REVIEW

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Efficacy and Safety of Lenvatinib versus Atezolizumab Plus Bevacizumab in the Treatment of Unresectable Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Hepatocellular carcinoma (HCC), the leading form of primary liver cancer, is strongly associated with liver cirrhosis and major risk factors such as hepatitis B and C, alcohol consumption, obesity, and non-alcoholic fatty liver disease. Despite treatment advancements, survival rates for unresectable HCC remain low. Lenvatinib and the combination of atezolizumab and bevacizumab (ATE/BEV) show promise, but further studies are needed to compare their clinical outcomes. This study aims to assess the efficacy and safety of LEN and ATE/BEV in unresectable HCC patients. **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 to gather studies on comparing LEN versus ATE/BEV for managing unresectable HCC. The quality assessment was assessed using the Newcastle-Ottawa Scale (NOS). Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and treatment-related adverse events (AEs) were evaluated using Review Manager 5.4 and RStudio 2024.04.1. **Results:** Twelve retrospective studies were included, comprising 6,620 samples. There was no difference in the OS (HR=0.72; 95%CI: 0.44-1.18, p=0.20), PFS (HR=0.90; 95%CI: 0.75-1.07; p=0.23), ORR (OR=1.16; 95%CI:0.86-1.56; p=0.34) and DCR (OR=1.14; 95%CI:0.97-1.34; p=0.12) between groups. Moreover, in viral and non-viral patients group, LEN showed similar OS and PFS compared with ATE/BEV. In terms of safety, LEN exhibited higher incidences of decreased appetite (OR=2.95; 95%CI:1.12-7.79; p=0.03), diarrhea (OR=2.61; 95%CI:2.06-3.32; p<0.00001), fatigue (OR=1.48; 95%CI:1.27-1.73; P<0.00001), hand-foot syndrome (OR=7.73; 95%CI:4.84-12.33; P<0.00001), and showed lower incidences of increased aspartate aminotransferase (OR=0.44; 95%CI:0.28-0.69; p=0.0004) compared to ATE/BEV. Moreover, LEN showed similar AEs in grade ≥ 3 AEs (OR=1.15; 95%CI:0.29-4.55; p=0.84), hypertension (OR=1.39; 95%CI:0.84-2.28; p=0.20), proteinuria (OR=1.10; 95%CI:0.75-1.60; p=0.63) compared to ATE/BEV. **Conclusion:** LEN was found to be non-inferior to ATE/BEV in terms of OS, PFS, ORR, DCR. However, LEN may be associated with a higher incidence of AEs.

Keywords: Atezolizumab- bevacizumab- hepatocellular carcinoma- Lenvatinib

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, occurring in approximately 85% of patients diagnosed with liver cirrhosis [1-3]. This cancer originates from hepatocytes that undergo malignant transformation. The primary risk factors for HCC development include hepatitis B (HBV) and C virus infections (HVC), excessive alcohol consumption, obesity, and non-alcoholic fatty liver disease (NAFLD) [4-6]. In 2022, there were over 866,136 new cases of liver cancer globally, making it a leading cause of cancer-related deaths worldwide [7]. Despite significant advances in understanding the etiology of HCC, the 5-year survival rate remains very low, at around 5%–14%. In cases where HCC leads to death, the patient's survival rate is influenced by various factors, including portal vein thrombosis, tumor size, alpha-fetoprotein (AFP) levels, and tumor stage

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[8]. In patients with localized, regional, and metastatic disease, the 5-year survival rates are 33%, 10%, and 2%, respectively [9]. Additionally, the length of survival is significantly influenced by the degree of cirrhosis or liver damage experienced by the patient. Patients with cirrhosis tend to have shorter survival times and more limited treatment options [10].

The diagnosis of hepatocellular carcinoma (HCC) is generally based on non-invasive criteria. However, tissue biopsy for hepatocellular carcinoma is increasingly utilized in clinical practice [11]. Vaccines and antiviral therapies can be applied for HBV and HCV infections in preventive measures. Meanwhile, treatment for HCC, including liver resection and liver transplantation, serves as the main curative method [12]. On the other hand, in early-stage HCC, surgery may not be required, and local ablation with radiofrequency can be performed. For intermediate-stage HCC, transarterial chemoembolization (TACE) has become the most frequently used treatment and is considered the standard of care over the past two decades [13]. Currently, systmic therapies such as immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs), and monoclonal antibodies have become primary options for unresectable hepatocellular carcinoma [14].

Lenvatinib acts as a multikinase inhibitor that targets various molecular pathways crucial for the growth and spread of HCC, particularly the vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) pathways involved in angiogenesis and tumor proliferation [15]. Based on phase III clinical trials (REFLECT), lenvatinib achieves an average overall survival (OS) of 13.6 months. In this trial, lenvatinib also demonstrated an acceptable safety profile, making it one of the systemic therapy alternatives for patients with advanced HCC [16]. On the other hand, atezolizumab plus bevacizumab (ATE/BEV) represents a significant combination therapy in the treatment of unresectable HCC, with synergistic effects from immunomodulatory and antiangiogenic mechanisms [16]. Atezolizumab, a PD-L1 inhibitor, enhances the immune response of the body against tumors, while bevacizumab inhibits the formation of new blood vessels through the VEGF pathway, which is necessary for tumor growth. According to the phase III clinical trial IMbrave150, the ATE/BEV combination significantly prolongs overall survival (OS) and progression-free survival (PFS) compared to sorafenib, with an average OS reaching 19.2 months [17].

Studies comparing lenvatinib and the combination of atezolizumab plus bevacizumab in the treatment of unresectable HCC have shown varying results. These inconsistencies highlight the need for a comprehensive meta-analysis to evaluate the efficacy of lenvatinib versus atezolizumab plus bevacizumab. 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, facilitating improved clinical decision-making for managing this challenging condition.

Materials and Methods

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. This study has been registered in PROSPERO (ID CRD42024624039).

Literature Selection

Literature searches were conducted in PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco to identify relevant studies up to July 2024, using the following keywords: "unresectable hepatocellular carcinoma" OR "unresectable HCC" AND "Lenvatinib" AND "Atezolizumab plus Bevacizumab" AND "Efficacy" AND "Safety". The literature searches were performed by NPSIR and NPRPD under supervisor of IGPS as a professional research 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) studies comparing Lenvatinib (LEN) and atezolizumab plus bevacizumab (ATE/BEV); (3) adult patients (18 years or older) diagnosed with unresectable HCC who met relevant diagnostic criteria; and (4) outcome indicators included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and incidence of side effects. The exclusion criteria included: (1) duplicate publications; (2) absence of a control group; (3) conference abstracts and case reports; (4) unpublish studies. The study data was also tried to be obtain through additional contact with corresponding author.

Study Quality Assessment

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. On the other hand, the Cochrane Risk-of-Bias assessment tool for randomized trials (Version 2) focuses on evaluating the quality of research methods. This tool assesses five key aspects of research design: the randomization process, adherence to planned interventions, management of missing outcome data, accuracy of outcome measurements, and selection of reported outcomes.

Data Extraction

The following data were extracted from each study: author name, publication year, country, study design, sample size, gender distribution, age, Child-Pugh class, ECOG score, and BCLC stage. The primary outcome for this meta-analysis was overall survival (OS), while secondary outcomes included progression-free survival (PFS), time to progression, objective response rate (ORR),

disease control rate (DCR), and incidence of side effects. 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

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 $I^2 < 50\%$ indicated that there was no statistical heterogeneity between trials. It indicates statistical heterogeneity between the research instead. More investigation on 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 $\alpha = 0.05$ (Figure 1).

Results

Literature Selection

A total of 930 records were identified through the initial search from online databases (PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco). As many as 39 articles were removed for duplication, and 686 studies were discarded after scanning the titles and abstracts. After a detailed reading and full text assessment, 165 articles were excluded cause by unmatched with the inclusion and exclusion criteria. As many as 27 studies lacked the related data. Finally, 12 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 6620 participants: 3745 in the lenvatinib group and 2875 in the ATE/BEV group. The published year ranged from 2022 to 2024. Based on study design, all studies are cohort study designs, most of which were retrospective, and only 1 study had a prospective design. A total of 3 studies were multicenter

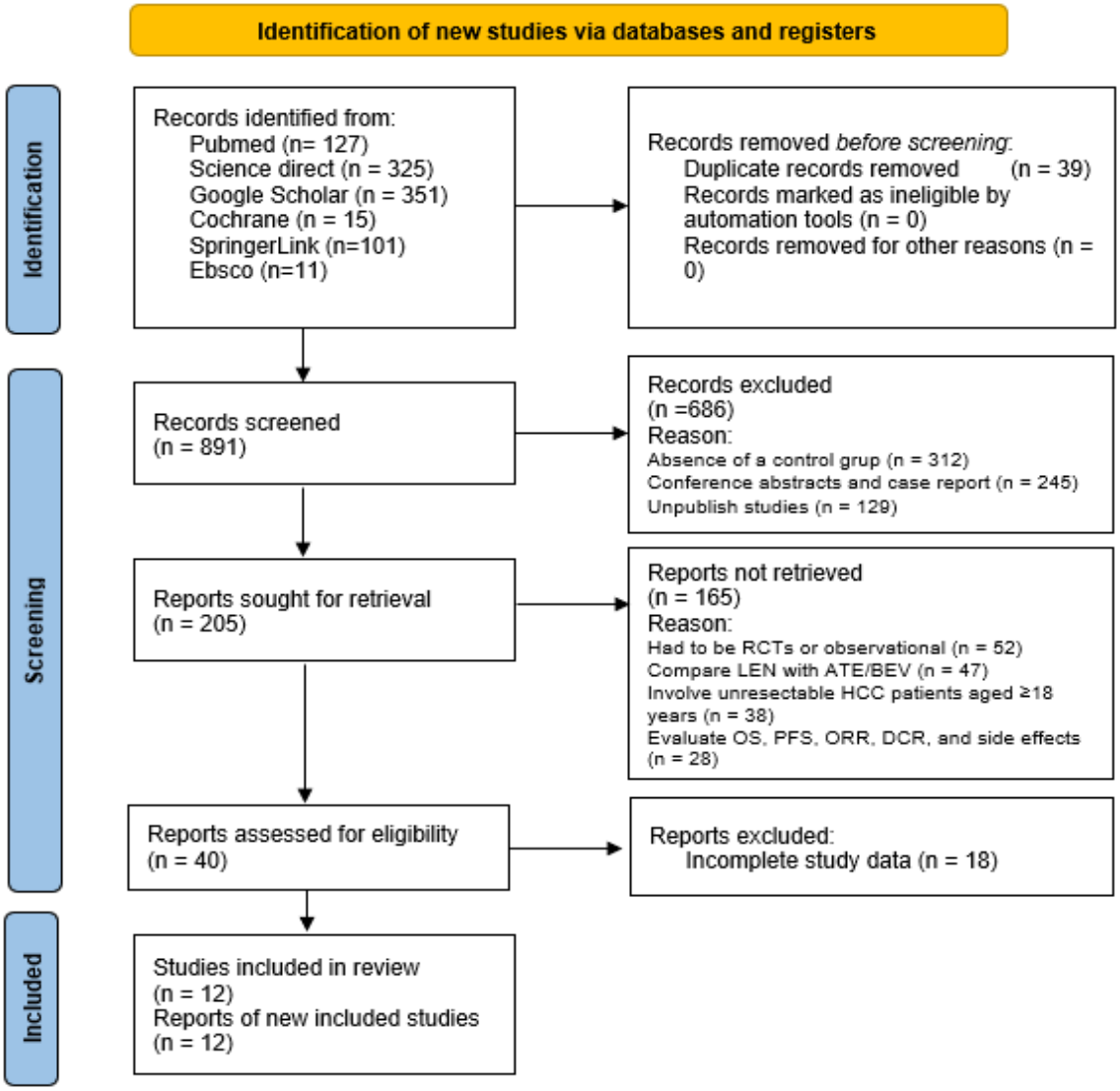

Figure 1. PRISMA Flowchart

studies, 6 studies were from Japan, 2 studies were from Korea, and only 1 study was from China. Most patients have Child-Pugh class A. Based on ECOG score, the majority of patients have ECOG score 0. According to the BCLC category, the most of patients belonged to the BCLC-B category. The NOS scores ranging from 7 to 9, indicating a high quality of data in all included studies. The characteristics of the included studies are summarized in Table 1.

Overall Survival (OS)

Three studies [20, 27, 30] that reported OS were included in the OS analysis of lenvatinib versus ATE/BEV in unresectable HCC. The meta-analysis indicated that there was no reported difference in the OS between the two groups in any of the included studies (HR=0.72; 95%CI: 0.44-1.18, p=0.20). A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.04, I^2 = 69%; Figure 2A).

Moreover, OS of viral infection analysis involved 3 studies [23, 25, 30]. In viral patients group, was no reported difference in the OS between the two groups in any of the included studies (HR=0.75; 95%CI: 0.46-1.22, p=0.24). A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.63, I^2 = 0%; Figure 2B).

OS of non-viral infection analysis involved 3 studies [20,23,27]. In non-viral patients group, was no reported difference in the OS between the two groups in any of the included studies (HR=0.81; 95%CI: 0.25-2.56, p=0.72). A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.0005, I^2 = 87%; Figure 2C).

Progression-Free Survival (PFS)

Four studies [21, 22, 27, 30] that reported PFS were included in the PFS analysis of lenvatinib versus ATE/BEV in unresectable HCC. The meta-analysis indicated there was no significant difference in the PFS between the two groups (HR=0.90; 95%CI: 0.75-1.07; p=0.23). A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.04, I^2 = 68%; Figure 3A).

Moreover, PFS of viral infection analysis involved 3 studies [21, 23, 25]. In viral patients group, there was no reported difference in the PFS between the two groups in any of the included studies (HR=0.84; 95%CI: 0.60-1.16, p=0.29). A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.94, I^2 = 0%; Figure 3B).

PFS of non-viral infection analysis involved 3 studies [20, 21, 23]. In non-viral patients group, there was no reported difference in the PFS between the two groups in any of the included studies (HR=0.89; 95%CI: 0.46-1.74, p=0.74). A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.04, I^2 = 68%; Figure 3C).

Objective Response Rate (ORR)

Eight studies[19–24, 28, 29] that reported ORR were

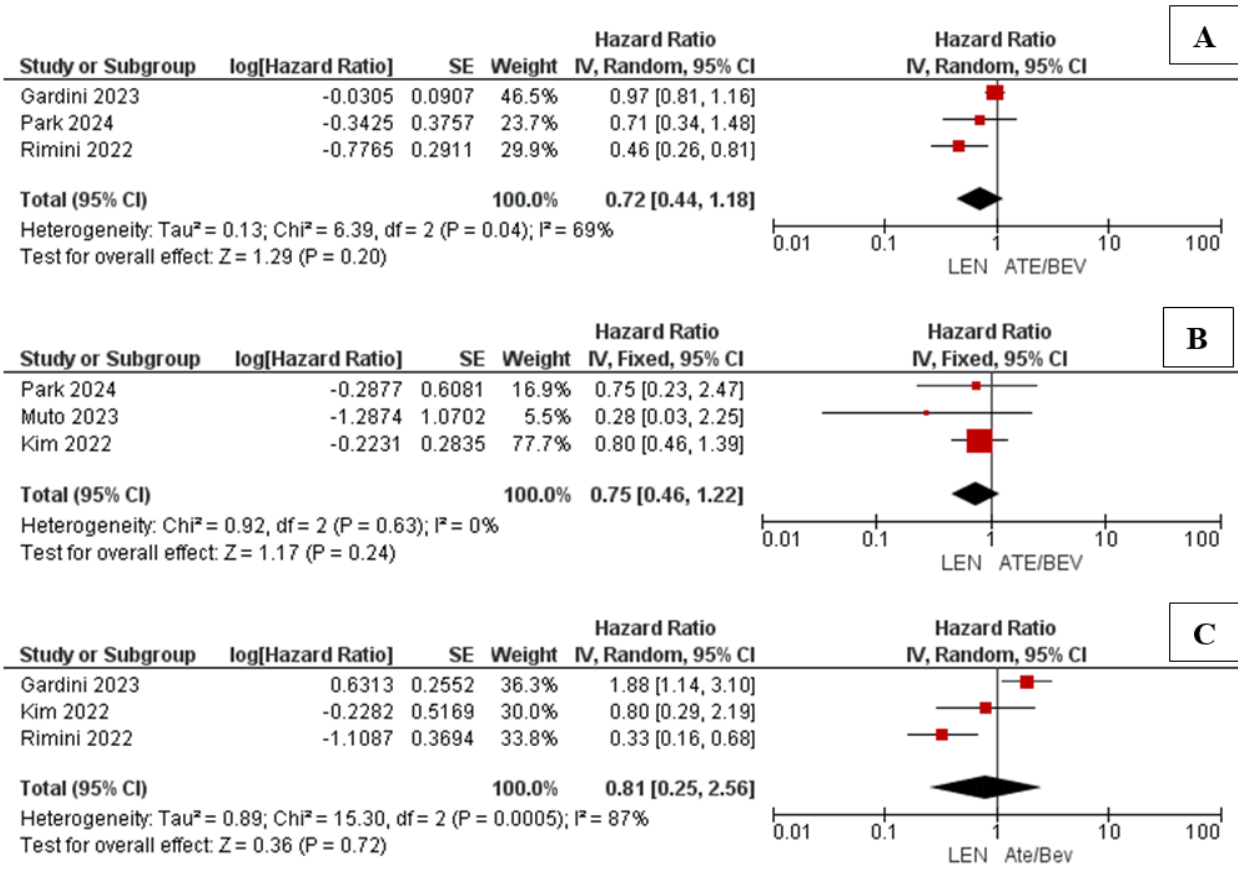

Figure 2. Forest Plot Comparing the A) OS, B) OS of viral etiology group, C) OS of non-viral etiology group between patients receiving lenvatinib and ATE/BEV

Table 1. Characteristic Study

Study, Year	Study Design	Country	Drug	Number of Sample	Male (N)	Female (N)	Range Age	Child-Pugh class: A/B		ECOG score: 0–1/2		BCLC		NOS
								A	B	0	>0	B	C	
Kimura, 2024[19]	Retrospective	Japan	LEN	41	35	6	58-86	N/A	N/A	29	7	N/A	N/A	8
			ATE/BEV	36	22	14	57-85	N/A	N/A	28	13	N/A	N/A	
Rimmini, 2022[20]	Prospective	Multicenter	LEN	187	148	39	<75/≥75 (319/250)	176	11	153	34	74	113	7
			ATE/BEV	187	146	41	<75/≥75 (111/79)	176	11	139	48	85	102	
Su, 2022[21]	Retrospective	China	LEN	46	38	8	39.8–86.9	41	5	24	22	16	30	8
			ATE/BEV	46	38	8	38.4–83.9	40	6	18	28	14	32	
Hiraoka, 2022[22]	Retrospective	Japan	LEN	57	41	16	69-79	39	18	47	10	34	23	9
			ATE/BEV	194	148	46	68-79	133	61	148	46	93	101	
Kim, 2022[23]	Retrospective	Korea	LEN	146	124	22	55-70	127	19	105	41	14	18	7
			ATE/BEV	86	70	16	56-71	82	4	36	50	132	68	
Niizeki, 2022[24]	Retrospective	Japan	LEN	152	127	25	31-93	N/A	N/A	N/A	N/A	78	68	7
			ATE/BEV	152	118	34	51-93	N/A	N/A	N/A	N/A	81	67	
Muto, 2023[25]	Retrospective	Japan	LEN	20	17	3	42-86	16	4	12	8	N/A	14	7
			ATE/BEV	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Hatanaka, 2023[26]	Retrospective	Japan	LEN	324	276	48	69-79	310	14	262	52	115	172	8
			ATE/BEV	324	276	48	70-80	310	14	274	50	122	172	
Gardini, 2023[27]	Retrospective	Multicenter	LEN	1343	1058	285	65-79	1211	132	1057	286	N/A	N/A	8
			ATE/BEV	864	682	182	64-78	778	86	679	185	N/A	N/A	
Maesaka, 2022[28]	Prospective	Japan	LEN	66	48	18	53-91	62	4	56	10	40	26	9
			ATE/BEV	66	50	16	49-93	64	2	60	6	31	35	
Persano, 2023[29]	Retrospective	Multicenter	LEN	1341	1032	309	≤70/>70 (598/714	1166	146	1088	224	554	758	7
			ATE/BEV	885	657	228	≤70/>70 (339/484)	769	54	615	208	335	488	
Park, 2024[30]	Retrospective	Korea	LEN	22	18	4	48.9-70.1	N/A	N/A	N/A	N/A	N/A	N/A	7
			ATE/BEV	30	24	6	50.3-69.3	N/A	N/A	N/A	N/A	N/A	N/A	

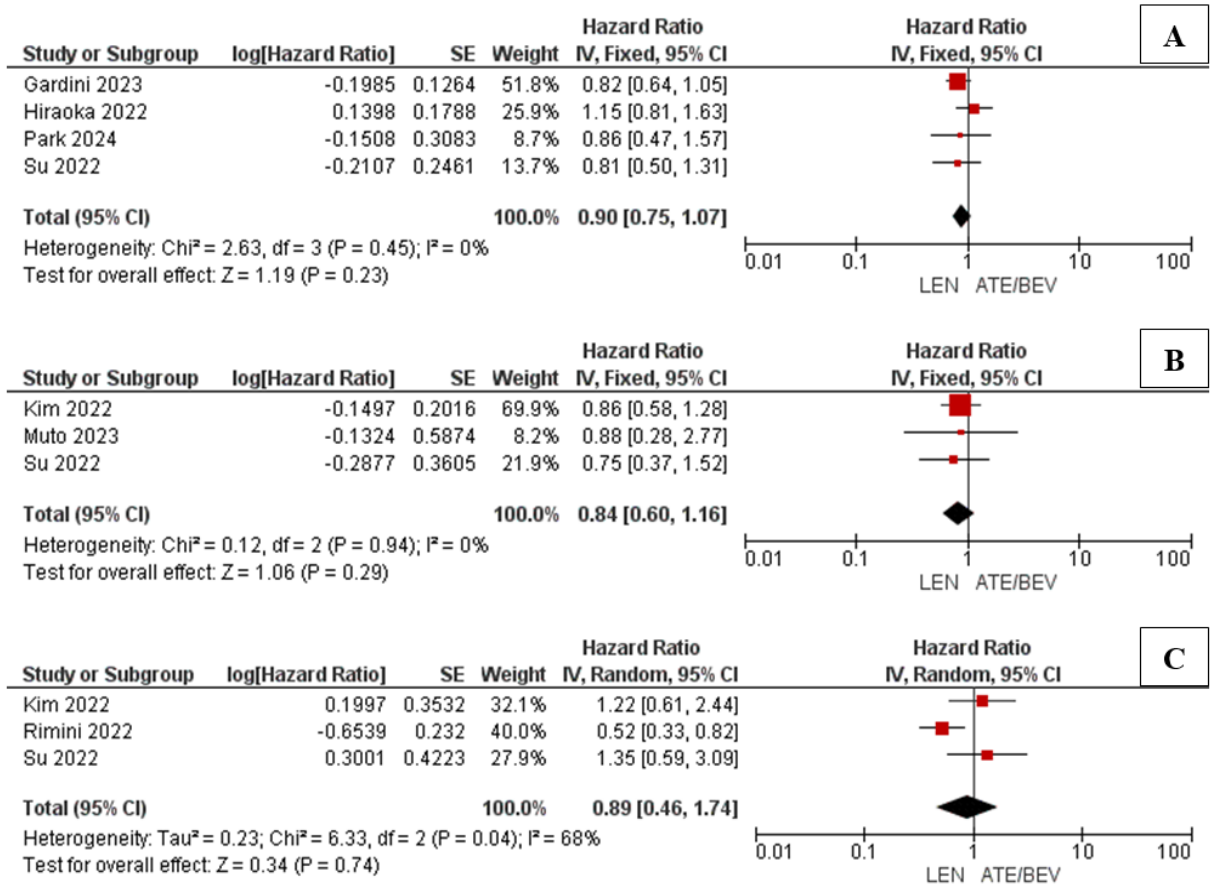

Figure 3. Forest Plot Comparing the A) PFS, B) PFS of viral etiology group, C) PFS of non-viral etiology group between patients receiving lenvatinib and ATE/BEV

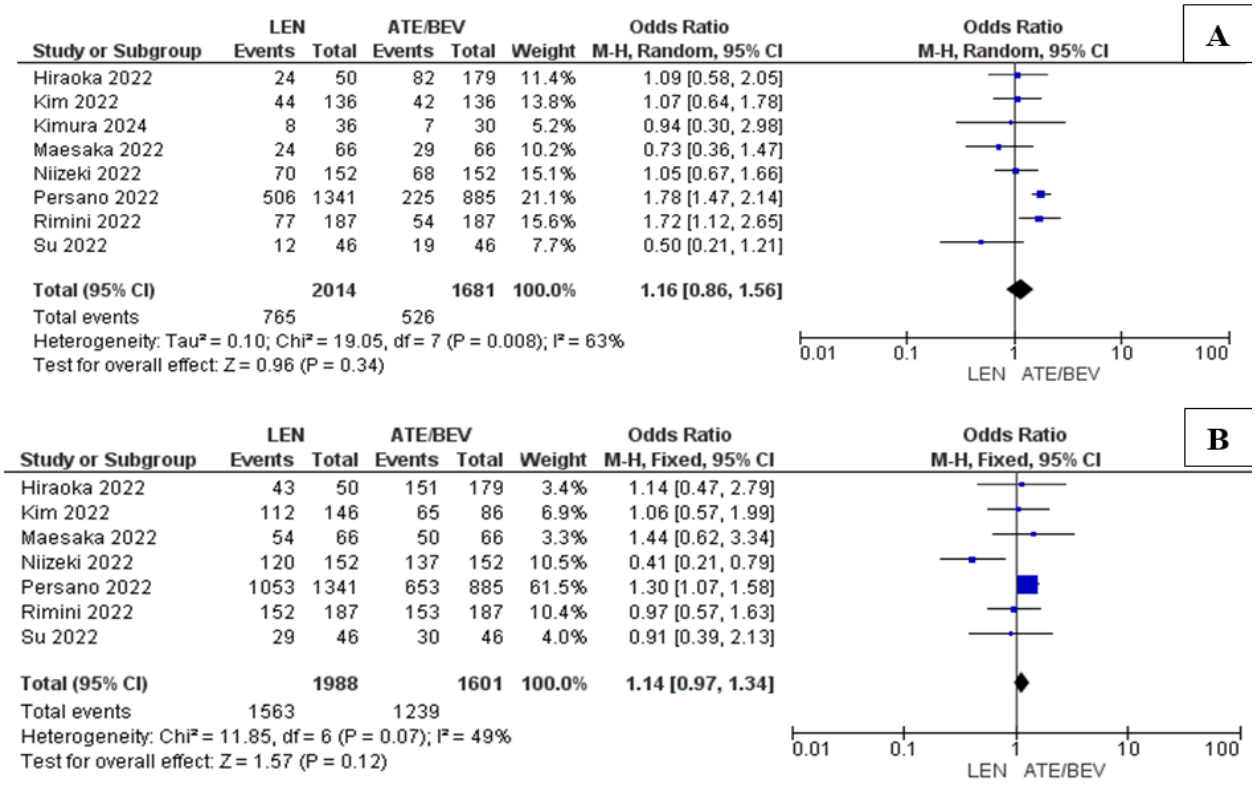

Figure 4. Forest Plot Comparing the A) objective response rate, B) disease control rate between patients receiving lenvatinib and ATE/BEV

included in the ORR analysis of lenvatinib versus ATE/BEV in unresectable HCC. The meta-analysis indicated that there was no reported difference in the ORR between the two groups in any of the included studies (OR=1.16; 95%CI:0.86-1.56; p=0.34). A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.008, I^2 = 63%; Figure 4A).

Disease Control Rate (DCR)

Seven studies [20–24, 28, 29] that reported DCR were included in the DCR analysis of lenvatinib versus ATE/BEV in unresectable HCC. The meta-analysis indicated that there was no reported difference in the DCR between the two groups (OR=1.14; 95%CI:0.97-1.34; p=0.12). A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.07, I^2 = 49%; Figure 4B).

Safety Evaluation

≥ Grade 3 Adverse Events

Three studies [19, 21, 23] that reported ≥ grade 3 adverse events were included in the analysis of lenvatinib

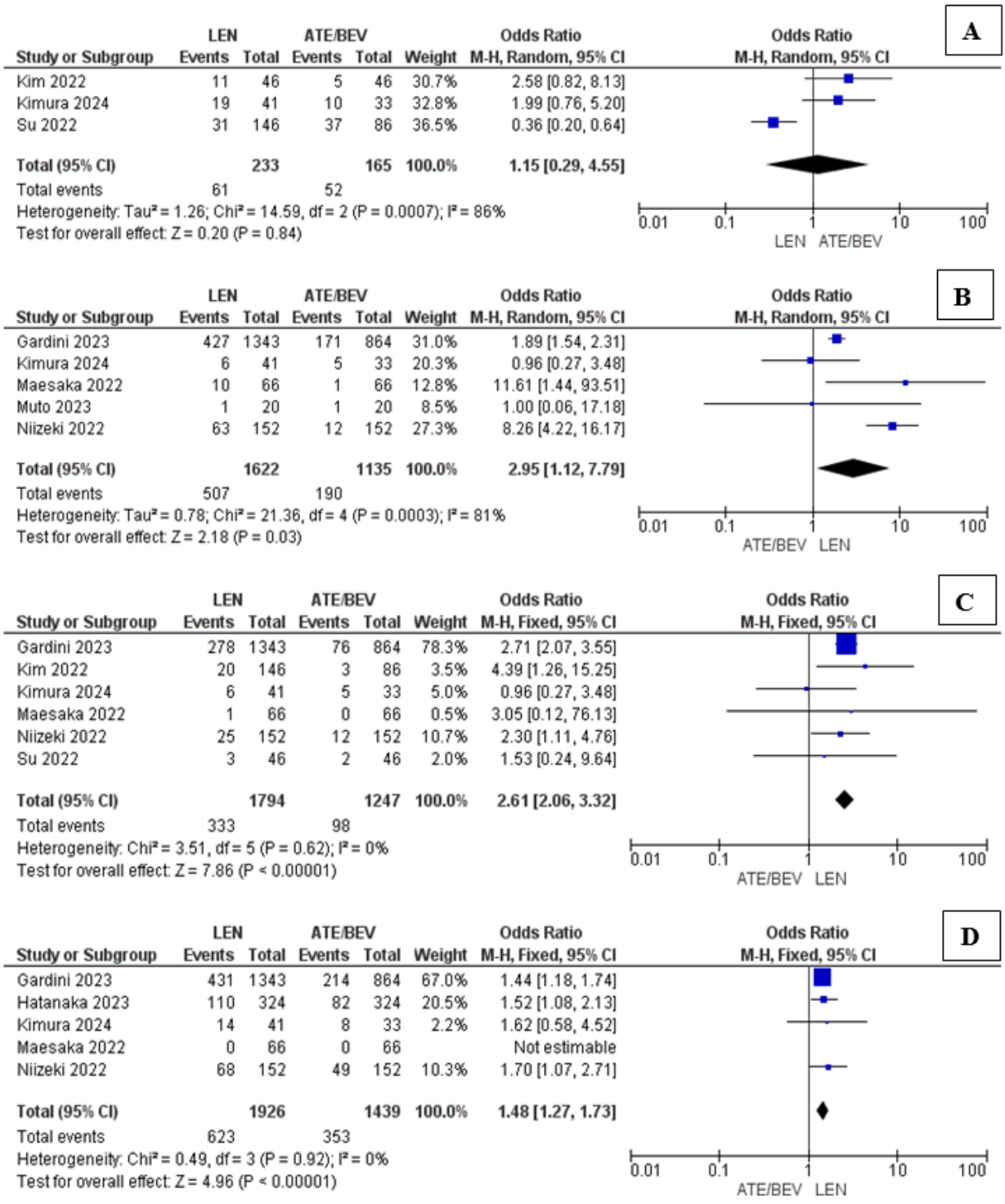

Figure 5. Forest Plot Comparing the Incidence of A) ≥ Grade 3 Adverse Events, B) decreased appetite, C) diarrhea, D) fatigue

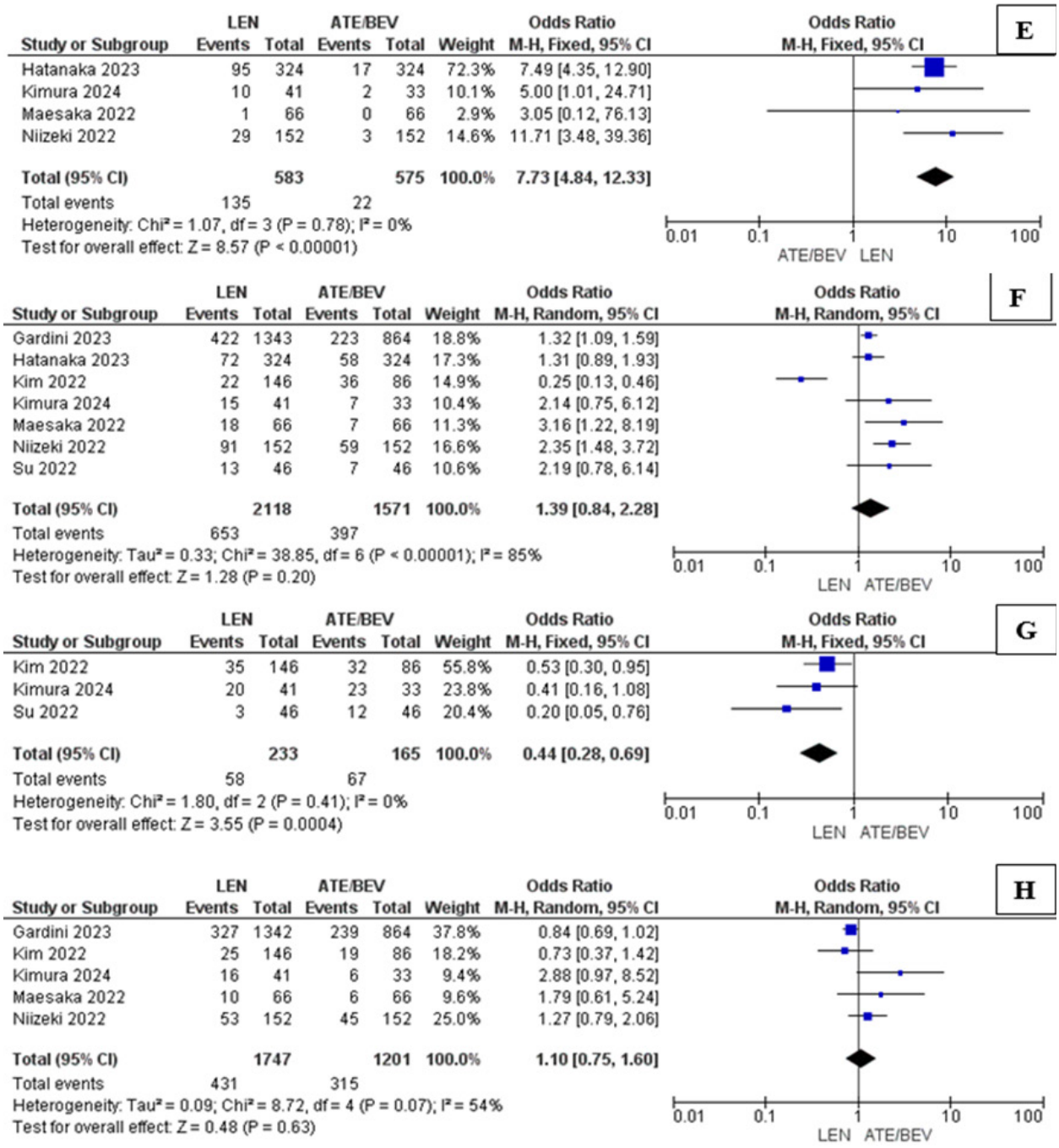

Figure 5. Forest Plot Comparing the Incidence of E) hand-foot syndrome, F) hypertension, G) increased AST, H) proteinuria

versus ATE/BEV in unresectable HCC. LEN showed similar AEs in ≥ grade 3 AEs (OR=1.15; 95%CI:0.29-4.55; p=0.84) compared to ATE/BEV. A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.0007, I^2 = 86%; Figure 5A).

Decreased Appetite

Five studies [19, 24, 25, 27, 28] that reported decreased appetite were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN exhibited higher incidences of decreased appetite (OR=2.95; 95%CI:1.12-7.79; p=0.03) compared to ATE/BEV. A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.0003, I^2 = 81%; Figure 5B).

Diarrhea

Six studies [19, 21, 23, 24, 27, 28] that reported diarrhea were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN exhibited higher incidences of diarrhea (OR=2.61; 95%CI:2.06-3.32; p<0.00001) compared to ATE/BEV. A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.62, I^2 = 49%; Figure 5C).

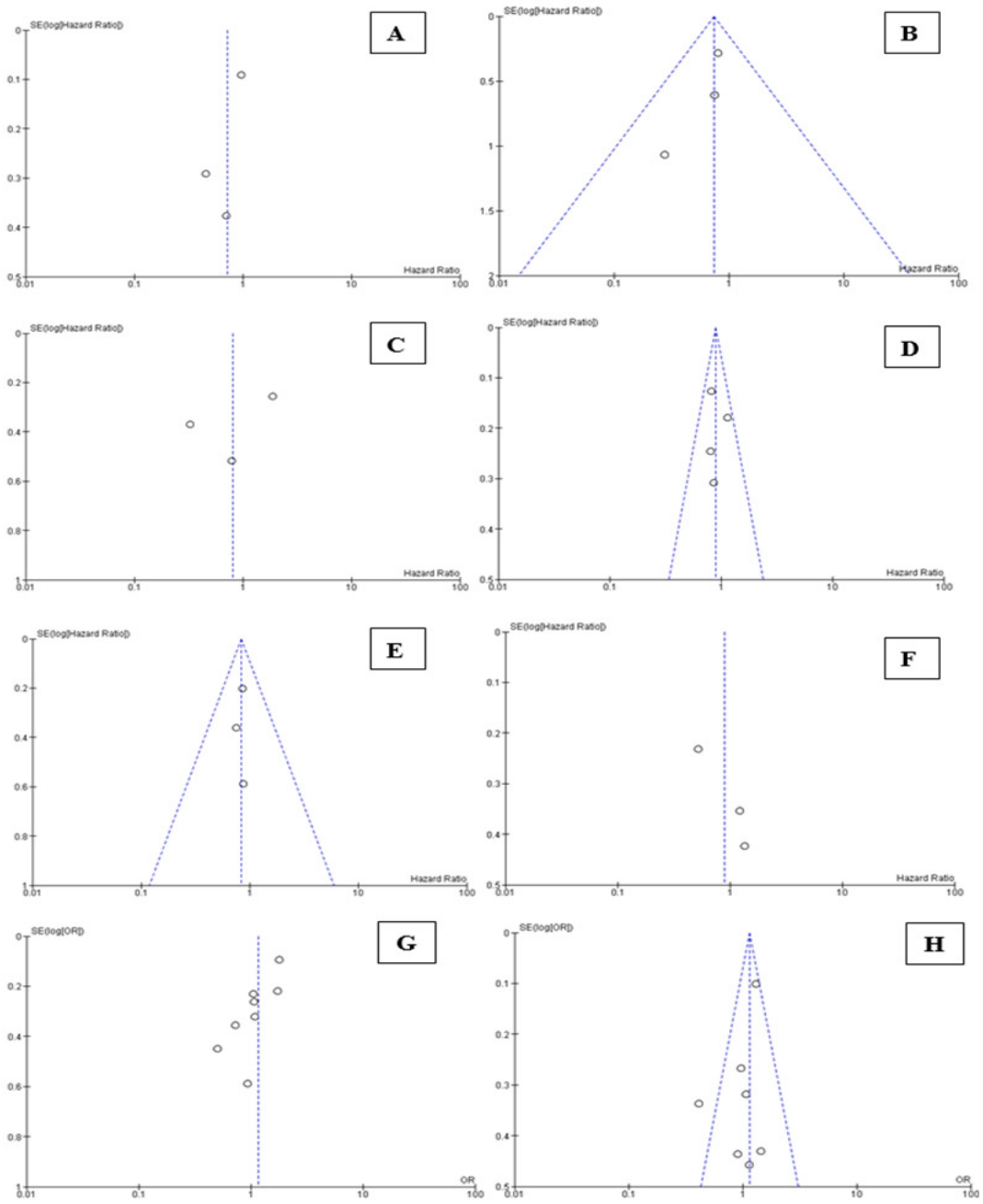

Figure 6. Funnel Plots of Efficacy LEN versus ATE/BEN in A) OS, B) OS of viral etiology group, C) OS of non-viral etiology group, D) PFS, E) PFS of viral etiology group, F) PFS of non-viral etiology group, G) ORR, H) DCR

Fatigue

Five studies [19, 24, 26–28] that reported fatigue were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN exhibited higher incidences of fatigue (OR=1.48; 95%CI:1.27-1.73; P<0.00001) compared to ATE/BEV. A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.92, I^2 = 0%; Figure 5D).

Hand-foot syndrome

Four studies [19, 24, 26, 28] that reported hand-foot syndrome were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN exhibited higher incidences of hand-foot syndrome (OR=7.73; 95%CI:4.84-12.33; P<0.00001) compared to ATE/BEV. A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.78, I^2 = 0%; Figure 5E).

Hypertension

Seven studies [19, 21, 23, 24, 26–28] that reported hypertension were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN showed similar AEs in hypertension (OR=1.39; 95%CI:0.84-2.28; p=0.20) compared to ATE/BEV. A random-effects model was used, as statistical heterogeneity was identified among the included studies (p<0.00001, I^2 = 85%; Figure 5F).

Increased AST

Three studies [19, 21, 23] that reported increased AST

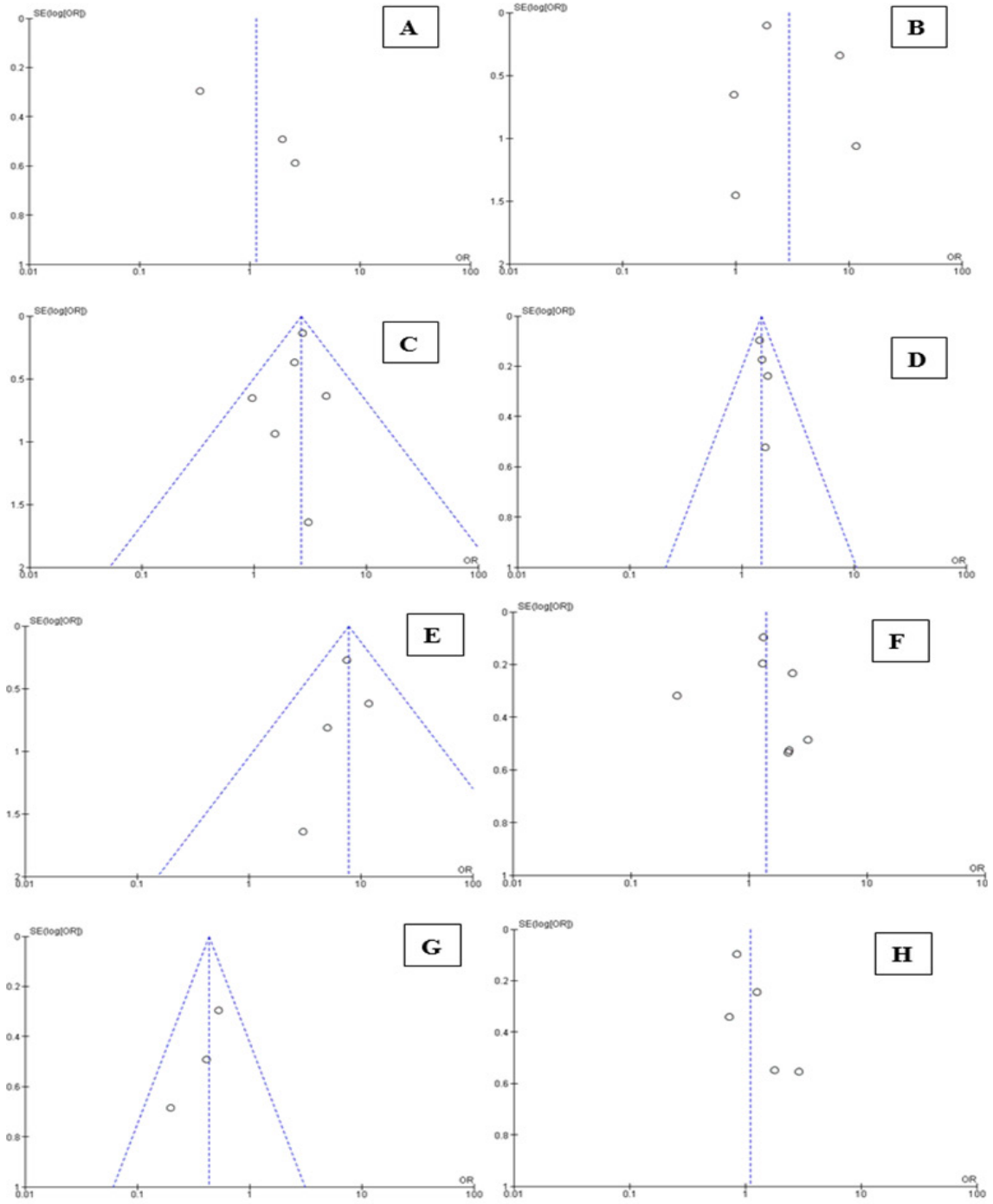

Figure 7. Funnel Plots of Safety LEN versus ATE/BEV in A) ≥ Grade 3 Adverse Events, B) decreased appetite, C) diarrhea, D) fatigue, E) hand-foot syndrome, F) hypertension, G) increased AST, H) proteinuria

were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN showed lower incidences of increased aspartate aminotransferase (OR=0.44; 95%CI:0.28-0.69; p=0.0004) compared to ATE/BEV. A fixed-effects model was used, there was no statistical heterogeneity identified among the included studies (p = 0.41, I^2 = 0%; Figure 5G).

Proteinuria

Five studies [19, 24, 27, 28, 31] that reported proteinuria were included in the analysis of lenvatinib versus ATE/BEV in unresectable HCC. LEN showed similar AEs in proteinuria (OR=1.10; 95%CI:0.75-1.60; p=0.63) compared to ATE/BEV. A random-effects model was used, as statistical heterogeneity was identified among the included studies (p = 0.07, I^2 = 54%; Figure 5H).

Risk of Bias Assessment

An analysis of the risk of publication bias was also carried out in this study and is reported in Figure 6 and 7. The results of the analysis show that the variables PFS (Figure 6D), DCR (Figure 6H), and diarrhea (Figure 7C) in the analysis of LEN versus ATE/BEV, 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 Plots indicating low risk of bias.

Discussion

First-line management for advanced hepatocellular carcinoma (HCC) includes atezolizumab plus bevacizumab (ATE/BEV) and lenvatinib as an alternative option in clinical practice. The efficacy and safety of these first-line therapies have shown varying results and require further comparison and research. The findings of the studies indicate no significant difference in overall survival (OS) and progression-free survival (PFS) between lenvatinib and ATE/BEV in patients with unresectable HCC. A study by Chung found no significant differences in objective response rate (ORR), PFS, and OS between the two groups, with ORRs of 26.1% for lenvatinib and 41.3% for ATE/BEV, and median PFS of 5.9 months for lenvatinib and 5.3 months for ATE/BEV. The incidence of adverse events was also similar between the groups (76% vs. 63%) [21]. This result aligns with this meta-analysis findings.

In a study by Rimini et al., involving 1,341 patients receiving lenvatinib and 864 receiving atezolizumab plus bevacizumab, after adjustment using inverse probability of treatment weighting (IPTW), no significant survival advantage was found for ATE/BEV compared to lenvatinib (HR 0.97; p = 0.739). However, for patients with viral infections, ATE/BEV showed improved OS compared to lenvatinib (HR: 0.76; p = 0.024). Conversely, for patients with non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD), lenvatinib extended OS (HR: 1.88; p = 0.014) [32]. In the same study Su demonstrated that lenvatinib and ATE/BEV have comparable efficacy as first-line treatments for advanced HCC, with no significant differences in ORR, PFS, or OS. Subgroup analysis emphasized that lenvatinib was not inferior to ATE/BEV, even in patients with complex characteristics such as advanced age, Child-Pugh class B, up-to-seven criteria exceedance, or portal vein invasion (VP4). However, age over 65 was identified as an independent factor associated with shorter PFS in the lenvatinib group. Regarding safety, the incidence of adverse events and the impact on liver function were similar between the two regimens, supporting good tolerability in patients with compensated liver function [21].

According to the results of a Phase III clinical trial, the REFLECT trial, lenvatinib was not inferior to alternative treatments, including sorafenib, in terms of overall survival (13.6 months vs. 12.3 months, HR = 0.92, 95%CI: 0.79-1.06) for patients with advanced HCC. Additionally, lenvatinib showed notable improvements in secondary efficacy outcomes, including PFS and ORR, compared to sorafenib [33]. As a first-line treatment option for advanced HCC, lenvatinib has been approved in the US, EU, and other countries based on the REFLECT trial, and it is the first drug used for this purpose in Japan. Combination immunotherapy with atezolizumab and bevacizumab improved outcomes, including OS, PFS, ORR, and disease control rate, compared to sorafenib monotherapy in a recent Phase III trial (IMbrave150) [34].

Lenvatinib is a multi-targeted kinase inhibitor that works on various carcinogenesis pathways and has become a globally recognized first-line systemic therapy for advanced hepatocellular carcinoma (HCC) [35, 36]. The oral administration of lenvatinib has proven effective in improving overall survival (OS) and progression-free survival (PFS) in large-scale Phase III clinical trials, showing non-inferiority compared to sorafenib [37–39]. This therapy has significantly improved the prognosis of patients with unresectable HCC since the development of tyrosine kinase inhibitor (TKI)-based therapies, underscoring lenvatinib's relevance in the context of HCC treatment, including in clinical practice [40, 41].

According to this meta-analysis, lenvatinib did not perform worse than ATE/BEV in terms of ORR and disease control rate (DCR) in patients with incurable HCC. Follow-up imaging revealed a significant drop in log10 AFP from baseline, indicating early treatment response with lenvatinib (LEN), which suggested that patients achieved disease control within four weeks in Hiraoka's trial [40]. Kuzuya et al. suggested that a good indicator of treatment response (PR, SD) is the drop in AFP ratio from baseline four weeks after starting treatment with sorafenib (SOR). In LEN treatment, a drop in log10 AFP from baseline within the first four weeks may also be indicative of therapeutic response [40]. The therapeutic efficacy of lenvatinib in HCC patients was further assessed in the Bang study. LEN showed an ORR of 20.0%, with a median PFS of 7.6 months and OS of 14.5 months in this multinational, multicenter retrospective review. According to Su's study, the ORR (lenvatinib vs. ATE/BEV: 26.1% vs. 41.3%, p = 0.1226) and DCR (lenvatinib vs. ATE/BEV: 63.0% vs. 66.7%, p = 0.8279) were comparable between the two groups [21, 42].

In terms of adverse events (AEs), lenvatinib exhibited fewer cases of elevated aspartate aminotransferase (AST) and more cases of decreased appetite, diarrhea, fatigue, and hand-foot syndrome. In the pivotal REFLECT study, 99% of patients in the lenvatinib group experienced treatment-emergent adverse events (TEAEs) (18.9 incidents per patient-year), while 94% of patients experienced treatment-related AEs. Lenvatinib recipients had TEAEs with severity greater than 3 in 75% of cases (3.2 episodes per patient-year), with treatment-related TEAEs accounting for 57% of cases [31]. Atezolizumab plus bevacizumab is the first approved immunotherapy combination for HCC, according to Gardini's study. However, it may take time for clinicians specializing in HCC to become proficient in administering this new drug, even though immunotherapy has an excellent safety profile and is easier to administer than TKIs [27].

In the Nizeki trial, ATE/BEV showed lower prevalence rates of fatigue, lack of appetite, and grade 3 or higher proteinuria compared to lenvatinib. Fatigue, proteinuria, and loss of appetite are common adverse events that lead to treatment discontinuation during systemic therapy. The ATE/BEV group experienced a lower discontinuation rate due to AEs than the lenvatinib group. One of the most intriguing aspects of clinical practice is the safety of ATE/BEV, which is well-tolerated and causes fewer adverse

events than lenvatinib. In contrast, lenvatinib-related AEs such as diarrhea, fatigue, proteinuria, and hand-foot syndrome are common, often emerging in the first two months of treatment and subsiding as patients progress [31, 43–47].

LEN also exhibited similar AEs compared to ATE/BEV in terms of grade ≥ 3 AEs, hypertension, and proteinuria. In the REFLECT study, 42% of lenvatinib-treated patients experienced hypertension, with 23% of cases classified as grade ≥ 3 [33]. One patient (0.2%) discontinued lenvatinib due to hypertension, and 3.6% of lenvatinib recipients experienced dose reduction due to hypertensive episodes. Subgroup analysis showed that patients over 75 years and female patients had a higher frequency of grade ≥ 3 hypertension [48]. Proteinuria, a common adverse event related to VEGF inhibitors, is thought to be associated with changes in glomerular architecture and compromised filtration function due to decreased nephrin synthesis. The development of proteinuria is influenced by hypertension and is linked to a higher risk of mortality, myocardial infarction, and renal failure [47]. Serious cases of proteinuria occurred in 0.6% of lenvatinib-treated patients. Proteinuria led to dose interruption in 6.9% and dose reduction in 2.5%, and three patients (0.6%) discontinued lenvatinib because of proteinuria [48].

Based on the results of this meta-analysis, Lenvatinib (LEN) demonstrates clinical effectiveness comparable to the combination of Atezolizumab/Bevacizumab (ATE/BEV) in terms of overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). These findings suggest that LEN can be considered a viable therapeutic alternative to ATE/BEV, particularly in patients who face limitations in the use of ATE/BEV due to factors such as cost, availability, or specific contraindications. However, LEN is generally associated with a higher incidence of adverse events, including anorexia, diarrhea, fatigue, and hand-foot syndrome. Severe adverse events (grade ≥ 3), such as hypertension and proteinuria, occur with similar frequency in both treatments, indicating the need for intensive monitoring of severe side effects when administering LEN. The efficacy of LEN remains consistent across both viral and non-viral etiologies, making it a flexible treatment option for diverse patient populations. Additionally, the lower incidence of elevated aspartate aminotransferase (AST) in the LEN group offers a particular benefit for patients with more vulnerable liver function. Considering this balance of efficacy and safety, LEN can be rationally utilized as either a first-line or adjunctive therapy, with careful management of adverse events.

This meta-analysis provides valuable insight into the comparative efficacy and safety of lenvatinib (LEN) and the combination of atezolizumab/bevacizumab (ATE/BEV) in the treatment of unresectable hepatocellular carcinoma (HCC), covering 6,620 samples from 12 retrospective studies. The findings suggest that LEN is as effective as ATE/BEV in terms of OS, PFS, ORR, and DCR, although LEN is associated with a higher incidence of adverse events such as anorexia, diarrhea, and hand-foot syndrome. The strength of this analysis lies in its comprehensive scope and in-depth evaluation of the side-effect profiles of both therapies. However, significant limitations include the reliance on observational studies without randomized controlled trials (RCTs), which may introduce selection bias, and the significant heterogeneity between the included studies, influenced by variations in patient characteristics and sample imbalances between groups. Additionally, the inclusion of only English-language publications may have missed relevant studies published in other languages, potentially affecting the generalizability of these findings.

In conclusion, Lenvatinib was found to be non-inferior to ATE/BEV in terms of OS, PFS, ORR, DCR in patients with unresectable HCC. In terms of safety, LEN exhibited higher incidences of decreased appetite, diarrhea, fatigue, hand-foot syndrome, and showed lower incidences of increased aspartate aminotransferase compared to ATE/BEV. Moreover, LEN showed similar AEs in grade ≥ 3 AEs, hypertension, proteinuria compared to ATE/BEV. However, larger prospective studies are necessary to validate these findings.

Author Contribution Statement

All authors contributed equally in the research processes. The idea for the study was conceived by J N.P.S.I.R. and D.A.S.; N.P.R.P.D. and K.W.A.K. screened articles for inclusion; K.W.A.K. and I.G.A.P.S. extracted and analyzed the data; the first draft of the manuscript was prepared by ., I.G.A.P.S and I.G.P.S., and edited by D.A.S. and I.K.M.; all authors reviewed the final version.

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Data Availability

The datasets used in this study are publicly available in international databases (PubMed, ScienceDirect, Google Scholar, Cochrane Library, SpringerLink, and Ebsco) and can be accessed using the search terms provided in the Methods section

Study Registration

This study has been registered in PROSPERO (ID CRD42024624039

Funding Statement

None.

Ethical Declaration

This meta-analysis is an review article that do not have any ethical declaration file.

Conflict of Interest

The authors declare that they have no conflict of interest regarding this study.

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