Checkpoint Inhibitors versus Lenvatinib monotherapy as treatment for advanced hepatocellular carcinoma: a meta-analysis

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Abstract: Lenvatinib, an FDA-approved first-line oral multi-kinase inhibitor for advanced hepatocellular carcinoma (aHCC), has demonstrated promise for treatment. Nevertheless, findings from the Leap-002 study suggest that the addition of anti-vascular drugs to Lenvatinib may not yield significant improvements in survival rate. This meta-analysis aims to comprehensively assess the effectiveness of Lenvatinib, both as a standalone treatment and in combination with immune checkpoint inhibitors (ICIs), in managing advanced aHCC patients. We retrieved relevant studies published up to March 1, 2023, from databases such as PubMed, the Cochrane Library, Web of Science, and Embase. Subsequently, we conducted an analysis using REVMAN 5.3 and Stata MP 14.0 software, following quality assessment and data extraction procedures. A random effects model was employed to calculate the risk ratio (HR) using a 95% confidence interval (CI). The initial literature search yielded 921 results. However, after multiple rounds of exclusion and the removal of unrelated studies, 26 papers met the screening criteria. After a thorough examination of the full texts, we found that 8 studies met the analysis criteria. The combination of Lenvatinib with ICIs demonstrated significant improvement in overall survival (OS) (HR=1.53, 95% CI: 1.34-1.74; P<0.001) and progression-free survival (PFS) (HR=1.51, 95% CI: 1.34-1.72; P<0.001). Furthermore, subgroup analysis, categorized by the duration of follow-up, revealed that for the 3-year combined OS (HR=2.21, 95% CI: 1.79-2.73; Z=7.40, P<0.05), the combination therapy significantly outperformed monotherapy, leading to a 2.21-fold increase in OS for patients during the 3-year follow-up period. Nevertheless, for non-3-year combinations (HR=1.206, 95% CI: 1.020-1.425; Z=2.19, P<0.05), there was merely a 1.206-fold increase in effectiveness compared to single therapy for follow-ups of both longer and shorter durations. This might be attributed to the insufficient representation of HBV-related aHCC cases and the Asian population in the study, along with the increased availability of second-line treatment options for advanced cancer, which can influence the observed effectiveness of immunotherapy.

Keywords: Lenvatinib, inhibitor, angiogenesis, hepatocellular cancer

Introduction

Liver cancer, ranking as the fourth most prevalent digestive system tumor among the leading causes of cancer-related deaths worldwide [1, 2], primarily comprises hepatocellular carcinoma (aHCC), which represents 70-85% of all liver cancer cases [3]. Surgical resection or liver transplantation stands as the most effective treatment for early aHCC [4]. However, the asymptomatic nature of aHCC in its early stages often results in the clinical diagnosis of locally advanced or metastatic disease, diminishing the likelihood of controlling tumor growth through surgery and leading to an unfavorable prognosis [5, 6].

Sorafenib was approved as the first systemic therapy for advanced aHCC, based on the findings of the SHARP and Asia Pacific trials [5, 7]. Nevertheless, for patients with advanced aHCC, there is a limited array of first-line treatment options when undergoing systemic therapy with Sorafenib [7-10].

Recently, Masatoshi Kudo et al. reported the results of the REFLECT trial, indicating that, in terms of overall survival (OS), Lenvatinib was

not as effective as Sorafenib. However, concerning all secondary efficacy endpoints, Lenvatinib exhibited statistically significant improvements on all of the secondary efficacy endpoints within the Lenvatinib group [11].

The rationale behind combining Lenvatinib with immune checkpoint inhibitors (ICIs) lies in Lenvatinib's dual capacity to inhibit angiogenesis and immunosuppression in the tumor microenvironment. This inhibition enhances the antitumor immune response and subsequently improves the clinical benefits of ICIs [12, 13]. Experimental data suggest that this combination holds promise for the treatment of liver cancer. In a mouse model of liver cancer, Lenvatinib combined with PD-1 signal blockade exhibited a promising anti-tumor effect when compared to any other therapeutic option [9]. However, findings from Leap-002 indicate that the combination of Lenvatinib with ICIs does not significantly enhance efficacy over the use of Lenvatinib alone, suggesting a need for further studies to provide more conclusive insights [14].

In the context of network meta-analysis (NMA), the best method for systematically reviewing and summarizing the available evidence regarding different treatment strategies without the need for direct comparison is a network meta-analysis. The primary endpoint was OS, while the secondary endpoint was PFS.

Materials and methods

Search strategy

To compare the effectiveness of first-line systemic therapy for aHCC, we conducted a network meta-analysis. The experiment includes the following characteristics: (1) Evaluates Lenvatinib and Lenvatinib combined with ICIs as first-line monotherapy; (2) Evaluates OS or PFS as the primary endpoint; (3) Inclusion of local area therapy alone or in combination with systemic therapy was not permitted. From January 1, 2021, to March 1, 2023, search the PUBMED database, WEB OF SCIENCE database, EMBASE database, and COCHRANE database only. Several major scientific societies in oncology, including the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), have published meeting minutes published as of March 1, 2023.

Ensure that the literature search is conducted in accordance with the standard reporting items for systematic reviews and meta-analyses. The PUBMED, COCHRANE LIBRARY, WEB OF SCIENCE, and EMBASE databases were searched from the beginning to March 1, 2023, to determine the efficacy of Lenvatinib and Lenvatinib combined with ICIs in aHCC. The search keywords or medical subject word (MESH) terms are as follows: Neoplasms, Hepatic, Neoplasms, Liver, Cancer of Liver, Hepatocellular Cancer, Lenvatinib and Inhibitor, Angiogenesis. The search strategy used in PUBMED is as follows: (((Lenvatinib) OR (Lenvima)) AND ((Neoplams, Hepatic) OR (Neoplams, Liver) OR (Cancer of Liver) OR (Hepatocellular Cancer) OR (Liver Cancer)) AND ((Angiogenesis Inhibitors) OR (ICIs)) OR (Inhibitor, Angiogenesis) OR (Angiogenesis Agents)). To identify other potentially qualified studies, the references in the study or related review are manually reviewed. Articles not written in English are excluded from literature search.

To extract the data, the three authors independently reviewed the full texts of eligible studies. Plenary meetings resolve any differences or disagreements in collected data through consensus. To extract the data, we used a table that contained the following items: the lead author, the publication date, the region, the study type, the sample size, the drug dose, as well as the main outcome indicators. Based on the reported number of events and the relevant *P*-values derived from logarithmic rank statistics, the risk ratios of the event time variables (OS and PFS) are directly extracted from the original study. **Table 1** introduces the 8 references under the PICOS principle.

Inclusion and exclusion criteria

A third author was consulted to resolve any differences between the two authors after the two independently screened the initial search results. For inclusion in the study, prospective or retrospective studies comparing Lenvatinib and Lenvatinib combined with ICIs for the treatment of aHCC had to meet the following criteria: (1) Inclusion of patients diagnosed with aHCC who received either Lenvatinib combined with ICIs or Lenvatinib monotherapy, regardless

Table 1. Eight references under the PICOS principle

	P (population)	I (intervention)	C (comparison)	O (outcome)	S (study design)
Fugun Wei 2021	Advanced aHCC	Lenvatinib plus Camrelizumab	Lenvatinib	Effectiveness and Safety	Cohort
Kang Chen 2022	Unresectable aHCC	Lenvatinib plus ICIs	Lenvatinib	Effectiveness and Safety	Cohort
Lei Zhao 2022	Unresectable aHCC	Lenvatinib plus Sintilimab	Lenvatinib	Effectiveness and Safety	Cohort
Qi Li 2022	Unresectable aHCC	Lenvatinib plus Camrelizumab	Lenvatinib	Effectiveness and Safety	Cohort
R.S. Finn 2022	Advanced aHCC	Lenvatinib plus Pembrolizumab	Lenvatinib	Effectiveness and Safety	RCT
Wen-Chi Wu 2022	Advanced aHCC	Lenvatinib plus Nivolumab	Lenvatinib	Effectiveness and Safety	Cohort
Xiaohui Wang 2023	Advanced aHCC	Lenvatinib plus ICIs	Lenvatinib	Effectiveness	Cohort
Yu-Xian Teng 2022	Advanced aHCC	Lenvatinib plus ICIs	Lenvatinib	Effectiveness	Cohort

of additional treatments; (2) Provision of reliable data for the comparison between combination therapy and Lenvatinib monotherapy; (3) Reporting of treatment outcome indicators, such as Overall Survival (OS) or Progression-Free Survival (PFS); (4) Reporting of Hazard Ratios (HR) with 95% Confidence Intervals (95% CI), directly obtainable.

Exclusion criteria: Studies were excluded if they met any of the following criteria: (1) Publication types: case reports, letters, animal trials, reviews, conference abstracts; (2) Reporting of survival curves and *p*-values without HR and 95% CI; (3) In cases of repeated publications or overlapping populations, only the latest and most comprehensive studies were included; (4) Studies not published in the English language. Whenever feasible, the most recent and comprehensive data from the same study were included in cases of repeated studies.

Quality assessment

Using the Newcastle Ottawa Scale (NOS) [15] or the JADAD scale, quality was assessed in cohort studies and randomized trials [16]. A NOS score greater than 6 is considered high-quality research, and a JADAD scale score greater than 2 is considered high-quality.

Statistical analysis

Statistical analysis was conducted using REVMAN 5.3 and Stata MP 14.0 software. In this meta-analysis, the primary endpoints were Overall Survival (OS) and Disease-Free Survival (DFS), with effect sizes represented by Hazard Ratios (HRs) and 95% confidence intervals. To evaluate binary variables, we used a 95% confidence interval. Heterogeneity between studies was assessed using the Cochran's Q test (C2) and the I^2 index. Heterogeneity was considered significant when I^2 exceeded 50% or when the *p*-value was less than 0.1. In cases of significant heterogeneity, we employed a random effects model for data synthesis; otherwise, a fixed effect model was used. Funnel plots were examined to detect potential publication bias, and a sensitivity analysis was performed by sequentially excluding each study to assess its impact. Statistical significance was defined as $P<0.05$.

Results

Literature search

Preliminary searches initially yielded 921 records. After removing 589 duplicates and reviewing titles and abstracts, 301 records were excluded. A detailed examination of full texts resulted in the exclusion of 26 more articles. These exclusions included 6 reviews, 3 studies lacking case controls, and 17 without relevant data. Consequently, eight articles were included for analysis [6, 14, 17-22]. **Figure 1** illustrates the literature selection process.

Study characteristics and quality assessment

All eligible studies involved a total of 1594 participants: 759 in the Lenvatinib group and 835 in the Lenvatinib combined ICIs group. These studies encompassed regions in Asia, Europe, and North America and were published between 2021 and 2023. Consistently, the drug was administered at a specific dosage. Patients weighing more than 60 kilograms received an initial dose of 400 mg twice a day, while those weighing less than 60 kilograms received 12 mg once a day or 8 mg once a day. Detailed

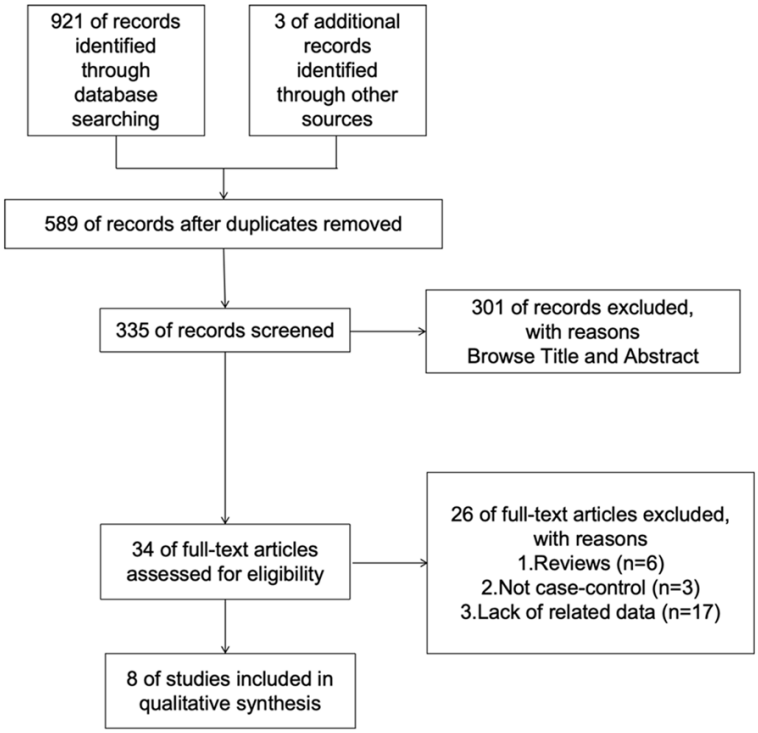

Figure 1. Flow chart of the study selection process.

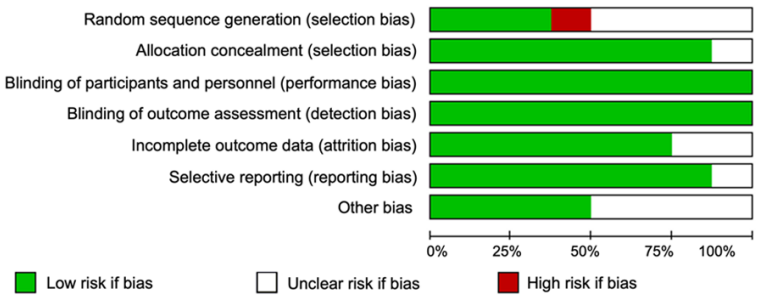

Figure 2. Assessment of risk of bias for RCT. Risk of bias graph.

results of the risk of bias assessment of the included studies are shown in **Figure 2**.

Efficacy analysis

Eight studies, involving 1594 patients [6, 14, 17-22], were analyzed for OS and PFS. Heterogeneity testing revealed an I^2 of 66% (>50%) and a Q test *p*-value of 0.004 (<0.1), indicating moderate heterogeneity between the selected studies (**Figures 3**, **4**). Given this heterogeneity, a random-effects model was employed for meta-analysis. The random-effects meta-analysis showed that for combined OS, the Hazard Ratio (HR) was 1.53 (95% CI: 1.34-1.74), which was statistically significant (z=6.33, P<0.001). In other words, patients receiving Lenvatinib combined with ICIs had a higher OS compared to those on Lenvatinib alone, with the combination being 1.96 times more effective. For combined PFS, the HR was 1.51 (95% CI: 1.34-1.72), (z=6.50, P<0.001). PFS was 1.51 times higher for patients on Lenvatinib combined with ICIs compared to those on Lenvatinib alone.

Sensitivity analysis

Removing any literature from this study will not impact the stability and reliability of the calculated results from the random-effects analysis (**Figure 5**).

Bias test

An analysis of funnel plots of OS and PFS was conducted to determine whether there are any publication biases affecting our research. The funnel plots of these studies are asymmetric (**Figure 6A**, **6B**), so we further conducted bias tests on them and found that OS (P=0.004<0.05) and PFS (P=0.007<0.05) indicate publication bias, which requires pruning to correct for bias.

Correction of bias by pruning and patching method

We used the pruning and patching method to correct the funnel plot asymmetry in OS. After four iterations, we obtained a virtual simulation for two articles. With a total of 10 pieces after this correction, there were no publication biases. The combined effect size for these 10 pieces resulted in an HR of 5.95 (4.09, 9.55) (**Figure 7A**). For PFS, after three iterations, we generated virtual literature results for two articles. After pruning, there were no publication biases among the 10 remaining pieces. Combining these nine pieces of literature produced an effect size HR of 5.94 (3.91, 10.24) (**Figure 7B**).

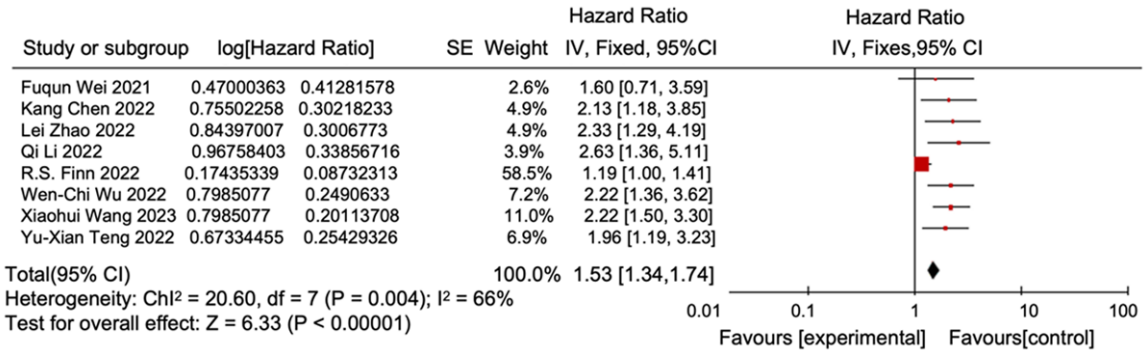

Figure 3. Forest plot on OS. OS, overall survival.

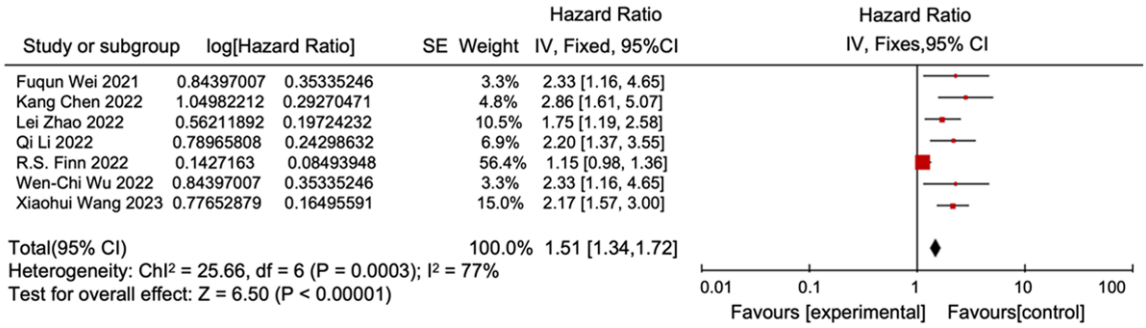

Figure 4. Forest plot on PFS. PFS, progression-free survival.

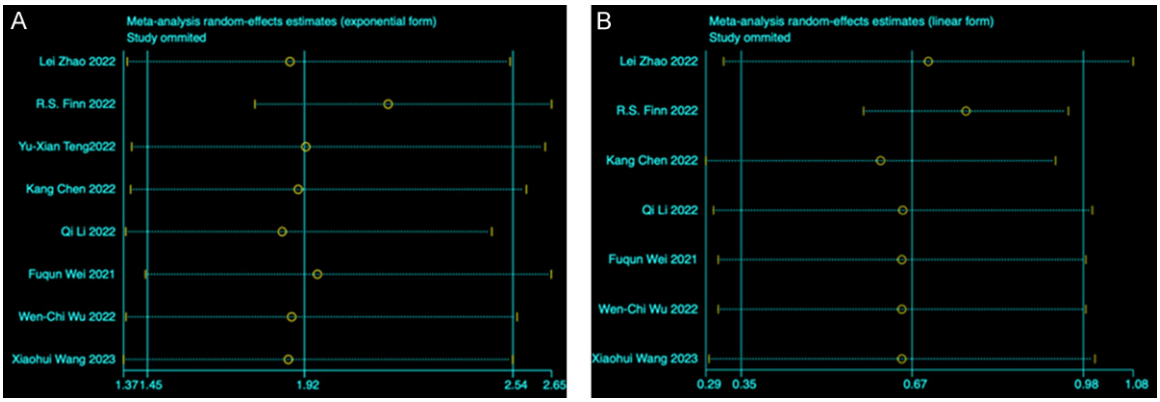

Figure 5. Sensitivity analysis based on OS (A) and PFS (B).

Examining the reasons for heterogeneity

We suspected that inconsistent OS effects might be due to varying follow-up periods (heterogeneity) and conducted a Meta regression to assess this factor. The results are detailed in **Tables 2**, **3**. The regression coefficients for OS and PFS indicated that the follow-up period significantly affects the treatment effect, confirming it as the source of heterogeneity. Consequently, we conducted a subgroup meta-analysis based on different follow-up periods. We divided the eight articles into two groups: a 3-year group and a non-3-year group and performed a separate meta-analysis on each group. Results were as follows: (1) There was no heterogeneity within the 3-year group for OS (I^2=0%, P=0.991), nor within the non-3-year group for OS (I^2=0%, P=0.484). However, there was moderate heterogeneity between the two

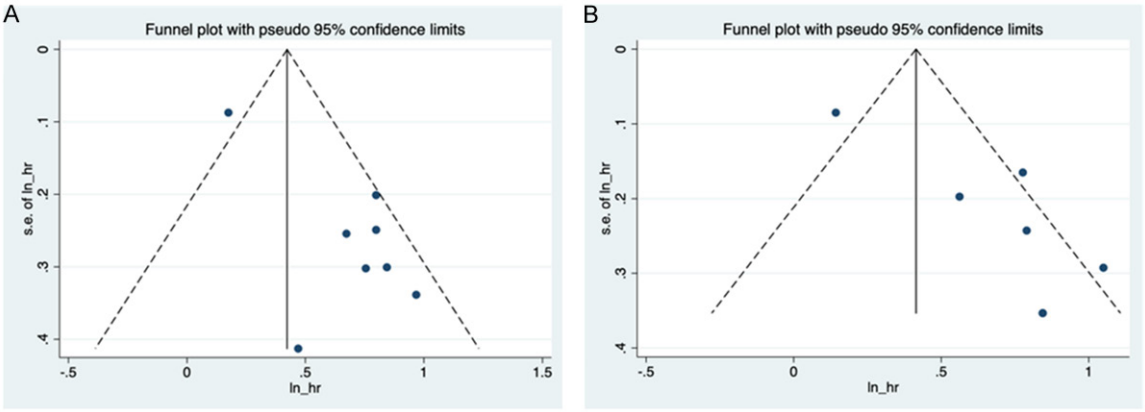

Figure 6. Funnel plots based on OS (A) and PFS (B).

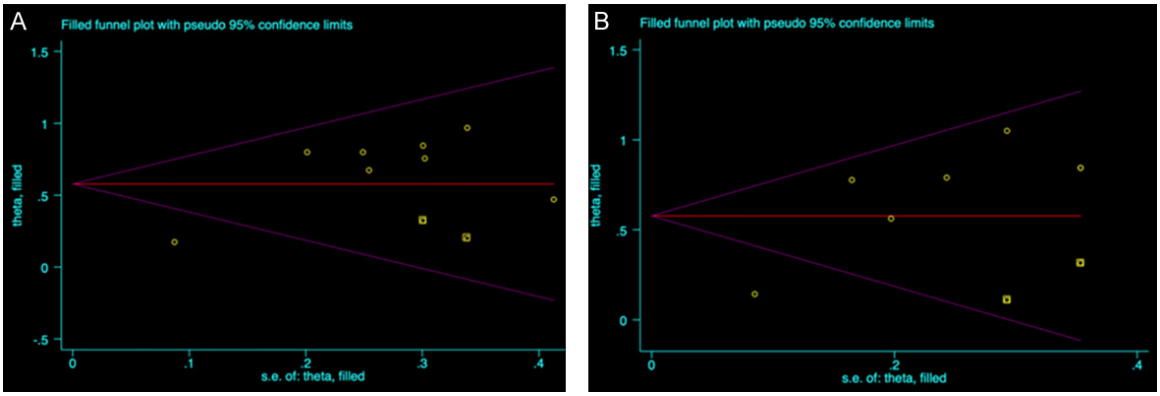

Figure 7. Corrected funnel plots based on OS (A) and PFS (B).

Table 2. Meta regression of OS

ln_hr	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
Follow-up Period	-0.607	0.137	-4.42	0.004	-0.942	-0.271
_cons	1.400	0.231	6.07	0.001	0.835	1.965

Table 3. Meta regression of PFS

ln_hr	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
Follow-up Period	-0.561	0.155	-3.62	0.015	-0.959	-0.163
_cons	1.325	0.246	5.39	0.003	0.693	1.956

groups (I^2=66%, P=0.004), indicating that follow-up time is the primary source of heterogeneity. Meta-grouping based on follow-up time was thus appropriate (**Table 4**). (2) For a 3-year follow-up with HR=2.211 (CI: 1.792-2.728), the effect size was significant (Z=7.40, P<0.05), indicating that combination therapy significantly outperformed monotherapy in 3-year OS, with a 2.211-fold improvement (**Table 5**). (3) After non-3-year follow-up, HR=1.206 (CI: 1.020-1.425), with a significant effect (Z=2.19, P<0.05). This means that for shorter or longer follow-up periods, combination therapy was not significantly better than monotherapy, resulting in only a 1.206-fold improvement (**Table 6**).

Subgroup bias test

Further offset testing was conducted on the funnel plot, and the results are as follows: (1) For the 3-year group, there was no publication bias, P=0.42>0.05; (2) For the non-3-year

Table 4. Meta regression of OS of 3-year group and non-3-year group

	Heterogeneity Statistic	Degrees of Freedom	p	I-squared
1	0.53	5	0.991	0.0%
2	0.49	1	0.484	0.0%
Overall	20.6	7	0.004	66.0%

Table 5. Meta regression of OS of 3-year group and non-3-year group

Study	ES	[95% Conf.	Interval]	% Weight
1				
Lei Zhao 2022	2.326	1.290	4.192	4.94
Yu-Xian Teng 2022	1.961	1.191	3.228	6.90
Kang Chen 2022	2.128	1.177	3.847	4.89
Qi Li 2022	2.632	1.355	5.110	3.89
Wen-Chi Wu 2022	2.222	1.364	3.621	7.20
Xiaohui Wang 2023	2.222	1.498	3.296	11.03
Sub-total I-V pooled ES	2.211	1.792	2.728	38.85
2				
R.S. Finn 2022	1.190	1.003	1.413	58.53
Fuqun Wei 2021	1.600	0.712	3.593	2.62
Sub-total I-V pooled ES	1.206	1.020	1.425	61.15
Overall I-V pooled ES	1.526	1.339	1.739	100.00

Table 6. Meta regression of OS of subgroups

Significance test(s) of ES=1		
1	z=7.40	P=0.000
2	z=2.19	P=0.029
Overall	z=6.33	P=0.000

group, there was no publication bias, P=0.369>0.05 (**Figure 8**; **Table 7**).

Discussion

Advanced hepatocellular carcinoma (aHCC) stands as one of the most common and formidable malignant tumors, significantly impacting public health. The requirement for effective systemic therapy in aHCC is paramount, given the large population of patients who no longer qualify for surgical intervention post-diagnosis. The results of the randomized control, multicenter, non-inferiority phase III clinical study REFLECT against Sorafenib were consecutively approved for the first-line treatment indication of advanced aHCC in 2018 by the European EMA, the US FDA, and the Chinese NMPA. Lenvatinib, along with sorafenib, has become the standard first-line treatment for advanced liver cancer in a phase III clinical trial with a non-inferiority design based on the REFLECT study [11]. Consequently, the landscape of first-line systemic treatment for advanced aHCC was limited to Sorafenib and Lenvatinib [10].

Recent advancements have elucidated Lenvatinib's unique mechanisms of action, making it a compelling option in aHCC treatment. It selectively targets multiple receptor tyrosine kinases linked to proangiogenic and oncogenic pathways, including FGFRs 1-4, PDGFRA, CKIT, and RET [23, 24]. Notably, Lenvatinib exhibits its prowess by effectively inhibiting FGFRs 1-4 when compared to Sorafenib [25]. Beyond this, emerging research has unearthed Lenvatinib's capacity for immunomodulation [26-28]. In combination with Pembrolizumab, it has demonstrated a significant clinical benefit, as evidenced by a 46% objective response rate (ORR) in aHCC patients [29]. Furthermore, a cost-effectiveness analysis suggests that Lenvatinib may present a cost-saving alternative to patients with aHCC while maintaining clinical efficacy at a lower cost than Sorafenib [30].

Based on data from the LEAP-002 study involving an Asian population, patients treated with Lenvatinib achieved a median Overall Survival (OS) of 22.4 months, marking the longest observed OS in a phase III clinical trial of Lenvatinib monotherapy as a first-line treatment for aHCC. This robust result reinforces Lenvatinib's position as a primary treatment option. Nevertheless, there is ongoing debate about whether combining Lenvatinib with Immune Checkpoint Inhibitors (ICIs) effectively enhances treatment outcomes. The current findings from the LEAP-002 study suggest that the combination therapy group did not exhibit significantly improved OS and Progression-Free Survival (PFS) compared to the Lenvatinib monotherapy group. Therefore, a comprehensive meta-analysis is necessary to assess the

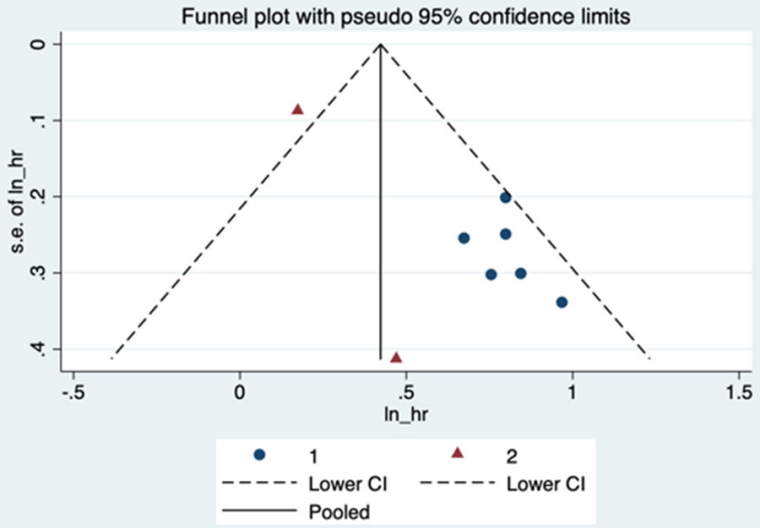

Figure 8. Funnel plots based on OS for subgroups.

treatment's efficacy. To our knowledge, this is the first and single group meta-analysis aimed at evaluating the efficacy of Lenvatinib and Lenvatinib combined with ICIs as first-line treatment for aHCC patients.

Eight studies involving 1594 patients reported OS and PFS. After heterogeneity testing, I^2= 66%>50%, and Q test P=0.004<0.1 (**Figures 3**, **4**), the results of meta-analysis using random effects showed that the OS (HR=1.53, 95% CI: 1.34-1.74; Z=6.33, P<0.001) of patients who got Lenvatinib combined with ICIs was higher than that of patients who used Lenvatinib alone. The OS of patients who used Lenvatinib in combination was 1.96 times higher than that of patients who used Lenvatinib alone. PFS (HR=1.51, 95% CI: 1.34-1.72; Z=6.50, P<0.001) indicated that the PFS of the combination medication wass 1.51 times higher than that of the single medication. These results are consistent with the results of most included studies, among which Lenvatinib combined with ICIs is not inferior to Lenvatinib alone in terms of OS and PFS. It is worth noting that subgroup analysis shows that if the follow-up time is too long or too short, it may have an impact on the observed results. For OS after 3 years of combination therapy (HR=2.211, 95% CI: 1.792-2.728; Z=7.40, P< 0.05), the results showed that combination therapy was 2.211 times higher (significant difference) than single therapy.. However, for OS after non-3-year combination (HR=1.206, 95% CI: 1.020-1.425; Z=2.19, P<0.05), it suggested that combination therapy was not significantly higher than single therapy. Therefore, more valuable prospective research is needed.

Significant differences exist in patient characteristics between the LEAP-002 study and other selected studies. These distinctions encompass mutations in non-alcoholic hepatitis-associated aHCC, the presence of extrahepatic spread (EHS), representation within the Asian population, and prior anti-tumor therapy [14]. These variations may impact the research outcomes and the efficacy of pembrolizumab combined with Lenvatinib. Currently, several studies have underscored that patients with HBV-related aHCC and individuals within the Asian population often experience more substantial benefits from immunotherapy [31-33]. In comparison to studies like SHR-1210-III-301, the proportion of patients with HBV-related aHCC and from Asian populations in the LEAP-002 study is relatively low [34]. In recent years, there has been an expanding range of second-line treatment options for advanced cancer, which helps prolong the overall survival (OS) following Lenvatinib progression. Conversely, the choice of combination therapy involving Lenvatinib and pembrolizumab after progression is relatively limited. In the LEAP-002 study, 44.1% and 52.1% of patients in the combination therapy group and the Lenvatinib monotherapy group proceeded to subsequent anti-tumor therapy, while 14.4% and 22.8% of patients received immunotherapy [14]. These factors, in comparison to historical data, may account for the higher overall survival rate associated with Lenvatinib monotherapy. This is also a significant reason why short-term studies such as that of Wei et al. did not demonstrate significant differences in survival times [20]. In the KEYNOTE-524 study (Phase 1b), the progression-free survival (PFS) of Lenvatinib combined with pembrolizumab was 8.6 months, which was marginal compared to the historical data of Lenvatinib monotherapy (7.4 months) [29].

Table 7. Metabias of subgroups

Follow-up Period	n	Begg's		Begg's		cont.	corr.	Egger's	
		score	s. d.	z	p	z	p	bias	p
1	6	3	5.323	0.56	0.573	0.38	0.707	0.71	0.420
2	2	1	1.000	1.00	0.317	0.00	1.000	0.91	.
Overall	8	4	5.416	0.74	0.460	0.55	0.580	0.71	0.369

Professor Llovet's experience suggests that the PFS risk ratio (HR) is 0.86, making it challenging to infer statistical differences in the overall survival rate (OS), particularly when compared to an HR of 0.6. However, due to the tail effect on survival, this prediction may not be applicable in the era of immunotherapy, rendering linear inference difficult. It's worth noting that the PD-1 antibody exhibited limited PFS improvement in an unselected population, as evidenced by the moderate enhancement of median PFS observed in the KEYNOTE-394 study by 0.3 months [35].

Nevertheless, our research has several limitations. First, some research results demonstrated significant heterogeneity, which was attributed to different study designs, demographics, follow-up time, and intervention measures. Another limitation was the evolution of second-line liver cancer treatment over time. The development of novel tyrosine kinase inhibitors and the emergence of cancer immunotherapy have both been found to affect OS in recent studies. Finally, most of the included studies were retrospective and non-random, indicating that unmeasured confounding factors and selection or recall bias may have influenced the results of these studies.

Conclusion

This system review and meta-analysis show that Lenvatinib combined with ICIs not only exhibits advantages over monotherapy not only for OS, but also PFS. However, a longer or shorter median follow-up time may lead to a decrease in advantage. However, given the limitations of this analysis, further large-scale and high-quality RCTs are needed in the future to ultimately determine this conclusion.

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Disclosure of conflict of interest

None.

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