REVIEW

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Efficacy of Lenvatinib Versus Sorafenib in the Treatment of Unresectable Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Hepatocellular carcinoma (HCC) was the third leading cause of cancer-related deaths in the world. Current global treatment recommendations suggest lenvatinib and sorafenib have been approved to treat unresectable HCC. Studies comparing lenvatinib versus sorafenib for unresectable HCC have shown conflicting results and no structured review has yet evaluated its efficacy and safety. This article aims to estimate the efficacy of lenvatinib and sorafenib in patients with unresectable HCC. **Methods:** This research was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) strategy. Literature searches were conducted through PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco. After quality assessment using the Newcastle-Ottawa Scale (NOS) and Cochrane Risk-of-bias, also data extraction, Review Manager 5.4 and RStudio 2024.04.1 software were used for analysis of overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR). **Results:** A total of 9 studies were included, comprising 3,821 samples. All studies were retrospective studies. Our meta-analysis showed that OS and PFS in patients receiving lenvatinib were significantly better than patients receiving sorafenib with a protective hazard ratio (HR) of 0.70 (95%CI: 0.57-0.87, p=0.001) and 0.65 (95%CI: 0.54-0.78; p < 0.00001) respectively. Moreover, in the viral patients group, lenvatinib showed similar OS compared with sorafenib (HR=1.02; 95%CI: 0.77-1.36, p=0.87). Lenvatinib exhibited better ORR (OR = 7.87; 95%CI: 2.02-30.75; p = 0.003) and DCR (OR = 1.99; 95%CI: 1.53-2.60; p < 0.00001) compared with sorafenib. **Conclusion:** Lenvatinib provided significant benefits in OS, PFS, ORR, and DCR compared to sorafenib in patients with unresectable HCC.

Keywords: Hepatocellular carcinoma- lenvatinib- sorafenib

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common types of liver cancer, caused by infections with hepatitis B or C viruses, excessive alcohol consumption, and other chronic liver diseases [1–3]. Globally, HCC led to 906,000 new cases and 830,000 deaths in 2020, making it the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death worldwide [4]. The 5-year survival rate was nearly 19%, but only 2% in metastatic HCC [5]. The progression of HCC typically occurs through a gradual process that begins with chronic hepatitis, leading to fibrosis, cirrhosis, and ultimately cancer. In cases of HBV infection, even in the absence of cirrhosis, patients have a significant risk of developing HCC. Conversely, in HCV infections, cirrhosis almost always precedes cancer [6]. In addition to viral factors, long-term alcohol consumption is known to accelerate liver damage and cause cirrhosis, which is a major predisposing condition for HCC [7]. The increasing prevalence of non-alcoholic fatty liver disease (NAFLD) in developed countries is attributed to unhealthy lifestyles and obesity, which trigger the occurrence of HCC even without significant cirrhosis [8].

The treatment of HCC heavily depends on the cancer stage at diagnosis. For patients with tumors in the early stages, the main options are surgical resection or liver transplantation [9]. However, many HCC patients are

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diagnosed at advanced stages, where local therapy options such as ablation or transarterial chemoembolization (TACE) are no longer adequate. For unresectable cases, systemic therapy becomes the primary step in treatment. Systemic therapy for unresectable HCC typically involves medications targeting specific molecular pathways in tumor growth and spread [5]. Sorafenib was the first oral multikinase inhibitor for the systemic treatment of advanced or unresectable HCC (uHCC) [10]. However, compared to sorafenib, atezolizumab increased survival rates and was authorized as the first-line treatment for uHCC [11]. Both are multikinase inhibitors that target receptor tyrosine kinases, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which are crucial for angiogenesis and tumor proliferation [12].

Sorafenib is the first systemic therapy that has been the standard of care for over a decade. Subsequently, lenvatinib has shown comparable efficacy in improving patient survival based on phase III clinical trials comparing the two drugs. Lenvatinib demonstrated non-inferiority to sorafenib in terms of overall survival (OS), with some advantages in progression-free survival (PFS) and objective response rate (ORR). Sorafenib is a systemic therapy for HCC based on the phase III SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial, which showed that sorafenib prolongs overall survival (OS) for HCC patients by 10.7 months compared to placebo (7.9 months) in unresectable patients [13]. On the other hand, according to the REFLECT clinical trial results, lenvatinib yields an average OS of 13.6 months, which is comparable to sorafenib's 12.3 months, but with advantages in tumor response and progression-free survival [14].

Studies comparing lenvatinib and sorafenib in the treatment of unresectable HCC have shown varying results. These inconsistencies in the outcomes highlight the need for a comprehensive meta-analysis to evaluate the efficacy of lenvatinib versus sorafenib. By systematically reviewing and analyzing existing research, the meta-analysis aims to provide clearer insights into which treatment option offers greater benefits for patients with unresectable HCC and better clinical decision-making for the treatment of unresectable HCC.

Materials and Methods

This meta-analysis uses Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. This study has been registered in PROSPERO (ID CRD42024623997).

Literature Selection

Using the following keywords, literature searches were conducted through PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco to find pertinent topics up until July 2024: "unresectable hepatocellular carcinoma" OR "unresectable HCC" AND "Lenvatinib" AND "Sorafenib" AND "Efficacy".

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis study were (1) the study had to be a type of randomized controlled trial (RCT) with or without blinds published in English both domestically and internationally and observational study (prospective and retrospective cohort, case-control, cross-sectional) studies were considered eligible for inclusion; (2) adult patients (over the age of 18) with an unresectable diagnosis who met the necessary diagnostic criteria; (3) Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) are examples of outcome indicators. The following were the study's exclusion criteria: (1) literature published repeatedly; (2) no control group; (3) conference papers and case reports.

Study Quality Assessment

Using the modified form of the Newcastle-Ottawa quality assessment scale (NOS) for observational study. Generally, this system used three aspects of the study design to assess quality: selection of the subject groups, comparability of subject groups, and ascertainment of the outcome. The total quality score ranged between 0 and 9. Meanwhile, the Cochrane Risk-of-bias assessment instrument for randomized trials (Version 2, quality assessment scale), the caliber of the research techniques was evaluated. The randomization procedure, departures from planned interventions, missing outcome data, outcome measurement, and choice of reported result are the five main components of research design that this method evaluates for quality [16].

Data Extraction

The following data were extracted from each study: name of the author, year of publication, nation, study design, sample size, number of males and females, age, Child-Pugh class, ECOG Score, and BCLC. The primary outcome of this meta-analysis was OS. The secondary outcomes were progression-free survival (PFS), time to progression, objective response rate (ORR), and disease control rate (DCR). Hazard Ratio (HR) and 95% CI for OS and PFS were among the information taken out of the chosen studies. One of the components included in the computations in this investigation was the 95% confidence interval (CIs). The HR is determined from the rebuilt data using the Kaplan-Meier curve if the data are displayed as a survival plot graph [17].

Statistical Analysis

RevMan 5.4 software was utilized for statistical analysis in this investigation. In computation data, a confidence interval (95% CI) and odds ratio (OR) are defined. To examine the heterogeneity among the studies, this study used the X^2 and I^2 tests. Fixed effect model analysis was performed if $P>0.1$ or $I2 < 50\%$ indicated that there was no statistical heterogeneity between trials. It indicates statistical heterogeneity between the research instead. More investigation into the heterogeneity's causes was required. A random effects model was employed for analysis after overt heterogeneity was eliminated. Using funnel charts, publication bias analysis was carried out and

subgroup analysis based on the type of included studies was carried out. Inspection threshold α = 0.05.

Results

Study Selection

A total of 1051 records were identified through the initial search from online databases (PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco). As many as 46 articles were removed for duplication, and 799 studies were discarded after scanning the titles and abstracts. After a detailed reading and full-text assessment, 189 articles were excluded cause by unmatched the inclusion and exclusion criteria. As many as 27 studies lacked the related data. Finally, 9 articles were included in this analysis, including 2 RCTs and 7 cohort studies. The entire literature search process follows the PRISMA Guideline 2022 and is summarized through a flowchart as follows (Figure 1).

Characteristics of Included Studies

The intervention was Lenvatinib monotherapy in the experimental group and Sorafenib in the control group. All eligible studies included a total of 3821 participants: 1822 in the lenvatinib group and 1999 in the sorafenib group. The published year ranged from 2020 to 2024. Based on study design, most of them are cohort study designs consisting of 4 prospective studies and 3 retrospective studies. A total of 2 studies used an RCT design. Patients were randomly assigned (1:1) to receive oral lenvatinib at a dose of 12 mg per day (for body weight ≥60 kg) or 8 mg per day (for body weights <60 kg) and sorafenib at a dose of 400 mg twice daily in 28-day cycles [18,19]. The regions studied included Asia and Europe, with the majority (4 studies) from Italy, 3 studies from Japan, 1 study from Korea, and 1 study from Germany. The characteristics of the included studies are summarized in Table 1. The bias risk of the RCT study was assessed using the Cochrane Risk-of-bias assessment instrument for randomized trials and determined to be low (Figure 7). Besides, the 7 cohort studies had NOS scores ranging from 7 to 9, indicating a high quality of data in all included studies.

Overall Survival (OS)

Eight studies [18, 20–26] that reported OS were included in the OS analysis of lenvatinib versus sorafenib in unresectable HCC. The meta-analysis indicated that OS in patients receiving lenvatinib was significantly better than patients receiving sorafenib with a protective hazard ratio (HR) of 0.70 (95%CI: 0.57-0.87, p=0.001). A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.002, I^2 = 59%; Figure 2).

Moreover, the OS of viral infection analysis involved 2 studies [20, 21]. Viral infection on this side refers to the group of HCC caused by hepatitis virus infection. In comparison, the other group is the group of HCC with

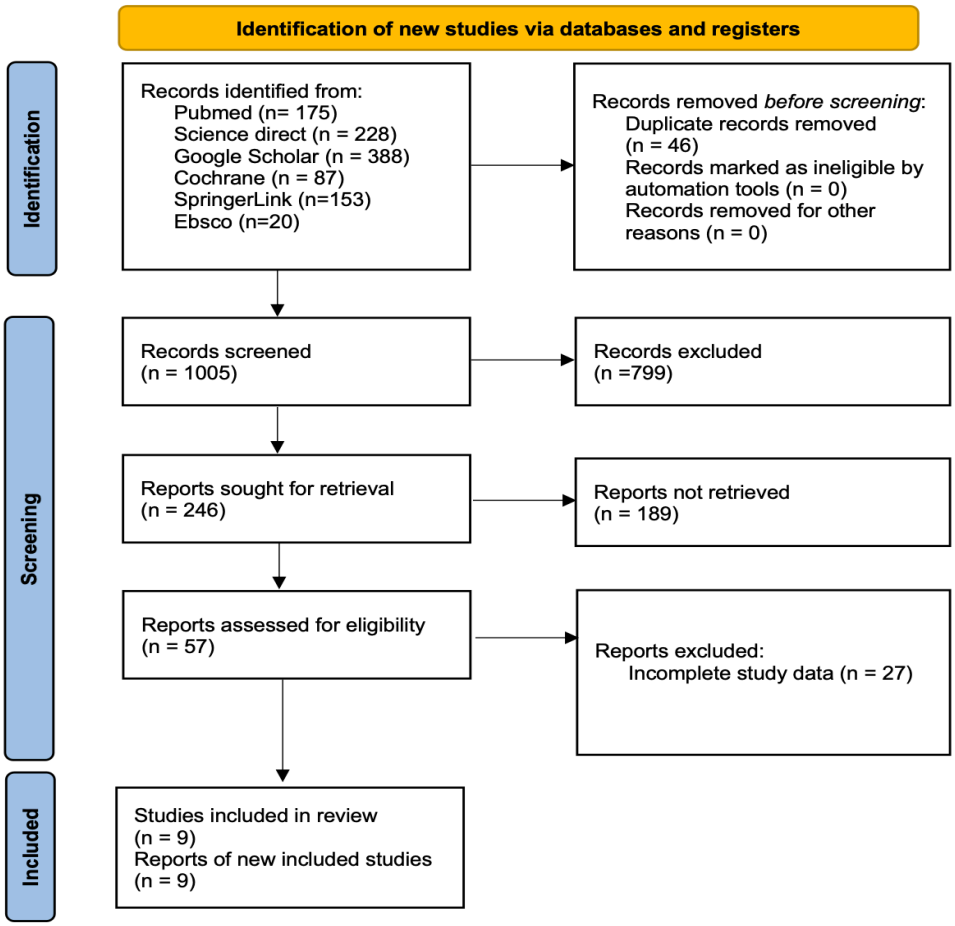

Figure 1. PRISMA Flowchart

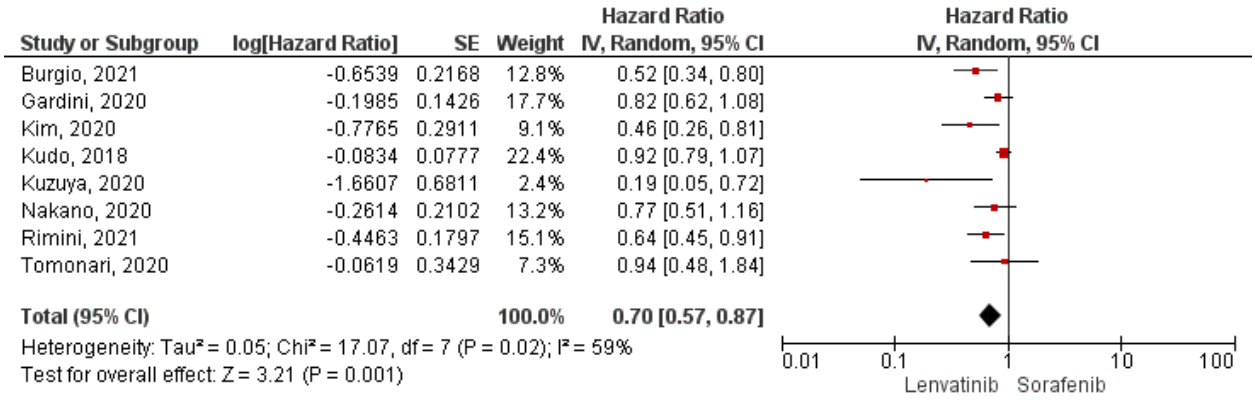

Figure 2. Forest Plot of Efficacy of Lenvatinib and Sorafenib in Patients with Unresectable HCC of Overall Survival (OS)

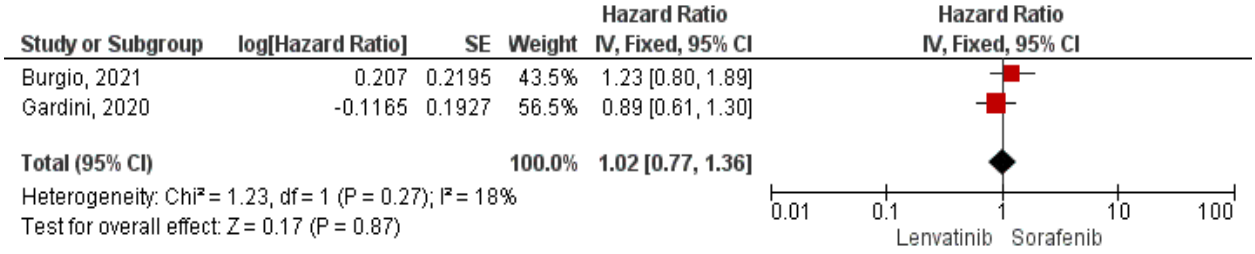

Figure 3. Forest Plot of Efficacy of Lenvatinib and Sorafenib in Patients with Unresectable HCC of Overall Survival (OS) of Viral Infection

other malignant causes other than infection, including metabolic causes, chronic alcohol consumption, or autoimmune. In the viral patient's group, lenvatinib showed similar OS compared with sorafenib (HR=1.02; 95%CI: 0.77-1.36, p=0.87). A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.27, I^2 = 18%; Figure 3).

Progression-Free Survival (PFS)

Seven studies [18–20, 22, 23, 25, 26] that reported PFS were included in the PFS analysis of lenvatinib versus sorafenib in unresectable HCC. The meta-analysis indicated that PFS in patients receiving lenvatinib was significantly better than patients receiving sorafenib with a protective hazard ratio (HR) of 0.65 (95%CI: 0.54-0.78; p < 0.00001). A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.005, I^2 = 68%; Figure 4).

Objective Response Rate (ORR)

Three studies [18,23,24] that reported ORR were included in the ORR analysis of lenvatinib versus sorafenib in unresectable HCC. The meta-analysis indicated that Lenvatinib exhibited better ORR (OR = 7.87; 95%CI: 2.02-30.75; p = 0.003) compared with sorafenib. A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.02, I^2 = 73%; Figure 5).

Disease Control Rate (DCR)

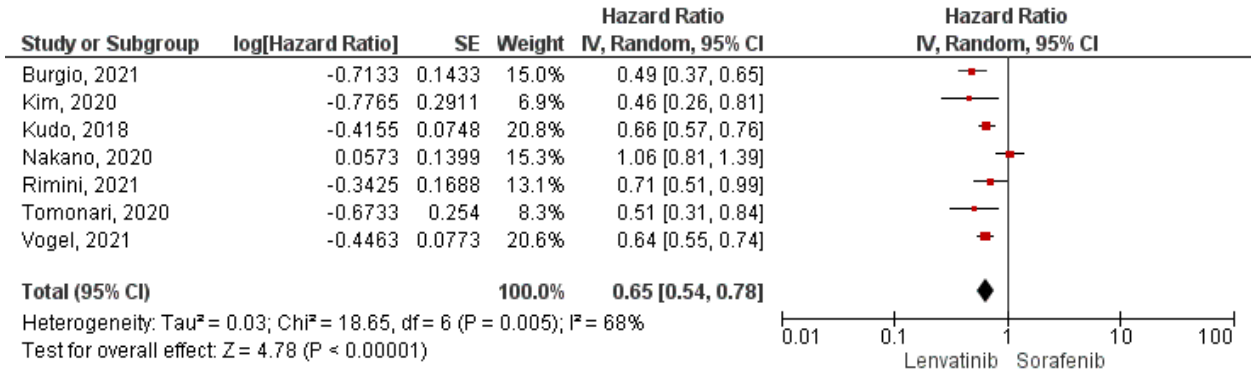

Figure 4. Forest Plot of Efficacy of Lenvatinib and Sorafenib in Patients with Unresectable HCC of Progression-Free Survival (PFS)

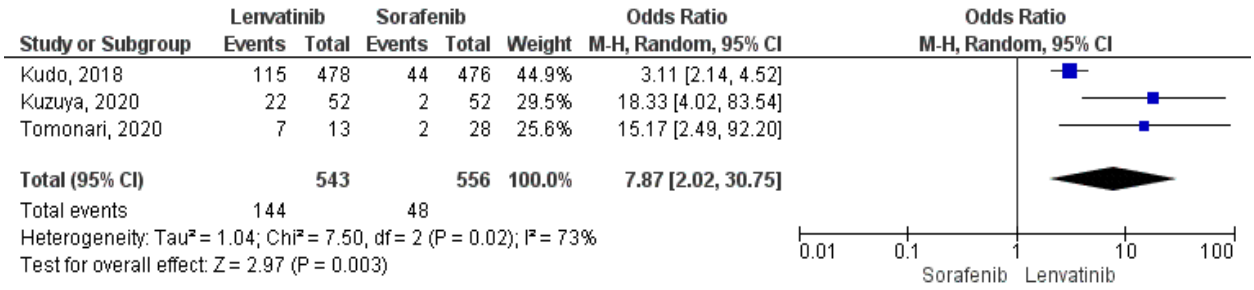

Figure 5. Forest Plot of Efficacy of Lenvatinib and Sorafenib in Patients with Unresectable HCC of Objective Response Rate (ORR)

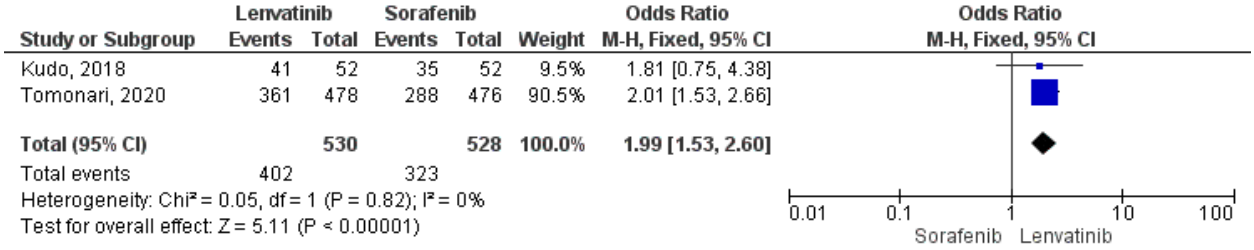

Figure 6. Forest Plot of Efficacy of Lenvatinib and Sorafenib in Patients with Unresectable HCC of Disease Control Rate (DCR)

Two studies [18,23] that reported DCR were included in the DCR analysis of lenvatinib versus sorafenib in unresectable HCC. The meta-analysis indicated that Lenvatinib exhibited better DCR (OR = 1.99; 95%CI: 1.53-2.60; $p < 0.00001$) compared with sorafenib. A fixed-effects model was used, and there was no statistical heterogeneity identified among the included studies ($p = 0.82$, $I^2 = 0\%$; Figure 6).

Risk of Bias Assessment

The bias risk of the RCT study was assessed using the Cochrane Risk-of-bias assessment instrument for randomized trials (Figure 7). The studies were found to have a low risk of bias. An analysis of the risk of publication bias was also carried out through funnel plots and is reported in Figure 8. The results of the analysis show that the variables OS (Figure 8A) and ORR (Figure 8D) have the potential for publication bias, one of which is influenced by study limitations due to relatively new research. However, most of the variables show a symmetric distribution in the Funnel Plot indicating a low risk of publication bias.

Discussion

Our meta-analysis demonstrates that lenvatinib provided significant benefits in OS, PFS, ORR, and DCR compared to sorafenib in patients with unresectable HCC. Lenvatinib is a selective, multi-targeted TKI of VEGFR1-3 and other receptor tyrosine kinases associated with proangiogenic and oncogenic pathways, including FGFR1-4, PDGFRα, cKIT, and RET. Compared to sorafenib, the distinguishing feature of lenvatinib is its potent activity against FGFR1-4 [12]. REFLECT

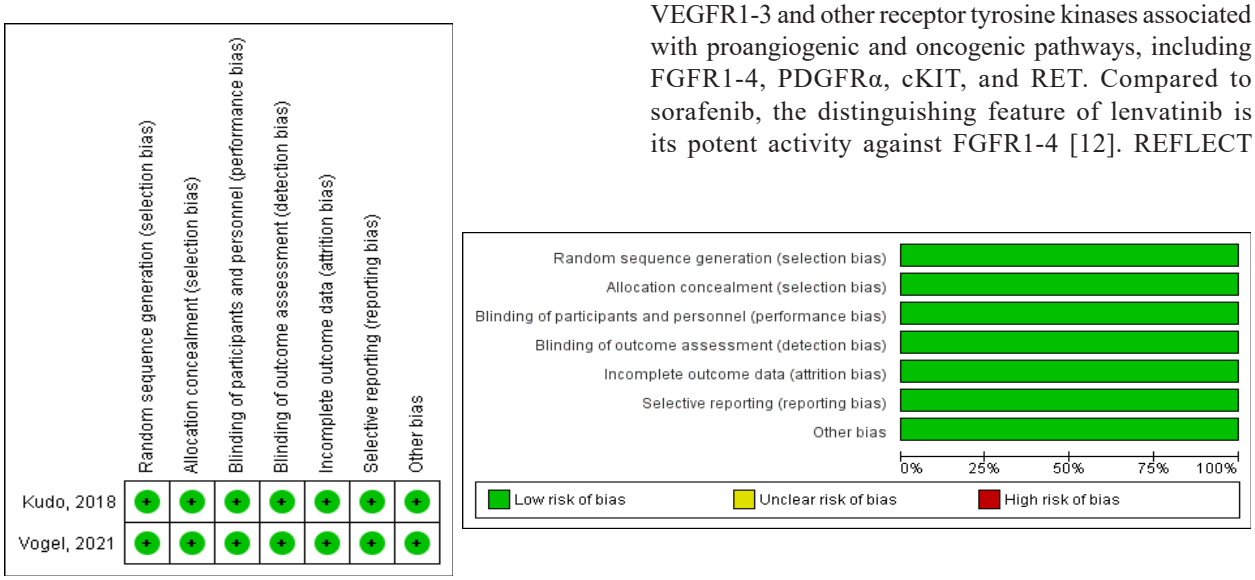

Figure 7. Risk of Bias Assessment Using Cochrane Risk-of-bias Assessment Instrument for Randomized

Table 1. Baseline Characteristics of Studies that Met the Inclusion and Exclusion Criteria, Selected through a Systematic Screening Process from electronic databases. The table provides detailed information on study design, country of origin, sample size, gender distribution, age range, Child-Pugh classification, ECOG performance status, BCLC staging, and disease etiology (viral and non-viral).

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		NOS
							Range Age	Mean	A	B	0	>0	B	C	Viral	Non-viral	
Kudo, 2018[18]	RCT	Italy	Lenvatinib	478	405	73	49.6-73	61.3	475	3	304	174	104	374	342	136	-
			Sorafenib	476	401	75	49.2-73.2	61.2	471	5	301	175	92	384	354	122	
Burgio, 2021[20]	Prospective	Italy	Lenvatinib	144	111	33	N/A	N/A	137	7	114	30	36	108	101	43	7
			Sorafenib	144	119	25	N/A	N/A	134	10	114	30	36	108	89	55	
Gardini, 2020[21]	Prospective	Italy	Lenvatinib	385	314	71	62.1-82-1	72.1	347	38	318	67	210	175	222	163	7
			Sorafenib	552	42	510	51.1-74.1	62.6	489	63	266	286	69	483	405	147	
Nakano, 2020[22]	Prospective	Japan	Lenvatinib	146	125	21	63.2-82.4	72.8	134	12	N/A	N/A	79	67	102	44	9
			Sorafenib	146	121	25	64.3-81.3	72.8	137	9	N/A	N/A	81	65	105	41	
Tomonari, 2020[23]	Retrospective	Japan	Lenvatinib	52	36	16	53–88	70	27	25	38	14	27	25	33	19	8
			Sorafenib	52	35	17	43-85	71	27	25	37	15	29	23	29	23	
Kuzuya, 2020[24]	Retrospective	Japan	Lenvatinib	13	11	2	70	53-92	8	5	12	1	N/A	N/A	4	9	8
			Sorafenib	13	11	2	69	60-78	7	6	8	5	N/A	N/A	16	28	
Kim, 2020[25]	Retrospective	Korea	Lenvatinib	44	39	5	N/A	51.0-66.3	36	8	41	3	N/A	N/A	N/A	N/A	8
			Sorafenib	61	51	10	N/A	58.0-70.5	56	5	59	2	N/A	N/A	N/A	N/A	
Rimini, 2021[26]	Prospective	Italy	Lenvatinib	92	75	17	N/A	N/A	87	5	70	22	36	56	56	36	7
			Sorafenib	92	81	11	N/A	N/A	85	7	65	27	36	56	56	36	
Vogel, 2021[19]	RCT	German	Lenvatinib	468	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-
			Sorafenib	463	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

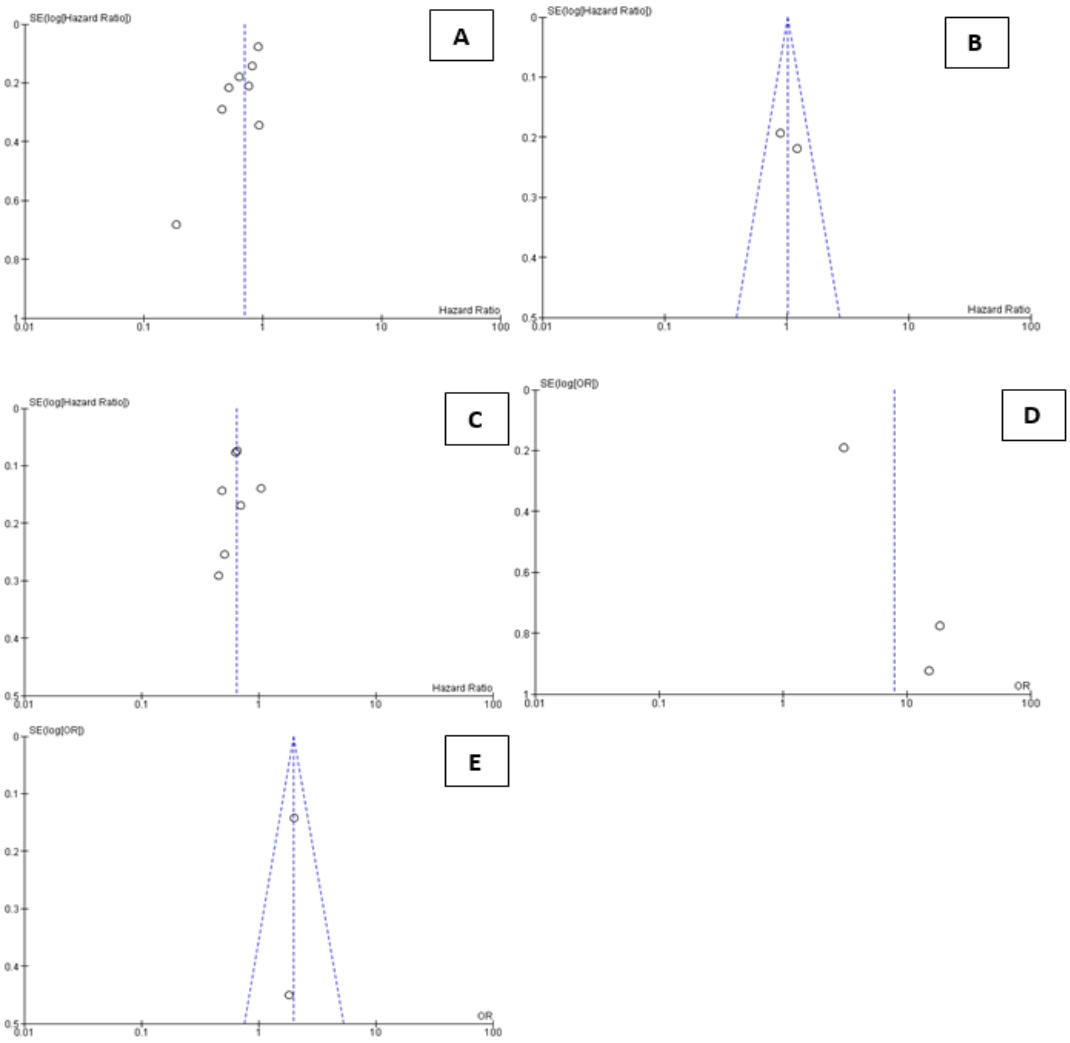

Figure 8. Funnel Plots based on (A) OS, (B) OS of Viral Infection, (C) PFS, (D) ORR, (E) DCR

clinical trial met its primary endpoint, demonstrating that lenvatinib was non-inferior to sorafenib for patients with uHCC based on the analysis of overall survival (OS; median 13.6 vs. 12.3 months; hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.79–1.06). In the REFLECT clinical trial, the objective response rates (ORR) with lenvatinib by blinded independent imaging review (IIR) were 40.6% per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and 18.8% per RECIST version 1.1 (RECIST v1.1) [18]. In comparison to this meta-analysis, Singal et al study using 64 patients showed lenvatinib also appeared to be effective in this setting, with the best clinical response reported as the complete or partial response for approximately half of all patients. Estimates of PFS and OS at 12 months were 52% and 57.8%, respectively [27].

Moreover, the ORR was also significantly higher in the Child-Pugh subclass A5 (44%) compared with the other subclasses [28]. In another real-world study, data from a Canadian multicenter database that enrolled 220 patients found the ORR and median OS were 22% and 13 months, respectively, and the outcomes were similar between lenvatinib as the first-line and as the late-line therapeutic regimen of HCC [29]. Recent real-world data including 466 patients in Italy reported the median PFS as being 9.0 and 4.9 months for the lenvatinib and sorafenib arm, respectively. Patients treated with lenvatinib showed a higher percentage response rate (29.4% vs. 2.8%; $p < 0.00001$) compared with those treated with sorafenib [29]. Previous studies conducted by Shimose, et al. [30] also support the results of this meta-analysis which shows that Lenvatinib has the potential to increase progression-free survival (PFS) in patients with HCC, in this study focused on intermediate-stage refractory HCC. In the multicenter cohort study, the comparison between progression-free survival of patients with Lenvatinib, sorafenib, and transarterial chemoembolization (TACE) was 5.8, 3.2, and 2.8 months. The data is also statistically supported which shows the protective hazard ratio of Lenvatinib compared to sorafenib which reached 0.56 (95%CI: 0.36-0.88; $p = 0.001$) and Lenvatinib compared to TACE of 0.23 (95%CI: 0.15-0.36; $p <0.001$). In addition, this study also showed that the objective response rates (ORR) of Lenvatinib were quite high, with a percentage reaching 66.7% [30].

The previous meta-analysis written by Hua, et al. [31] compared Lenvatinib and sorafenib in hepatocellular carcinoma patients in general in a real-world study analysis. In line with the results of this meta-analysis, the analysis also showed that Lenvatinib had a significantly better DCR compared to sorafenib with an odds ratio (OR) value reaching 2.17 (95%CI: 1.64-2.86; p <0.001). The meta-analysis also showed that the ORR value of Lenvatinib was better than sorafenib, with an OR reaching 5.36 (95%CI: 3.24-8.40; p <0.001). Meanwhile, the overall survival and progression-free survival values also showed positive results from Lenvatinib compared to sorafenib which was reported to significantly increase OS and PFS with a mean difference (MD) of OS reaching 1.20 (95%CI: 0.92-1.48; p <0.001) and MD of PFS reaching 5.30 (95%CI: 4.26-6.33; p <0.001) [31].

Lenvatinib is a multi-target tyrosine kinase inhibitor (TKI) that acts on key receptors involved in tumor growth and angiogenesis, including vascular endothelial growth factor receptors (VEGFR1-3), fibroblast growth factor receptors (FGFR1-4), platelet-derived growth factor receptor alpha (PDGFRα), RET, and KIT [32, 33]. Simultaneous targeting of VEGFR and FGFR is one of the main reasons for the superior efficacy of lenvatinib compared to sorafenib, which primarily inhibits only VEGFR, PDGFRβ, and RAF kinase. FGFR, in particular, plays a critical role in the liver tumor microenvironment, primarily through involvement in vascular regeneration and secondary angiogenic resistance. By inhibiting FGFR, lenvatinib can prevent the escape mechanism that often causes treatment failure of conventional angiogenesis inhibitors such as sorafenib. The combination of VEGFR and FGFR inhibition provides more comprehensive control of angiogenesis, contributing to improved progression-free survival and disease control rates [34, 35].

Hepatocellular carcinoma is highly dependent on angiogenesis for its growth and spread. Preclinical studies have shown that lenvatinib has a stronger inhibitory affinity for VEGFR than sorafenib, with a lower IC50 with IC50 reaching 2.85 μM in the study conducted by Pan, et al (2022). This effect results in a more significant decrease in tumor vascularization, thereby reducing the supply of oxygen and nutrients required for tumor cell proliferation [36]. In addition, lenvatinib also targets the FGFR pathway, which plays a role in supporting angiogenesis by stimulating new blood vessel formation when VEGFR is inhibited. Thus, lenvatinib inhibits not only primary angiogenesis but also compensatory angiogenic mechanisms. This contributes to an increase in ORR, as the tumor is unable to adapt to the pressure of the therapy given [37, 38]. In addition, lenvatinib has also been reported to affect the tumor microenvironment which further increases its effectiveness in cases of unresectable HCC [39, 40].

The results of this review indicate that Lenvatinib has great potential to be used more widely in clinical services. This meta-analysis has also involved several clinical trials that showed positive results. As previously explained, the REFLECT clinical trial showed that the overall survival of uHCC patients with Lenvatinib was better than sorafenib with a median OS reaching 13.6 vs. 12.3 months.19 This is also supported by a randomized open-label phase 3 trials study conducted by Vogel et al. [19] which showed positive results from administering lenvatinib compared to sorafenib as first-line treatment for uHCC which showed that Lenvatinib can improve the quality of life of patients with relatively lower side effects compared to sorafenib with HR for quality of life-related to fatigue reaching 0.83 (95%CI: 0.69-0.99), related to the pain of 0.80 (95%CI: 0.66-0.96), and related to diarrhea of 0.52 (95%CI: 0.42-0.65) [19].

Nonetheless, our study has several limitations. First, significant heterogeneity among studies in some outcomes was observed, which could be attributed to parameters such as different study designs, population demographics, follow-up times, and interventions. Second, our analysis was limited by studies published in English, and therefore omission of relevant articles published in other languages is a possibility. Finally, most of the included studies were cohort studies and nonrandomized, suggesting that unmeasured confounders and selection or recall bias may have influenced the results of these studies. This meta-analysis also has not conducted an analysis related to the safety profile of lenvatinib compared to sorafenib which could be used as evaluation material for further similar studies.

In conclusion, our meta-analysis showed that lenvatinib has better efficacy compared to sorafenib in the treatment of unresectable hepatocellular carcinoma. This is indicated by the overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) values which were significantly better in patients with lenvatinib compared to sorafenib.

Author Contribution Statement

All authors contributed in all of the processes to make this article. N.P.S.I.R. and D.A.S. are involved in article concept and drafting; N.P.R.P.D. and I.K.C.Y. are involved in literature searching and data extracting; I.G.A.P.S. and I.K.W.A.K. are involved in data analysis and interpretation; while I.G.P.S. and I.K.M. are involved in manuscript editing and supervising. All authors have reviewed the final version of this article.

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Ethical Declaration

This meta-analysis is a review article that does not have any ethical declaration file.

Data Availability

The corresponding author will provide the datasets used and/or analyzed during the current work upon reasonable request.

Study Registration

This systematic review and meta-analysis has been registered in the PROSPERO database with the registration number CRD42024624039.

Conflict of Interest

All authors declare there was no conflict of interest regarding this study.

References

1. Ito T, Nguyen MH. Perspectives on the underlying etiology of HCC and its effects on treatment outcomes. J Hepatocell Carcinoma. 2023;10:413-28. https://doi.org/10.2147/JHC.S347959.
2. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1). https://doi.org/10.1038/s41572-020-00240-3.
3. Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol. 2019;70(2):284-93. https://doi.org/10.1016/j.jhep.2018.10.008.
4. Foglia B, Turato C, Cannito S. Hepatocellular carcinoma: Latest research in pathogenesis, detection and treatment. Int J Mol Sci. 2023;24(15):12224. https://doi.org/10.3390/ijms241512224.
5. Leowattana W, Leowattana T, Leowattana PT. Systemic treatment for unresectable hepatocellular carcinoma. World J Gastroenterol. 2023;29(10):1551-68. https://doi.org/10.3748/wjg.v29.i10.1551.
6. Russo FP, Zanetto A, Pinto E, Battistella S, Penzo B, Burra P, et al. Hepatocellular carcinoma in chronic viral hepatitis: Where do we stand? Int J Mol Sci. 2022;23(1). https://doi.org/10.3390/ijms23010500.
7. Matsushita H, Takaki A. Alcohol and hepatocellular carcinoma. BMJ Open Gastroenterol. 2019;6(1). https://doi.org/10.1136/bmjgast-2018-000260.
8. Teng YX, Xie S, Guo PP, Deng ZJ, Zhang ZY, Gao W, et al. Hepatocellular carcinoma in non-alcoholic fatty liver disease: Current progresses and challenges. J Clin Transl Hepatol. 2022;10(5):955-64. https://doi.org/10.14218/JCTH.2021.00586.
9. Angeli-Pahim I, Chambers A, Duarte S, Zarrinpar A. Current trends in surgical management of hepatocellular carcinoma. Cancers. 2023;15(22):1-21. https://doi.org/10.3390/cancers15225378.
10. Ntellas P, Chau I. Updates on systemic therapy for hepatocellular carcinoma. Am Soc Clin Oncol Educ Book. 2024;44(1). https://doi.org/10.1200/edbk_430028.
11. Mandlik DS, Mandlik SK, Choudhary HB. Immunotherapy for hepatocellular carcinoma: Current status and future perspectives. World J Gastroenterol. 2023;29(6):1054-75. https://doi.org/10.3748/wjg.v29.i6.1054.
12. Matsuki M, Hoshi T, Yamamoto Y, Ikemori-Kawada M, Minoshima Y, Funahashi Y, et al. Lenvatinib inhibits angiogenesis and tumor fibroblast growth factor signaling pathways in human hepatocellular carcinoma models. Cancer Med. 2018;7(6):2641-53. https://doi.org/10.1002/cam4.1517.
13. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial. J Hepatol. 2012;57(4):821-9. https://doi.org/10.1016/j.jhep.2012.06.014.
14. Lee MMP, Chan LL, Chan SL. The role of lenvatinib in the era of immunotherapy of hepatocellular carcinoma. J Liver Cancer. 2023;23(2):262-71. https://doi.org/10.17998/jlc.2023.07.17.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372. https://doi.org/10.1136/bmj.n71.
16. Cassai AD, Boscolo A, Zarantonello F, Pettenuzzo T, Sella N, Geraldini F, et al. Enhancing study quality assessment: An in-depth review of risk of bias tools for meta-analysis—a comprehensive guide for anesthesiologists. J Anesth Analg Crit Care. 2023;3(1):44. https://doi.org/10.1186/s44158-023-00129-z.
17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452-8. https://doi.org/10.1038/bmt.2012.244.
18. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Alma Mater Studiorum Università di Bologna Archivio Istituzionale della Ricerca: This is the accepted manuscript of: Kraljevic S, Tamai T, Ren M, Cheng AL. Hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. 2024;No. August.
19. Vogel A, Qin S, Kudo M, Su Y, Hudgens S, Yamashita T, et al. Lenvatinib versus sorafenib for first-line treatment of unresectable hepatocellular carcinoma: Patient-reported outcomes from a randomised, open-label, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol. 2021;6(8):649-58. https://doi.org/10.1016/S2468-1253(21)00110-2.
20. Burgio V, Iavarone M, Di Costanzo GG, Marra F, Lonardi S, Tamburini E, et al. Real-life clinical data of lenvatinib versus sorafenib for unresectable hepatocellular carcinoma in Italy. Cancer Manag Res. 2021;13:9379-89. https://doi.org/10.2147/CMAR.S330195.
21. Casadei-Gardini A, Scartozzi M, Tada T, Yoo C, Shimose S, Masi G, et al. Lenvatinib versus sorafenib in first-line treatment of unresectable hepatocellular carcinoma: An inverse probability of treatment weighting analysis. Liver Int. 2021;41(6):1389-97. https://doi.org/10.1111/liv.14817.
22. Nakano M, Kuromatsu R, Niizeki T, Okamura S, Iwamoto H, Shimose S, et al. Primary treatment with molecular-targeted agents for hepatocellular carcinoma: A propensity score-matching analysis. Hepatol Commun. 2020;4(8):1218-28. https://doi.org/10.1002/hep4.1535.
23. Tomonari T, Sato Y, Tani J, Hirose A, Ogawa C, Morishita A, et al. Comparison of therapeutic outcomes of sorafenib and lenvatinib as primary treatments for hepatocellular carcinoma with a focus on molecular-targeted agent sequential therapy: A propensity score-matched analysis. Hepatol Res. 2021;51. https://doi.org/10.1111/hepr.13597.
24. Kuzuya T, Ishigami M, Ito T, Ishizu Y, Honda T, Ishikawa T, Fujishiro M. Sorafenib vs. lenvatinib as first-line therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Anticancer Res. 2020;40(4):2283-90. https://doi.org/10.21873/anticanres.14193.
25. Kim S, Kim KH, Kim BK, Park JY, Ahn SH, Kim DY, Kim SU. Lenvatinib is independently associated with the reduced risk of progressive disease when compared with sorafenib in patients with advanced hepatocellular carcinoma. J Gastroenterol Hepatol (Australia). 2020;36(5):1317-25. https://doi.org/10.1111/jgh.15355.
26. Rimini M, Shimose S, Lonardi S, Tada T, Masi G, Iwamoto H, et al. Lenvatinib versus sorafenib as first-line treatment in hepatocellular carcinoma: A multi-institutional matched case-control study. Hepatol Res. 2021;51(12):1229-41. https://doi.org/10.1111/hepr.13718.
27. Singal AG, Nagar SP, Hitchens A, Davis KL, Iyer S. Real-

world effectiveness of lenvatinib monotherapy in previously treated unresectable hepatocellular carcinoma in US clinical practice. Cancer Rep. 2023;6(1):1-11. https://doi.org/10.1002/cnr2.1679.
28. Ogushi K, Chuma M, Uojima H, Hidaka H, Numata K, Kobayashi S, et al. Safety and efficacy of lenvatinib treatment in Child-Pugh A and B patients with unresectable hepatocellular carcinoma in clinical practice: A multicenter analysis. Clin Exp Gastroenterol. 2020;13:385-96. https://doi.org/10.2147/CEG.S256691.
29. Amaro CP, Allen MJ, Knox JJ, Tsang ES, Lim HJ, Lee-Ying RM, et al. Efficacy and safety of lenvatinib in the real-world treatment of hepatocellular carcinoma: Results from a Canadian multicenter database (HCC CHORD). Am Soc Clin Oncol. 2021.
30. Shimose S, Kawaguchi T, Tanaka M, Iwamoto H, Miyazaki K, Moriyama E, et al. Lenvatinib prolongs the progression-free survival time of patients with intermediate-stage hepatocellular carcinoma refractory to transarterial chemoembolization: A multicenter cohort study using data mining analysis. Oncol Lett. 2020;20(3):2257-65. https://doi.org/10.3892/ol.2020.11758.
31. Hua X, Yin Z, Liang J, Chen W, Gong H. Efficacy and safety comparison between lenvatinib and sorafenib in hepatocellular carcinoma treatment: A systematic review and meta-analysis of real-world study. Eur J Gastroenterol Hepatol. 2024;36(1):120-8. https://doi.org/10.1097/MEG.0000000000002668.
32. Wang M, Yao X, Bo Z, Zheng J, Yu H, Xie X, et al. Synergistic effect of lenvatinib and chemotherapy in hepatocellular carcinoma using preclinical models. J Hepatocell Carcinoma. 2023;10:483-95. https://doi.org/10.2147/JHC.S395474.
33. Chen Z, Xie H, Hu M, Huang T, Hu Y, Sang N, et al. Recent progress in treatment of hepatocellular carcinoma. Am J Cancer Res. 2020;10(9):2993-3036.
34. Butt NUH, Baytas SN. Advancements in hepatocellular carcinoma: Potential preclinical drugs and their future. Curr Pharm Des. 2023;29(1):2-14. https://doi.org/10.2174/1381612829666221216114350.
35. Zhao Y, Zhang YN, Wang KT, Chen L. Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy. Biochim Biophys Acta Rev Cancer. 2020;1874(1):188391. https://doi.org/10.1016/j.bbcan.2020.188391.
36. Pan J, Zhang M, Dong L, Ji S, Zhang J, Zhang S, et al. Genome-scale CRISPR screen identifies LAPTM5 driving lenvatinib resistance in hepatocellular carcinoma. Autophagy. 2023;19(4):1184-98. https://doi.org/10.1080/15548627.2022.2117893.
37. Catalano M, Casadei-Gardini A, Vannini G, Campani C, Marra F, Mini E, et al. Lenvatinib: Established and promising drug for the treatment of advanced hepatocellular carcinoma. Expert Rev Clin Pharmacol. 2021;14(11):1353-65. https://doi.org/10.1080/17512433.2021.1958674.
38. Baxter MA, Glen H, Evans TRJ. Lenvatinib and its use in the treatment of unresectable hepatocellular carcinoma. Future Oncol. 2018;14(20):2021-9. https://doi.org/10.2217/fon-2017-0689.
39. Donne R, Lujambio A. The liver cancer immune microenvironment: Therapeutic implications for hepatocellular carcinoma. Hepatology (Baltimore, Md.). 2023;77(5):1773-96. https://doi.org/10.1002/hep.32740.
40. Yamauchi M, Ono A, Amioka K, Fujii Y, Nakahara H, Teraoka Y, et al. Lenvatinib activates anti-tumor immunity by suppressing immunoinhibitory infiltrates in the tumor microenvironment of advanced hepatocellular carcinoma. Commun Med. 2023;3(1):152. https://doi.org/10.1038/s43856-023-00390-x.