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ORIGINAL RESEARCH

Real-World Comparison of Lenvatinib and Sorafenib as First-Line Treatments for Hepatocellular Carcinoma: A Multicenter Study

Mira Kang[1,*], Won Chul Cha[2,*], Dong Hyun Sinn[3], Woo Kyoung Jeong[4], Do Young Kim[5], Min Ji Lee[6], Subin Lim[6], DongKyu Kim[6], Kyu-Pyo Kim[7], Baek-Yeol Ryoo[7], Won-Mook Choi[8], Kang Mo Kim[8], Ki-Hun Kim[9], Doik Lee[10], Eui Jun Choi[10], Choungwon Jung[10], Joohyun Kim[10], Jung Yong Hong[11]

[1]Health Promotion Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [6]Real-World Evidence Team, ALYND, Yonsei University Health System, Seoul, Republic of Korea; [7]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [9]Division of Liver Transplantation and Hepatobiliary Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Real World Solutions, IQVIA Solutions Korea Ltd., Seoul, Republic of Korea; [11]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

*These authors contributed equally to this work

Correspondence: Jung Yong Hong, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul, Republic of Korea, Tel +82-2-3410-1211, Fax +82-2-3412-3996, Email jungyong.hong@samsung.com

Introduction: Lenvatinib and sorafenib remain viable first-line (1L) options for patients ineligible for newer therapies. This study uses real-world data (RWD) to compare the effectiveness and safety of lenvatinib and sorafenib, addressing gaps between clinical trials and real-world practice.

Materials and Methods: This retrospective, multi-center study utilized the Liver Cancer IN Korea (LINK) database, including HCC patients diagnosed between January 2015 and June 2022 who received 1L lenvatinib or sorafenib. Effectiveness and safety were assessed with real-world overall survival (rwOS), time to treatment discontinuation (rwTTD), time to next treatment (rwTTNT), and incidence of adverse events of special interest (AESI). Propensity score matching was employed to adjust for potential bias.

Results: Post-matching, lenvatinib demonstrated a longer median rwOS of 9.56 months (95% CI: 8.25–10.78) compared to 7.13 months (95% CI: 6.44–7.82) of sorafenib, and longer medians for rwTTD (3.65 months, 95% CI: 3.09–4.07 vs 2.04 months, 95% CI: 1.87–2.30) and rwTTNT (6.51 months, 95% CI: 5.62–7.62 vs 3.71 months, 95% CI: 3.45–4.34). Regarding AESI, lenvatinib was significantly associated with lower rates of hand-foot syndrome (incidence rate ratio, IRR 0.55, 95% CI: 0.33–0.88, $p = 0.013$) and most hepatotoxicity-related events, but a higher rate of proteinuria (IRR 2.40, 95% CI: 1.49–3.98, $p < 0.001$).

Conclusion: Leveraging RWD, our study demonstrated that 1L lenvatinib may offer a survival advantage over 1L sorafenib in HCC patients, with both treatments exhibiting safety profiles consistent with clinical trials. RWD complements clinical trials by validating long-term outcomes and addressing patient populations excluded from pivotal studies, guiding therapeutic decisions in clinical practice.

Keywords: hepatocellular carcinoma, lenvatinib, sorafenib, real-world evidence

Introduction

Hepatocellular carcinoma (HCC) is a primary liver malignancy that poses a significant global health burden, accounting for 75%-85% of primary liver cancer cases worldwide and ranking among the leading causes of cancer-related deaths.[1] Despite

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advancements in therapeutic approaches and relatively high rate of early diagnosis in regions like South Korea, treating HCC remains challenging due to its high recurrence rates and associated mortality, necessitating systemic therapy.[2,3] Sorafenib has been the standard first-line (1L) treatment for unresectable HCC since its introduction in 2008,[4,5] with lenvatinib emerging in 2018 as a viable alternative after demonstrating non-inferiority in the REFLECT trial.[6–8]

More recently, the therapeutic landscape of HCC has seen considerable growth, driven by the introduction of immune checkpoint inhibitors and combination therapies.[9] Pivotal studies such as IMBRAVE 150, HIMALAYA, and CHECKMATE have been instrumental in this expansion, introducing therapies like atezolizumab plus bevacizumab,[10] tremelimumab plus durvalumab,[11] and nivolumab with ipilimumab,[12] respectively, broadening the array of treatment options. However, not all patients are eligible for these combination therapies, including those who have undergone liver transplantation (LT) or with underlying conditions such as autoimmune diseases or those requiring corticosteroid or immunosuppressive therapy.[9,13,14] For these instances, lenvatinib and sorafenib remain valuable options as 1L therapeutic regimens.

Despite their continued relevance, studies comparing lenvatinib and sorafenib showed inconsistent results in real-world settings.[15] While clinical trials are considered the gold standard for evaluating drug efficacy and safety, their findings in controlled settings often do not translate directly to real-world clinical practice.[16] Given the limited large-scale real-world comparative data on lenvatinib and sorafenib in the South Korean population, bridging this gap is crucial for enhancing clinical understanding. Leveraging the comprehensive real-world data from the Liver Cancer IN Korea (LINK) database,[17] this study aims to provide a robust analysis of the comparative effectiveness and safety of lenvatinib and sorafenib in a large, diverse patient cohort, thereby offering a reliable basis for clinical decision-making.

Materials and Methods

Study Cohort Selection and Matching

Utilizing the LINK research database, we included patients newly diagnosed with HCC between 1 January 2015 and 30 June 2022, who received either lenvatinib or sorafenib as 1L therapy. We applied the following additional exclusion criteria to account for potential bias before receiving 1L: patients with a history of liver transplantation at any point, and patients who underwent hepatectomy, loco-regional therapy, or radiation therapy within 28 days before initiating 1L treatment.[8] Patients were further excluded if insufficient data were available to determine the baseline condition.

To adjust for potential confounders and baseline characteristics discrepancies, we performed propensity score (PS) matching between the lenvatinib and sorafenib cohorts using one-to-one nearest-neighbor approach within a caliper of 0.20. PS were estimated using variables selected based on literature reviews and consultations with clinical experts, that were expected to impact the treatment selection: age, sex, body mass index (BMI), smoking history, drinking history, modified albumin-bilirubin (mALBI) grade at diagnosis, mALBI grade at initiation of 1L, metastasis presence, and alpha-fetoprotein (AFP).

Real-World Outcomes and Safety Profiles

Treatment effectiveness was evaluated using the endpoints established for real-world oncology studies:[18] real-world OS (rwOS; time from 1L initiation to death), real-world time to treatment discontinuation (rwTTD; time from 1L initiation to 1L discontinuation or death), and real-world time to next treatment (rwTTNT; time from 1L initiation to the start of subsequent line of therapy or death).

Safety profiles were assessed by identifying newly observed adverse event of special interest (AESI): hypertension, hand-foot syndrome (HFS), proteinuria, hepatotoxicity-related events such as increase in alanine aminotransferase (ALT), increase in aspartate aminotransferase (AST), increase in alkaline phosphatase (ALP), increase in gamma-glutamyl transferase (GGT), increase in blood bilirubin, and bilirubinuria. AESI were identified using relevant Korean Standard Classification of Diseases-7 (KCD-7) diagnosis codes, prescription records, and/or laboratory results. Laboratory-identified AESI were defined as Grade 1 or higher according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[19] Only the first occurrence of each AESI was considered during the assessment window, which spanned from the day after 1L initiation to the earliest of either 28 days after the last dose or one day before the start of subsequent line of therapy.

Statistical Analysis

Patient demographics and clinical characteristics for each cohort were summarized using descriptive statistics. Continuous variables were summarized with inverse variance weighted means and standard errors (SE) to account for the data pooled from multiple sites, while categorical variables were summarized using frequencies and proportions. The chi-square test and the absolute standardized mean difference (aSMD) were used to measure covariate balance between two treatment cohorts. The Kaplan-Meier (KM) method was used to estimate rwOS, rwTTD, and rwTTNT with 95% confidence intervals (CI), and differences were evaluated using the Log rank test. The incidence rate of each AESI was summarized using the number of patients experiencing the event and total person-years (PY), with differences evaluated using the incidence rate ratio (IRR) test. All statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), with two-sided tests and a significance level set at 0.05.

Results

Patient Characteristics and Treatment

Among 30,565 patients of LINK database who were newly diagnosed with HCC between 1 January 2015 and 30 June 2022, our study included 1,361 eligible patients who received either lenvatinib or sorafenib as 1L (lenvatinib, n = 359; sorafenib, n = 1,002) before PS matching. Of these, 686 patients were included after PS matching with a 1:1 ratio (lenvatinib, n = 343; sorafenib, n = 343) (Figure 1).

Demographics and clinical characteristics before and after PS matching are shown in Table 1. Before PS matching, the median follow-up duration was longer in the lenvatinib cohort than in the sorafenib cohort (13.22 months vs 12.29 months). Regardless of PS matching, hepatitis B and liver cirrhosis were identified as the most common disease etiology and comorbidity in both cohorts, and the most frequent initial treatment types followed the order of lenvatinib or sorafenib, transarterial therapy, and hepatectomy in both cohorts.

The proportions of male patients ($p < 0.001$) and former/current drinkers ($p = 0.002$) were significantly higher in the sorafenib cohort, whereas the proportion of patients with mALBI grade 1/2a at diagnosis ($p = 0.016$) was significantly higher in the lenvatinib cohort before PS matching. After PS matching, all baseline characteristics considered for PS matching were well balanced between the two cohorts with aSMD consistently below 0.1 (Table 1).

Following initial treatment with lenvatinib or sorafenib, 26.18% of patients in the lenvatinib cohort received sorafenib as a second-line therapy, while 21.66% of patients in the sorafenib group switched to other TKIs apart from lenvatinib. The proportion of patients not receiving any second-line treatment was similar in both cohorts (lenvatinib: 59.33%, sorafenib: 60.58%) (Supplementary Figure S1). These treatment patterns remained consistent after PS matching.

Real-World Treatment Effectiveness

The KM-estimated median rwOS was 9.56 months (95% CI: 8.25–10.78) in the lenvatinib cohort, which was longer than the median rwOS of 7.13 months (95% CI: 6.44–7.82) in the sorafenib cohort with statistical significance ($p = 0.001$) (Figure 2). After PS matching, the median rwOS remained longer in the lenvatinib cohort compared to the sorafenib cohort, and the difference between the cohorts was statistically significant (9.56 months, 95% CI: 8.25–10.78 vs 7.43 months, 95% CI: 6.44–9.26; $p = 0.013$).

When stratified and assessed by the patient characteristics expected to affect prognosis, the lenvatinib cohort (n = 41) showed longer median rwOS in the Child-Pugh class B patients compared to the sorafenib cohort (n = 41) with statistical significance (7.06 months, 95% CI: 2.86-NA vs 3.09 months, 95% CI: 1.87–4.44; $p = 0.010$) (Table 2). No significant difference was observed between the two cohorts in other subgroups.

Lenvatinib consistently exhibited longer median values for rwTTD and rwTTNT with significant difference between the cohorts regardless of PS matching (Figure 3). After PS matching, the median rwTTD was 3.65 months (95% CI: 3.09–4.07) in the lenvatinib cohort and 2.04 months (95% CI: 1.87–2.30) in the sorafenib cohort, and the median rwTTNT was 6.51 months (95% CI: 5.62–7.62) in the lenvatinib cohort and 3.71 months (95% CI: 3.45–4.34) in the sorafenib cohort.

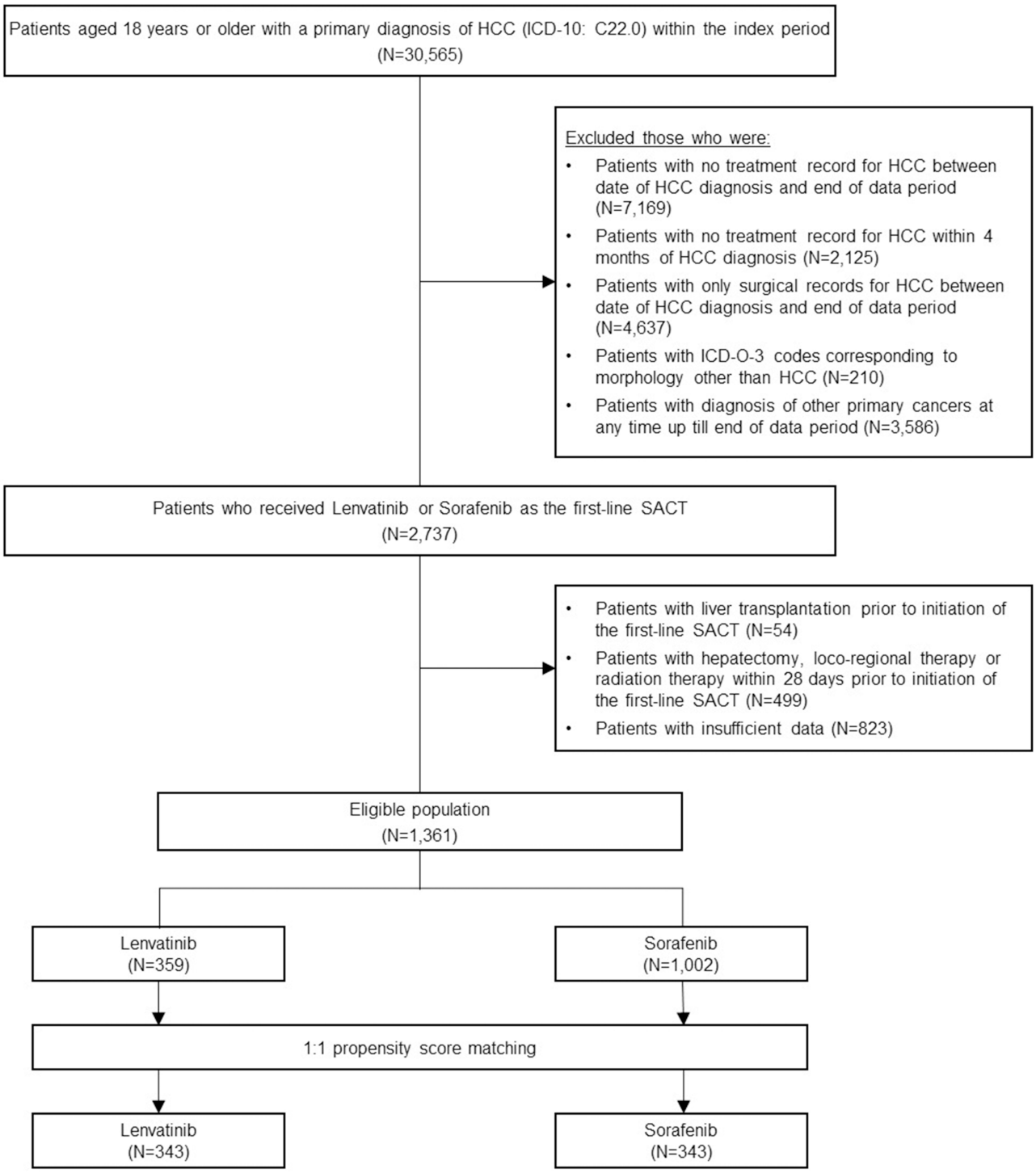

Figure 1 Selection and matching flow of the eligible patients.
Abbreviations: HCC, hepatocellular carcinoma; ICD-10, International Classification of Diseases-10th Edition; ICD-O-3, International Classification of Diseases for Oncology-3rd Edition; SACT, systemic anti-cancer therapy.

Table 1 Demographic and Clinical Characteristics Before and After Propensity Score Matching

		Before PS Matching						After PS Matching					
		Lenvatinib		Sorafenib		P-value[a]	aSMD	Lenvatinib		Sorafenib		P-value[a]	aSMD
		N	%	N	%			N	%	N	%		
		359	100.00	1002	100.00			343	100.00	343	100.00		
Patient Demographics													
Age group at 1L initiation[b] (years)	Mean (SE) Median (Q1 – Q3)	59.62 (0.60) 59.00 (53.00–67.00)		58.51 (0.32) 58.00 (52.00–65.00)				59.20 (0.62) 59.00 (52.00–67.00)		59.07 (0.59) 58.50 (51.50–66.50)			
	≥60 <60	177 182	49.3 50.7	449 553	44.81 55.19	0.160	0.090	162 181	47.23 52.77	159 184	46.36 53.64	0.878	0.018
Sex[b]	Male Female	292 67	81.34 18.66	893 109	89.12 10.88	<0.001[c]	0.221	288 55	83.97 16.03	291 52	84.84 15.16	0.833	0.024
BMI group at diagnosis[b] (kg/m^2)	Obese: ≥25 Non-obese: <25	130 229	36.21 63.79	360 642	35.93 64.07	0.975	0.006	122 221	35.57 64.43	118 225	34.4 65.6	0.810	0.025
Smoking history[b]	Former/Current smoker Never smoker	234 125	65.18 34.82	697 305	69.56 30.44	0.143	0.094	229 114	66.76 33.24	234 109	68.22 31.78	0.744	0.031
Drinking history[b]	Former/Current drinker Never drinker	240 119	66.85 33.15	766 236	76.45 23.55	<0.001[c]	0.214	237 106	69.1 30.9	235 108	68.51 31.49	0.934	0.013
Clinical Characteristics													
ECOG PS at diagnosis	0 1-2 3-4 Unknown/Missing	162 80 3 114	45.13 22.28 0.84 31.75	447 304 8 243	44.61 30.34 0.80 24.25	0.008[d]	0.116	159 74 3 107	46.36 21.57 0.87 31.20	166 103 4 70	48.40 30.03 1.17 20.41	0.005[d]	0.190
CP class at diagnosis	Class A Class B/C Unknown/Missing	234 52 73	65.18 14.48 20.33	647 276 79	64.57 27.54 7.88	<0.001[c]	0.163	220 50 73	64.14 14.58 21.28	238 69 36	69.39 20.12 10.50	<0.001[c]	0.214
mALBI grade at diagnosis[b]	Grade 1/2a Grade 2b/3	264 95	73.54 26.46	615 387	61.38 38.62	<0.001[c]	0.262	249 94	72.59 27.41	250 93	72.89 27.11	1.000	0.007
mALBI grade at 1L initiation[b]	Grade 1/2a Grade 2b/3	214 145	59.61 40.39	496 506	49.5 50.5	0.001[d]	0.204	205 138	59.77 40.23	206 137	60.06 39.94	0.059	0.006

(*Continued*)

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Table 1 (Continued).

		Before PS Matching						After PS Matching					
		Lenvatinib		Sorafenib		P-value[a]	aSMD	Lenvatinib		Sorafenib		P-value[a]	aSMD
		N	%	N	%			N	%	N	%		
		359	100.00	1002	100.00			343	100.00	343	100.00		
Disease etiology	Hepatitis B	280	77.99	793	79.14			267	77.84	271	79.01		
	Hepatitis C	25	6.96	70	6.99			23	6.71	22	6.41		
	Alcohol-related liver disease	59	16.43	189	18.86			58	16.91	55	16.03		
Comorbidities	Liver cirrhosis	55	15.32	134	13.37			52	15.16	43	12.54		
	Hypertension	12	3.34	36	3.59			11	3.21	10	2.92		
	Diabetes mellitus	10	2.79	28	2.79			9	2.62	9	2.62		
No. of tumors	1-3	175	48.75	496	49.50	0.150	0.002	163	47.52	178	51.90	0.472	0.082
	4+	8	2.23	9	0.90			7	2.04	5	1.46		
	Unknown/Missing	176	49.03	497	49.60			173	50.44	160	46.65		
Metastases at diagnosis[b]	Presence	66	18.38	191	19.06	0.839	0.017	65	18.95	65	18.95	1.000	0.000
	Absence	293	81.62	811	80.94			278	81.05	278	81.05		
AFP group at diagnosis[b]	≥200	171	47.63	518	51.7	0.208	0.081	165	48.1	175	51.02	0.492	0.058
	<200	188	52.37	484	48.3			178	51.9	168	48.98		
Initial treatment	Lenvatinib or sorafenib	154	42.90	466	46.51	0.062	0.092	151	44.02	150	43.73	0.566	0.014
	Transarterial therapy	137	38.16	368	36.73			130	37.90	131	38.19		
	Hepatectomy	47	13.09	132	13.17			42	12.24	47	13.70		
	Liver transplantation	4	1.11	7	0.70			3	0.87	2	0.58		
	Local ablation therapy	13	3.62	12	1.20			13	3.79	6	1.75		
	EBRT	4	1.11	17	1.70			4	1.17	7	2.04		

Notes: [a]Chi-squared test. [b]Variables used for propensity score matching. [c]$p < 0.001$. [d]$p < 0.01$.

Abbreviations: PS, propensity score; aSMD, absolute standardized mean difference; 1L, first-line; SE, standard error; Q1, first quartile; Q3, third quartile; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CP, Child-Pugh; mALBI, modified albumin-bilirubin; AFP, alpha fetoprotein; EBRT, external beam radiation therapy.

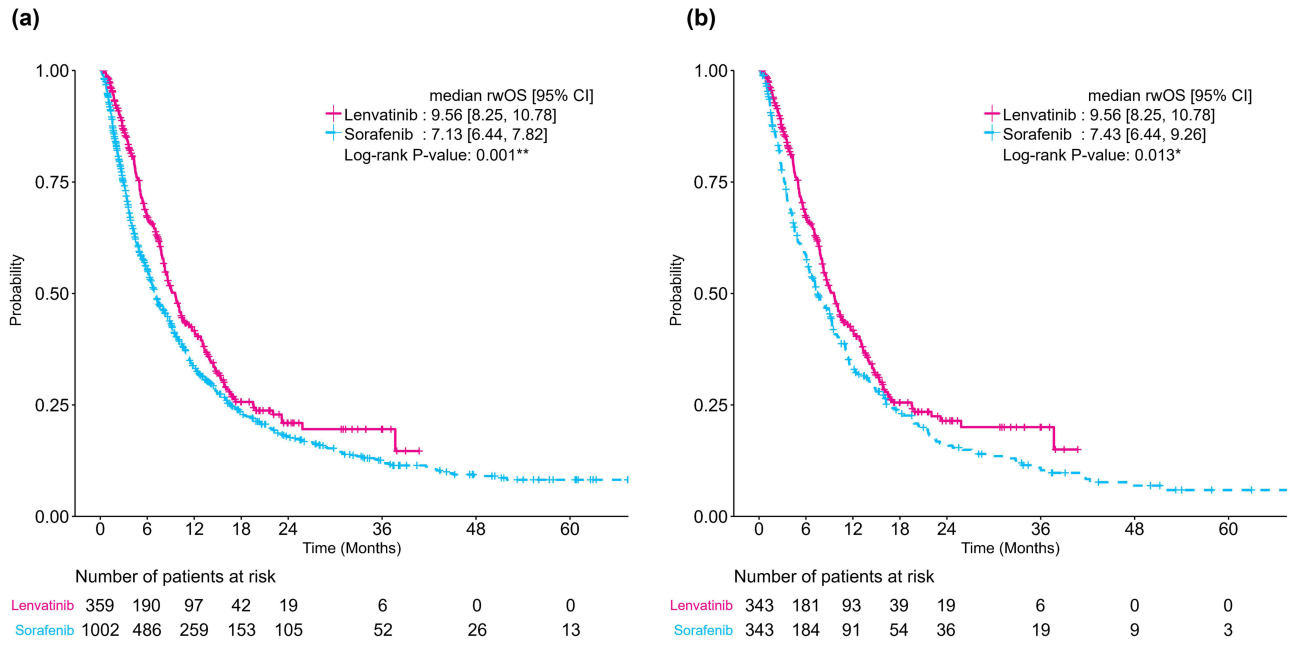

Figure 2 Real-world overall survival following the initiation of 1L lenvatinib and 1L sorafenib (**a**) before PS matching and (**b**) after PS matching. *p < 0.05. **p < 0.01.
Abbreviations: rwOS, real-world overall survival; PS, propensity score; CI, confidence interval.

Adverse Event of Special Interest (AESI)

For AESI, the lenvatinib cohort was significantly associated with lower rates of HFS ($p < 0.001$) and all hepatotoxicity-related events (ALT $p < 0.001$; AST $p < 0.001$; ALP $p < 0.001$; GGT $p = 0.014$) except for blood bilirubin ($p = 0.248$), whereas the sorafenib cohort was significantly associated with lower rates of hypertension ($p < 0.001$), proteinuria ($p < 0.001$), and bilirubinuria ($p = 0.008$). The trend persisted after PS matching while the associations of the sorafenib group for hypertension (IRR 1.58, 95% CI: 0.77–3.43, $p = 0.247$) and bilirubinuria (IRR 1.11, 95% CI: 0.79–1.56, $p = 0.585$) were no longer significant (Figure 4).

Table 2 Real-World Overall Survival by Propensity Score-Matched Subgroups

PS-Matched Subgroups		Lenvatinib		Sorafenib		P-value[a]
		N	Median rwOS [95% CI]	N	Median rwOS [95% CI]	
CP class at diagnosis	Class A	213	9.59 [7.82, 11.70]	213	9.33 [7.16, 11.07]	0.812
	Class B	41	7.06 [2.86, NA]	41	3.09 [1.87, 4.44]	0.010[b]
	Class C		NE[c]		NE[c]	
mALBI grade at initiation of 1L	Grade 1	131	13.27 [10.51, 15.84]	131	11.04 [9.36, 14.36]	0.262
	Grade 2a	61	8.67 [7.62, 13.93]	61	7.39 [4.70, 12.35]	0.287
	Grade 2b	109	5.95 [5.03, 7.82]	109	6.05 [4.30, 9.07]	0.746
	Grade 3		NE[c]		NE[c]	

Notes: [a]Log-rank test. [b]p < 0.05. [c]Not estimated due to limited number of patients.
Abbreviations: PS, propensity score; rwOS, real-world overall survival; CI, confidence interval; CP, Child-Pugh; mALBI, modified albumin-bilirubin; 1L, first-line; RPVI, radiological portal vein invasion; NA, Not Available; NE, Not Evaluable.

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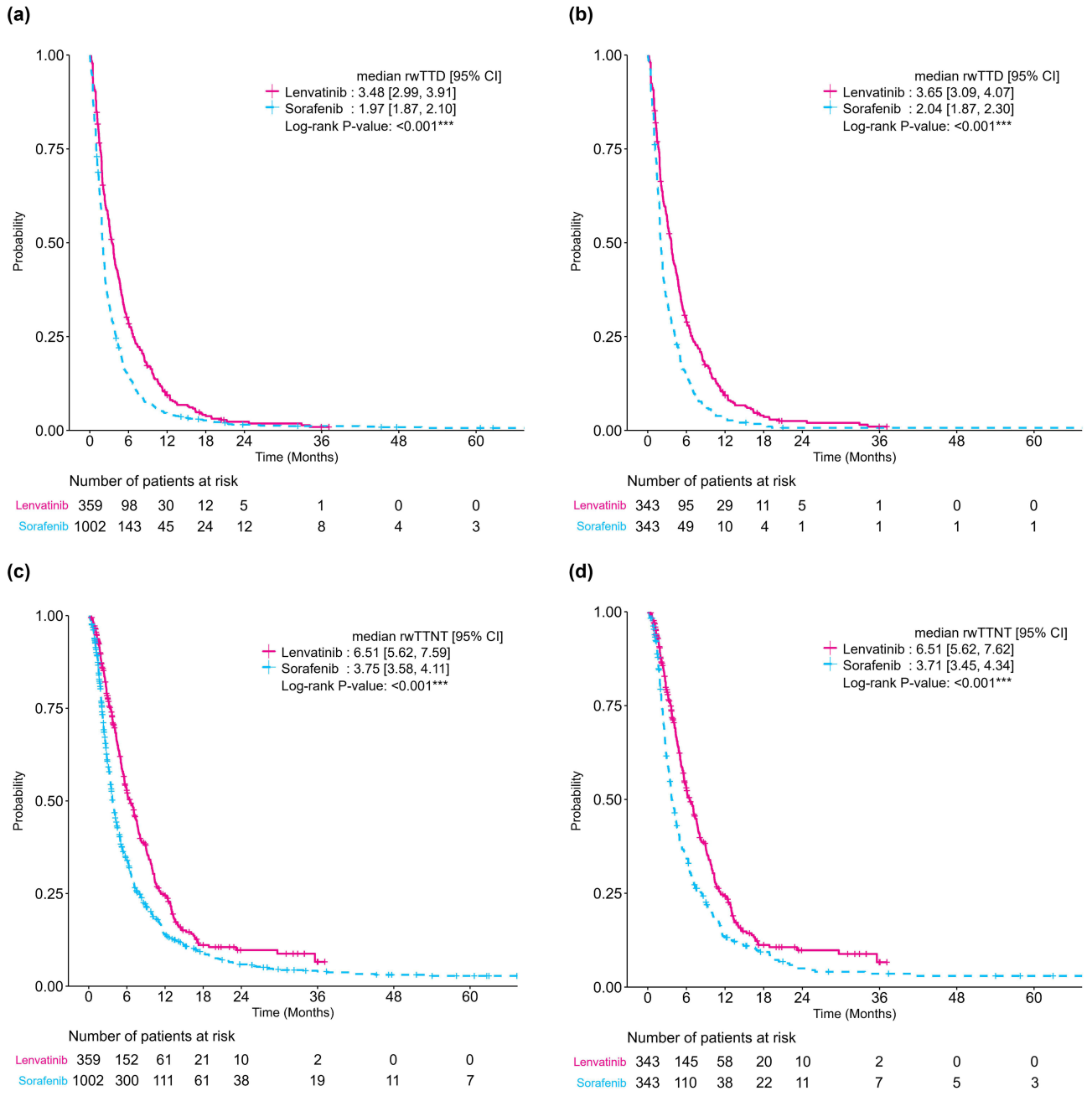

Figure 3 Real-world time to discontinuation and time to next treatment following the initiation of 1L lenvatinib and 1L sorafenib (**a** and **c**) before PS matching and (**b** and **d**) after PS matching. ***p < 0.001.

Abbreviations: rwTTD, real-world time to treatment discontinuation; PS, propensity score; CI, confidence interval; rwTTNT, real-world time to next treatment.

Discussion

This multi-center study provides robust real-world evidence comparing lenvatinib and sorafenib in 1L HCC treatment. Our findings confirm a statistically significant survival advantage for lenvatinib over sorafenib, with a median rwOS of 9.56 months (95% CI: 8.25–10.78 months) compared to 7.43 months (95% CI: 6.44–9.26 months), respectively ($p < 0.013$). Additionally, the lenvatinib-treated group showed prolonged outcomes in terms of median rwTTD and rwTTNT, serving as proxies for real-world progression-free survival (PFS). These results align with previous studies and reinforce lenvatinib's applicability in clinical practice. Although median rwOS in our study was slightly shorter than that reported in the REFLECT trial, our findings validate those results in a broader real-world population, including ineligible for

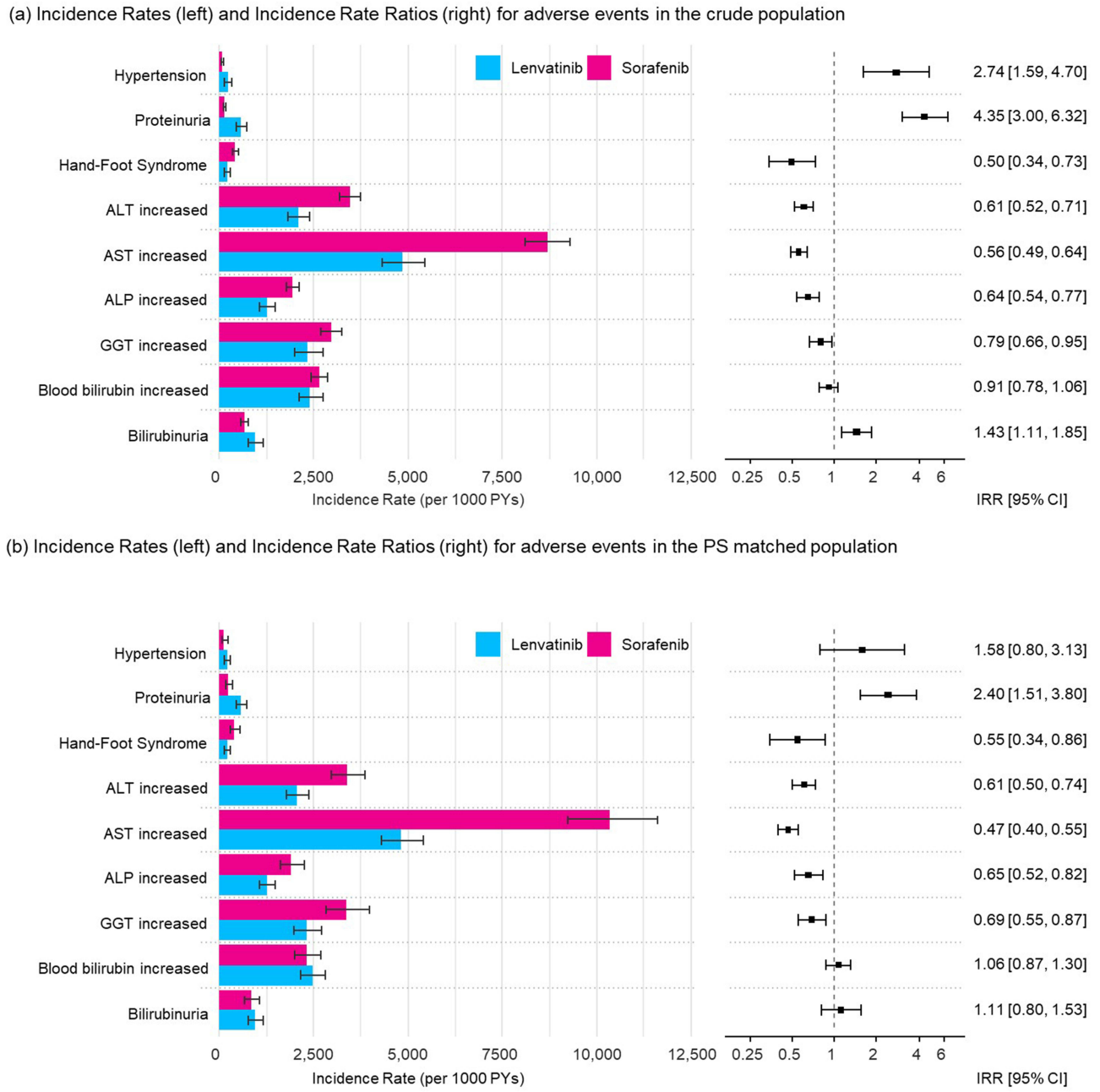

Figure 4 Incidence of adverse event of special interest (**a**) before PS matching and (**b**) after PS matching. Arrows indicate that values extend beyond the range shown. †per 1000 person-years. *incidence rate ratio test $p < 0.05$.

Abbreviations: AESI, adverse event of special interest; PS, propensity score; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

clinical trials. A hospital-based retrospective study in a similar real-world setting to our study reported comparable results. This study involved Korean lenvatinib users regardless of fulfilling the REFLECT eligibility criteria, with 21.6% of patients having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥ 1 and a median rwOS of 10.5 months.[20] Our findings not only align with those of the REFLECT trial but also confirm their replicability and relevance in real-world settings.

Safety findings were consistent with prior research, with hepatotoxicity, predominantly AST elevation, being the most frequent adverse event in both lenvatinib and sorafenib cohorts.[8,15,21,22] Regardless of PS adjustment, sorafenib cohort exhibited higher risks for HFS and hepatotoxicity except for bilirubin-related abnormalities, and lenvatinib cohort

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exhibited higher risks for proteinuria. The findings further support the distinct safety profiles of both agents, emphasizing the need for personalized toxicity management.

By leveraging the LINK database,[23] which represents over a quarter (26.72%; n=25,248) of Korea's HCC cases between 2015 and 2020, our study offers broader generalizability compared to prior Korean studies, which were often limited by small sample sizes and homogeneity.[20,24–29] This substantial dataset not only provides a robust foundation for our analysis but also enhances the generalizability of our findings by encompassing a wide range of baseline characteristics and diverse clinical settings. Additionally, our cohort includes patients typically excluded from trials like REFLECT, such as those with Child-Pugh class B, tumor occupying more than 50% of the liver volume, and major portal vein or bile duct invasion.[8,30] This inclusion broadens the utility of our findings, reflecting the complex real-world scenarios faced in clinical practice. For instance, in Korea, sorafenib is reimbursed for patients with Child-Pugh Class B and a score of 7 or below, whereas lenvatinib is only approved for patients with Child-Pugh Class A. Our study, which demonstrates lenvatinib's comparable survival outcomes to sorafenib in these patients, may further suggest the potential for lenvatinib's use in patients with a Child-Pugh score of B7.

Despite these strengths, there are some inevitable limitations to consider when interpreting the results. First, the lenvatinib cohort primarily consists of patients captured since the introduction of lenvatinib in 2018, resulting in variations in patient inclusion timeframes and shorter follow-up period compared to the sorafenib cohort, which may affect long-term outcome assessments. The differing inclusion period may have also coincided with shifts in supportive care practices. For example, the 2018 Korean HCC guidelines introduced updated recommendations for antiviral therapy, such as broader use of direct-acting antivirals (DAAs), and emphasized structured surveillance strategies including ultrasound and alpha-fetoprotein testing, which may have influenced supportive care and clinical outcomes differently in each cohort.[3]

Second, the scope of our analysis was constrained by the variables available in the LINK database. Specifically, the time lag between the actual event occurrence—particularly death—and its detection in the database might have led to overestimation of the OS in study population. Also, the clinical details such as symptoms, imaging findings, and BCLC staging were unavailable, necessitating operational definitions of hepatotoxicity based solely on laboratory values. Although we adjusted for measurable confounders, unmeasured changes in the treatment environment may remain. As a result, we could not definitively distinguish drug-induced liver injury from disease progression. Nonetheless, the observed safety profile was consistent with prior studies.[8,15,21,22]

Third, interpretation of treatment-duration endpoints warrants caution. rwTTD and rwTTNT may reflect a range of specific clinical or behavioral factors for discontinuation, such as disease progression, treatment-related adverse events, or patient choice, which were not systematically captured in the current dataset. While this limits the granularity of interpretation, rwTTD and rwTTNT remain a useful proxy for understanding progressions in real-world settings.

Fourth, the study population consisted predominantly of patients with Hepatitis B-related HCC (approximately 80%), which may limit direct generalizability to regions where other etiologies predominate. At the same time, this demographic reflects South Korea's epidemiological reality, where HBV causes 65–75% of HCC cases. Using data from three top tertiary hospitals, the study offers real-world evidence for an important subgroup of HCC patients.

Further studies should address these limitations by adopting extended, well-aligned follow-up periods, integrating comprehensive clinical data, and accounting for subsequent therapies to clarify their impact on outcomes. These approaches will facilitate more detailed interpretation of treatment patterns and a rigorous assessment of long-term effectiveness and safety.

Conclusions

The therapeutic landscape for HCC continues to evolve rapidly, with new treatments promising improved patient outcomes. Nevertheless, our understanding of their real-world impact remains limited. RWE studies will be essential in guiding clinical decision-making by complementing RCT data, offering insights beyond the controlled environment of clinical trials and providing a more holistic perspective on drug effectiveness, safety profiles, and patient outcomes.[30,31]

Abbreviations

HCC, hepatocellular carcinoma; 1L, first-line; LT, liver transplantation; LINK, Liver Cancer in Korea; PS, propensity score; BMI, body mass index; mALBI, modified albumin-bilirubin; AFP, alpha-fetoprotein; rwOS, real-world overall survival; rwTTD, real-world time to treatment discontinuation; rwTTNT, real-world time to next treatment; AESI, adverse event of special interest; HFS, hand-foot syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; KCD-7, Korean Standard Classification of Diseases-7; CTCAE, Common Terminology Criteria for Adverse Events; SE, standard error; aSMD, absolute standardized mean difference; KM, Kaplan-Meier; CI, confidence interval; PY, person-year; IRR, incidence rate ratio; PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Data Sharing Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Access to anonymized patient-level data is restricted to participating site staff who are registered and approved by Institutional Review Boards, and such data will be provided either as encrypted files or within an encrypted system. Aggregated data outputs, however, are available from the authors [Won Chul Cha, Kyu-Pyo Kim, Do Young Kim] upon reasonable request and with permission from Data Review Boards [http://www.e-irb.com; DFIT@amc.seoul.kr; irb@yuhs.ac].

Ethics Approval and Informed Consent

This study was reviewed and approved by the Institutional Review Boards of Samsung Medical Center (SMC, 2023-08-075), Severance Hospital (SVC, 4-2023-0135), and Asan Medical Center (AMC, 2023-0388), and has been granted an exemption from requiring written informed consent.

Consent for Publication

All tables and figures presented in this manuscript were generated as part of the study and do not include any identifiable personal information, images, videos, or recordings of individuals. As such, specific consent for publication is not required. The authors confirm that all content complies with the journal's ethical and publication standards and are prepared to provide documentation if requested by the editorial office.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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