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ORIGINAL RESEARCH

Lenvatinib Plus PD-1 Inhibitors versus Regorafenib in Patients with Advanced Hepatocellular Carcinoma After the Failure of Sorafenib: A Retrospective Study

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Purpose: To evaluate the clinical outcomes of lenvatinib plus PD-1 inhibitors (LP) and regorafenib (R) in patients with advanced hepatocellular carcinoma (HCC) after sorafenib failure.

Methods: From June 2018 to September 2021, 68 patients from a single center who received lenvatinib combined with PD-1 inhibitors or regorafenib after sorafenib treatment failure were analyzed. The tumor response and survival outcomes were compared between the LP group and R group. Prognostic factors for OS and PFS were determined using Cox proportional hazard regression models.

Results: The ORR increased in the LP group (19.5% vs 7.4%, p =0.294), and the DCR was better in the R group (73.2% vs 44.4%, p =0.017). Additionally, median PFS and OS were not significantly different between the LP group and R two groups in survival analysis (PFS: 5.3 months vs 3.0 months, p =0.633; OS: 11.8 months vs 8.0 months, p =0.699). The common adverse events (≥grade 3) were hand-foot skin reactions (13.1%). In multivariate analyses, AFP≥400 ng/mL and ECOG PS 2 were independent risk factors for poor prognosis.

Conclusion: The LP group appeared to have a trend of greater tumor response and a higher disease control rate than the R group among patients with sorafenib-resistant HCC, although PFS and OS did not differ significantly between the two groups.

Keywords: hepatocellular carcinoma, lenvatinib, PD-1 inhibitors, regorafenib, sorafenib, overall survival

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers in the world, and its incidence and mortality are on the rise.[1] It is estimated that by 2040, there will be 1.4 million newly diagnosed cases (an increase of 55.0% from 2020), and 1.3 million people will die of liver cancer (an increase of 56.4% from 2020).[2] Due to the insidious onset of HCC, early diagnosis is difficult, and many patients are diagnosed at a late stage.[3,4] Treatment methods for advanced HCC include transarterial chemoembolization (TACE), radiofrequency ablation (RFA), hepatic artery infusion chemotherapy (HAIC), molecular-targeted drug therapy and immunotherapy.[5–10] According to the results of the SHARP and Asia-Pacific HCC trials, sorafenib is the preferred therapy for those with late-stage HCC.[11,12] However, owing to its rapid progression and intolerable side effects, many tumors are resistant to sorafenib, and the therapeutic efficacy remains poor.

The approval of new regimens, including targeted therapy and immunotherapy, has changed the second-line therapeutic landscape for patients with HCC. In the RESORCE trial,[13] regorafenib effectively prolonged the survival of patients with sorafenib resistance. From the perspective of cost-effectiveness analysis, regorafenib is the most standard second-line treatment option in the era of molecular targeted therapy.[14,15] Moreover, immune checkpoint inhibitors (ICIs) have also shown efficacy for sorafenib-resistant HCC. The advent of the CheckMate 040 study and KEYNOTE-224 study profoundly changed the systemic treatment pattern of advanced HCC.[16,17] However, the ORR is still low, and the survival time is limited in these second-line therapy patients.

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Lenvatinib can target a variety of molecular targets, such as VEGFR1-3, FGFR1-4, PDGFR, KIT, and RET, which have driving effects on cancers. Thyroid cancer, kidney cancer, liver cancer, and endometrial cancer have all been treated with lenvatinib on a large scale.[18,19] Although the overall survival (OS) of lenvatinib was not inferior to that of sorafenib (13.6 months vs 12.3 months) according to REFLECT, the progression-free survival (PFS) was significantly better (7.4 months vs 3.7 months, p<0.0001).[20] The NCCN guidelines also recommend that lenvatinib be selected as a second-line treatment for sorafenib-resistant HCC.[21] The Keynote-524 study showed that the combination of lenvatinib and PD-1 inhibitors can significantly improve treatment efficacy and progression-free survival.[22] According to preclinical research, lenvatinib plus PD-1 inhibitors produce a synergistic impact, improving the immune microenvironment and fostering anticancer immunity.[23,24] Combination therapy offers a potentially effective treatment protocol, but few reports have been published on its therapeutic effects in patients with sorafenib-resistant HCC. Therefore, we performed a comparative study to evaluate the clinical outcomes of lenvatinib plus PD-1 inhibitors (LP) and regorafenib (R) in patients with sorafenib-resistant HCC.

Materials and Methods
Patients
Between June 2018 and September 2021, 85 patients with sorafenib-refractory HCC who received lenvatinib plus PD-1 inhibitors or regorafenib were recruited. After screening based on the inclusion and exclusion criteria, 68 cases were ultimately enrolled in the study, including 41 cases in the LP group and 27 cases in the R group. The study protocol was approved by The Ethics Committee of the Second Affiliated Hospital of Nanchang University. All patients provided informed consent prior to treatment. The study was conducted according to the Declaration of Helsinki.

The inclusion criteria were as follows: (1) HCC was diagnosed according to American Association for the Study of Liver Disease (AASLD) guidelines;[10] (2) Barcelona Clinic Liver Cancer (BCLC) stage B/C; (3) sorafenib-resistant HCC patients had received LP/R; (4) performance score of Eastern Cooperative Oncology Group (ECOG PS) 0–2 score; (5) Child–Pugh (CP) A/B; and (6) received at least 2 cycles of LP/R.

The exclusion criteria were as follows: (1) malignant tumor other than HCC; (2) severe organ dysfunction; (3) missing clinical data; and (4) loss to follow-up.

Treatment Procedures
Tislelizumab, sintilimab, camrelizumab, and pembrolizumab are PD-1 inhibitors that are administered intravenously at 200 mg every 3 weeks. The initial oral dose of lenvatinib is 8 mg/day for individuals whose body weight is below 60 kg and 12 mg/day for those whose weight is over 60 kg. The patients received regorafenib orally at a dose of 160 mg once daily for 3 weeks and 1 week off. All treatment drug dosage reductions and local treatment combinations (TACE/HAIC) followed the recommendations of the multidisciplinary tumor board.

Efficacy and Safety Assessments
The status of tumor growth and metastasis was evaluated according to the RESIST1.1 and mRECIST standards based on contrast-enhanced CT/MRI, which was performed every 6–8 weeks. Laboratory tests, including biochemical tests, alpha-fetoprotein (AFP) levels and thyroid function tests, were performed at each follow-up visit. Objective response rate (ORR)= [complete response (CR)+partial response (PR)]/total number of cases. Disease control rate (DCR) = [CR+PR+ disease stability (SD)]/total number of cases. Progression-free survival (PFS) was defined as the time interval from the initial treatment to PD or death. Overall survival (OS) was defined as the time interval from the initial treatment to death or last day of follow-up. The grade of adverse events (AEs) was recorded using the National Cancer Institute General Toxicity Criteria (NCI-CTC 5.0). All patients were followed up after treatment until reaching the OS endpoint or the last follow-up date (January 1, 2023).

Statistical Analysis

The statistical tools SPSS (version 26.0; IBM Corporation) and R (version 4.2.1) were used for all statistical analyses. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Survival curves were constructed using the Kaplan–Meier method and compared using the log rank test. To identify the variables that were independently associated with PFS and OS, variables with p <0.05 in the univariate analysis were further adopted into the Cox proportional hazards regression model. P<0.05 was considered statistically significant.

Results

Patients

The study selection process is illustrated in Figure 1. From June 2018 to September 2021, 85 HCC patients who had not responded to sorafenib were enrolled and given LP or R therapy. After filtering based on the inclusion criteria, 68 patients participated in the study. Seventeen patients were excluded. Of these, 10 were excluded because of incomplete data, and 7 were excluded due to a lack of follow-up data.

There were no significant differences in the clinical characteristics of the patients, including age, sex, ECOG PS, CP A/B, BCLC B/C, hepatitis B virus (HBV) infection, liver cirrhosis, AFP, portal vein tumor thrombus and extrahepatic metastasis, between the LP group and the R group, as shown in Table 1 (p>0.05). After developing sorafenib resistance, 41 and 27 patients received LP and R treatments, respectively. Of all the patients, 62 (91.2%) were male, and 6 (8.8%) were female. Forty-seven patients (60.1%) had advanced-stage HCC, and 21 had BCLC stage B HCC (39.9%). The CP scores were A (n = 54), with 85.4% in the LP group and 70.4% in the R group. Among the patients, 44 (64.7%) presented with extrahepatic metastases, and 19 (27.9%) presented with portal vein thrombosis. Twenty-four patients (58.5%) in the LP group and 21 patients (77.8%) in the R group received TACE/HAIC therapy.

Subsequent Treatment

Following the progression of the disease, 24 patients had additional therapies, as shown in Table 2. In the LP group, 14 (34.1%) patients received new treatment after progression, including HAIC+ PD-1 inhibitors + apatinib (2), atezolizumab + bevacizumab (1), PD-1 inhibitors + regorafenib (4), apatinib (1), PD-1 inhibitors + apatinib (2), radiotherapy (1), and regorafenib (3). After termination of the study treatment, 10 patients (37.4%) in the R group received third-line therapy, including PD-1 inhibitors + regorafenib (1), PD-1 inhibitors + apatinib (1), PD-1 inhibitors +lenvatinib (4), TACE +PD-1 inhibitors +lenvatinib (2), and lenvatinib (2).
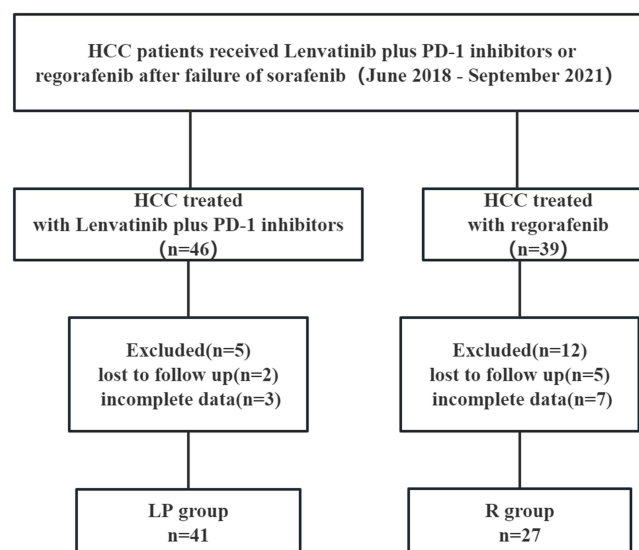
Figure 1 Flow diagram of study participants.

Table 1 Characteristics of Patients in This Study

Characteristics n (%)	LP (n=41)	R (n=27)	P-value
Age			0.856
≥50	28 (68.3)	19 (70.4)	
<50	13 (31.7)	8 (29.6)	
Gender			0.738
Male	37 (90.2)	25 (92.6)	
Female	4 (9.8)	2 (7.4)	
ECOG PS			0.844
0	13 (31.7)	7 (25.9)	
1	20 (48.8)	15 (55.6)	
2	8 (19.5)	5 (18.5)	
Child-Pugh			0.135
A	35 (85.4)	19(70.4)	
B	6(14.6)	8(29.6)	
BCLC			0.473
B	14(34.1)	7(25.9)	
C	27(65.9)	20(74.1)	
HBV infection			0.069
YES	35(85.4)	18(66.7)	
NO	6(14.6)	9(33.3)	
Liver cirrhosis			0.979
YES	32(78.0)	21(77.8)	
NO	9(22.0)	6(22.2)	
Portal vein tumor thrombus			0.160
YES	14(34.1)	5(18.5)	
NO	27(65.9)	22(81.5)	
Extrahepatic spread			0.190
YES	24(58.5)	20(74.1)	
NO	17(41.5)	7(25.9)	
Combination of TACE or HAIC			0.101
YES	24(58.5)	21(77.8)	
NO	17(41.5)	6(22.2)	
Baseline AFP ng/mL			0.657
≥400	16(39.0)	12(44.4)	
<400	25(61.0)	15(55.6)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance status; HBV, hepatitis B virus; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

Treatment Outcomes and Survival Outcomes

Tumor responses are shown in Table 3. One patient (2.4%) in the LP group but 0 patients in the R group achieved CR, whereas 7 (17.1%) and 2 (7.4%) patients achieved PR, as determined by RECIST1.1. Between the LP/R groups, there was no appreciable change in ORR (19.5% vs 7.4%; p = 0.294). One patient (3.7%) in the R group and 3 (7.3%) patients in the LP group experienced CR, whereas 9 (22.0%) and 3 (11.1%) patients achieved PR, as determined by mRECIST. The ORR was higher in the LP group (29.3% vs 14.8%, p =0.755), and the DCR was better in the R group (73.2% vs 44.4%, p= 0.017). The median PFS in the LP group was 5.3 months (95% CI, 4.0–7.2), and it was 3.0 months (95% CI, 2.3–6.3) in the R group [p = 0.633; Figure 2A]. The median OS was 11.8 months (95% CI, 9.2–16.2) in the LP group and 8.0 months (95% CI, 6.5–22.0) in the R group [p =0.699; Figure 2B].

Table 2 Subsequent Treatment

	LP n (%)		R n (%)	
Accepted subsequent treatments	14	34.1	10	37.4
HAIC+ PD-1 inhibitors +apatinib	2	4.9	0	
Atezolizumab + bevacizumab	1	2.4	0	
PD-1 inhibitors+ regorafenib	4	9.8	1	3.7
Apatinib	1	2.4	0	0.0
PD-1 inhibitors +apatinib	2	4.9	1	3.7
PD-1 inhibitors +lenvatinib	0		4	14.8
TACE + PD-1 inhibitors+ lenvatinib	0	0.0	2	7.4
Radiotherapy	1	2.4	0	
Lenvatinib	0	0.0	2	7.4
Regorafenib	3	7.3	0	
Best supportive care	16	39.0	9	33.3

Abbreviation: HAIC, hepatic arterial infusion chemotherapy; TACE, transcatheter arterial chemoembolization; PD-1 inhibitors, programmed cell death-1 inhibitors.

Table 3 Response to Treatment

Variable	RECIST1.1			mRECIST		
	LP(n=41) (%)	R(n=27) (%)	P value	LP(n=41) (%)	R(n=27) (%)	P value
Complete response	1(2.4)	0(0)		3(7.3)	1(3.7)	
Partial response	7(17.1)	2(7.4)		9(22.0)	3(11.1)	
Stable disease	22(53.7)	10(37.0)		18(43.9)	8(29.6)	
Progressive disease	11(26.8)	15(55.6)		11(26.8)	15(55.6)	
Overall response rate	8(19.5)	2(7.4)	0.294	12(29.3)	4(14.8)	0.755
Disease control rate	30(73.2)	12(44.4)	0.017	30(73.2)	12(44.4)	0.017

Abbreviations: RESICT, response evaluation criteria in solid tumors; mRESICT, modified response evaluation criteria in solid tumors.

Treatment Toxicities

AEs that occurred throughout treatment with LP/R are shown in Table 4. During the time of the trial, there were no treatment-related fatalities. The most common symptoms in the LP group were hypertension (41.5%), hand-foot skin
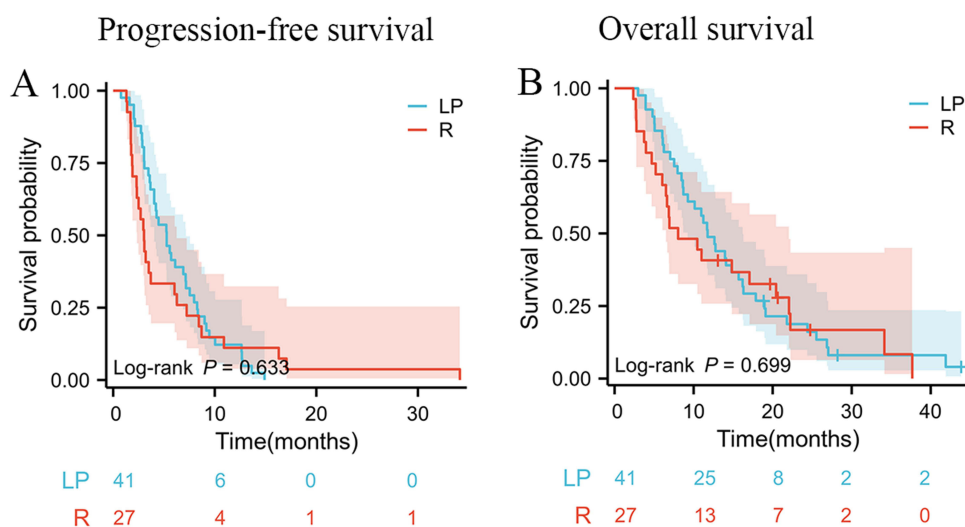
Figure 2 OS and PFS with sorafenib resistance HCC who were treated with LP or R, respectively. (**A**) Kaplan–Meier analysis of PFS. (**B**) Kaplan–Meier analysis of OS.

Table 4 Summary of Adverse Events

Adverse Events	LP (n = 41)		R (n = 27)	
	Any Grade n (%)	Grade ≥ 3 n (%)	Any Grade n (%)	Grade ≥ 3 n (%)
Fever	4(9.8)	1(2.4)	2(7.4)	0
Diarrhea	8(19.5)	1(2.4)	4(14.8)	0
Fatigue	7(17.1)	0	2(7.4)	0
Hoarseness	4(9.8)	0	2(7.4)	0
Hypertension	17(41.5)	0	5(18.5)	
Proteinuria	9(22.0)	2(4.9)	4(14.8)	0
Nausea	2(4.9)	0	1(3.7)	0
Hand-foot skin reaction	15(36.6)	4(9.8)	12(44.4)	4(14.8)
Oral mucositis	4(9.8)		2(7.4)	
Thrombocytopenia	6(14.6)	1(2.4)	3(11.1)	1(3.7)
Anemia	5(12.2)	0	4(14.8)	0
Hyperbilirubinemia	4(9.8)	0	7(25.9)	0
Elevated AST level	5(12.2)	1(2.4)	4(14.8)	2(7.4)
Hypothyroidism	7(17.1)	0	4(14.8)	0
ICIs-Induced hepatitis.	2(4.9)	0	0	0
ICIs-Induced pneumonia	1(2.4)	0	0	0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ICIs, Immune Checkpoint Inhibitors.

reactions (HFSR, 36.6%), and proteinuria (22.0%). The most typical AE grade (≥3) was hypertension (9.8%). The most frequent AEs in the R group were HFSR (44.0%), hyperbilirubinemia (25.9%), and hypertension (18.5%). The most frequent severe AEs during regorafenib treatment were HFSR (n=4, 14.8%) and elevated AST levels (n =2, 7.4%).

Prognostic Factor Analysis

According to the univariate analysis, ECOG PS (HR 2.745, 95% CI 1.449–5.200, p =0.002), HBV infection (HR 0.479, 95% CI 0.263–0.870, p =0.016), and AFP (HR 3.000, 95% CI 1.798–5.004, p<0.001) remained independent predictors of PFS (Table 5).

Table 5 | Univariate and Multivariate Analysis of Risk Factors for Progression-Free Survival

Variables	Univariate Analysis			Multivariate Analysis		
	H.R	95% CI	P-value	H.R	95% CI	P-value
Gender (M vs F)	1.778	0.749–4.222	0.192			
Age (<50 vs≥50)	0.750	0. 441–1.274	0.287			
ECOG PS (2 vs 0–1)	2.745	1.449–5.200	0.002	2.721	1.372 –5.395	0.004
BCLC (B vs C)	1.241	0.732–2.103	0.423			
Child-Pugh (A vs B)	1.423	0.785 –2.582	0. 245			
HBV (yes vs no)	0.479	0.263 –0.870	0.016	0.568	0.300 –1.075	0.082
Liver cirrhosis (yes vs no)	0.963	0.551–0.813	0.907			
Microvascular invasion (yes vs no)	1.355	0.792–2.317	0.268			
Extrahepatic spread (yes vs no)	1.425	0.854 –2.377	0.176			
AFP (≥400ng/mL vs <400ng/mL)	3.000	1.798 –5.004	<0.001	3.270	1.938 –5.516	<0.001
Combination of TACE or HAIC (yes vs no)	0.932	0.487–1.786	0.833			
Treatment option (LP vs R)	1.132	0.679–1.886	0.634			

Abbreviations: H.R, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance status; AFP, alpha fetoprotein; BCLC, Barcellola Clinic Liver Cancer; HBV, hepatitis B virus; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy.

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Predictors of worse PFS according to the multivariate analysis were ECOG PS 2 score (HR 2.721, 95% CI 1.372–5.395, p =0.004) and AFP≥400 ng/mL (HR 3.000, 95% CI 1.798–5.004, p < 0.001). In the two groups, the univariate analysis showed that ECOG PS (HR 3.474, 95% CI 1.812–6.660, p<0.001), Child–Pugh (HR 2.90, 95% CI 1.29–6.54, p=0.010) and AFP (HR 2.661, 95% CI 1.572–4.505, p < 0.001) were significantly correlated with OS (Table 6). Predictors of worse OS were ECOG PS 2 score (HR 4.530, 95% CI 2.291–8.960, p < 0.001) and AFP≥400 ng/mL (HR 3.111, 95% CI 1.790–5.407, p < 0.001).

After stratification by ECOG PS, the median PFS in the ECOG PS 0–1 score group was significantly higher than that in the ECOG PS 2 score group [5.3 months (95% CI, 4.0–7.2) vs 3.0 months (95% CI, 1.9–4.1), p=0.001, Figure 3A], and the differences in OS outcomes were also statistically significant [12.8 months (95% CI, 10.1–19.0) vs 4.0 (95% CI, 3.0–6.8) months, p <0.001, Figure 3B]. After stratification by AFP, the median PFS in the AFP<400 ng/mL group was significantly longer than that in the AFP≥400 ng/mL group [6.5 months (95% CI, 5.3–8.7) vs 2.7 months (95% CI, 2.1–3.7), p <0.001, Figure 3C]. Similarly, the differences in OS outcomes were also statistically significant [14.1 months (95% CI, 11.7–22.2) vs 6.6 months (95% CI, 5.1–11.1), p <0.001, Figure 3D].

Discussion

Numerous current guidelines for treatment options after sorafenib resistance in hepatocellular carcinoma include lenvatinib, regorafenib, ramucirumab, and PD-1/PD-L1 inhibitors.[25,26] With the great success of the IMbrave150[27] and KEYNOTE-524 study,[22] immunotherapy combined with targeted therapy has become the optimal choice for targeted therapy in advanced HCC.Although the immunosuppressive microenvironment of HCC promotes immune tolerance and evasion through multiple mechanisms, molecularly targeted drugs can improve the immune microenvironment and synergize the effects.[28,29] Therefore, it is important to explore the efficacy of immunotherapy combined with targeted therapy in the second-line treatment of advanced hepatocellular carcinoma. Lenvatinib combined with PD-1 inhibitors for sorafenib-resistant HCC has seldom been reported; therefore, we conducted exploratory analyses to determine whether any clinical benefit factors were associated with survival time. This retrospective single-center study compared the clinical outcomes of using LP/R for sorafenib-resistant HCC patients, including tumor response, prognostic outcomes, and adverse events. Although this study did not show a statistically significant prolongation of survival time, the benefit of tumor response seemed to increase, and there was a clear difference in the DCR. The multivariate analyses found that the prognosis of sorafenib-resistant patients with AFP ≥ 400 ng/mL and ECOG PS 2 was poor.

Our findings demonstrated that the median PFS and OS of the patients treated with LP were 5.3 and 11.8 months, respectively. According to RECIST1.1, the ORR and DCR of patients treated with LP were 19.5% and 73.2%, respectively. In contrast to earlier research findings, which showed safe and acceptable outcomes, our results are

Table 6 Univariate and Multivariate Analysis of Risk Factors for Overall Survival

Variables	Univariate Analysis			Multivariate Analysis		
	H.R	95% CI	P-value	H.R	95% CI	P-value
Gender (M vs F)	1.459	0.576–3.698	0.426			
Age (<50 vs≥50)	1.024	0.594 –1.766	0.933			
ECOG PS (2 vs 0–1)	3.474	1.812 –6.660	<0.001	4.530	2.291 –8.960	<0.001
BCLC (B vs C)	1.377	0.788 –2.408	0.262			
Child-Pugh (A vs B)	2.90	1.29–6.54	0.010	1.181	0.622 –2.244	0.611
HBV (yes vs no)	0.660	0.469–1.616	0.870			
Liver cirrhosis (yes vs no)	1.107	0.580–2.113	0.758			
Microvascular invasion (yes vs no)	1.150	0.661–1.999	0.621			
Extrahepatic spread (yes vs no)	1.610	0.945–2.742	0.08			
AFP (≥400ng/mL vs <400ng/mL)	2.661	1.572–4.505	<0.001	3.111	1.790–5.407	<0.001
Combination of TACE or HAIC (yes vs no)	0.974	0.568–1.670	0.923			
Treatment option (LP vs R)	1.108	0.657–1.869	0.699			

Abbreviations: H.R, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance status; AFP, alpha fetoprotein; BCLC, Barcellola Clinic Liver Cancer; HBV, hepatitis B virus; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy.
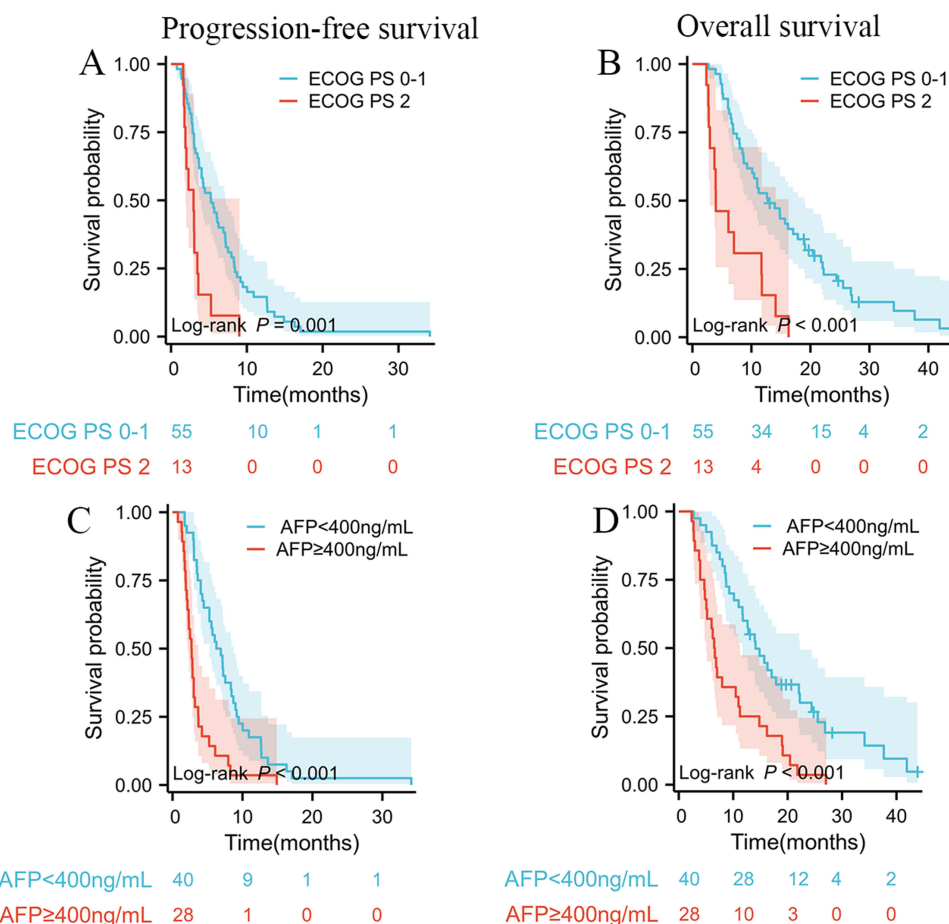
Figure 3 Kaplan–Meier analysis of OS and PFS of patients with ECOG PS and AFP in total population. (**A**) Kaplan–Meier curves for PFS stratified by ECOG PS (0–I vs 2). (**B**) Kaplan–Meier curves for OS stratified by ECOG PS (0–I vs 2). (**C**) Kaplan–Meier curves for PFS stratified by AFP (<400ng/mL vs ≥400ng/mL). (**D**) Kaplan–Meier curves for OS stratified by AFP (<400ng/mL vs ≥400ng/mL).

different. The RESCUE study demonstrated that camrelizumab plus apatinib is a prospective regimen for second-line treatment of advanced HCC, with an ORR of 22.5% and a median OS of 21.8 months (17.3–26.8).[30] Only patients with CP class A, ECOG PS 0–1, and intrahepatic vessel invasion (24.2%) were included in the RESCUE. Moreover, compared with previous single molecular targeting agent trials involving patients with sorafenib-resistant HCC, the PFS in the LP group had certain benefits.[13,31–33] Another small study also showed that LP is a hopeful new strategy for second-line or later treatment of patients.[34]

In patients treated with regorafenib, the ORR, DCR, median PFS, and median OS were 7.4%, 44.4%, 3.0 months, and 8.0 months, respectively. These results are worse than the ORR, DCR, median PFS, and median OS of 11.0%, 65.2%, 3.2 months, and 10.6 months, respectively, in the Phase III RESORCE trial.[13] These disparities likely resulted from several factors, including differences in patient characteristics, such as a larger proportion of patients with HBV infection (66.7%), ECOG PS 2 score (18.5%), and CP class B (29.6%). However, they have been similarly described in several recent studies on real-world experiences.[35–37]Although these results suggested that LP group appeared to have a trend of greater tumor response and a higher disease control rate than the R group among patients with sorafenib-resistant HCC (ORR, 19.5% vs 7.4%, p = 0.294; DCR, 73.2% vs 44.4%, p= 0.017), there were different conclusions regarding the ORR. Interestingly, when compared with the LP group and R group, the combination regimen did not show an obvious advantage in improving the prognosis of patients. The median PFS and OS were not significantly different between the LP group and R group in the prognosis analysis (PFS 5.3 months vs 3.0 months, p =0.633; OS 11.8 months vs 8.0

months, p =0.699). The author's team believed that the sample size was insufficient to assess the effect of treatment on survival. Importantly, combination immunotherapy is recommended, as it may effectively slow tumor growth.

Multivariate analysis failed to demonstrate that treatment option (LP vs R) may be an independent risk factor for PFS/OS. However, ECOG PS and AFP were also independent risk factors, as revealed by the multivariate analysis of the whole population. Further analysis indicated that patients with better physical condition (ECOG PS 0–1 score) had longer PFS (5.3 months vs 3.0 months, p=0.001) and OS (12.8 months vs 4.0 months, p <0.001). Kaplan–Meier analysis also indicated that patients with lower levels of AFP (<400 ng/mL) had longer PFS (6.5 months vs 2.7 months, p <0.001) and OS (14.1 months vs 6.6 months, p <0.001). Considerable research has suggested that tumor burden and physical status are important factors that may affect the efficacy of systematic treatment of HCC.[38,39]

From a clinical perspective, our findings support the adverse reaction incidence of previous studies.[16,34–36] The study found that the frequency of severe AEs was 13.1% for hand-foot skin reactions and 4.9% for elevated AST levels. All AEs had noticeably higher percentages in the LP group, with the leading five AEs being hypertension (41.5), hand-foot skin reaction (36.6%), proteinuria (22.0%), diarrhea (19.5%), and hypothyroidism (17.1%). Immune-related adverse effects (irAEs) related to immunotherapy were observed during the study period. Despite the lack of experience in the treatment of irAEs, no serious side reactions were recognized in the immunotherapy group, and all were resolved with symptomatic treatment.

This study had several strengths. The therapeutic effects of lenvatinib plus PD-1 inhibitors or regorafenib alone in patients with sorafenib-resistant were investigated. Using real-world data, our study describes the basic characteristics of sorafenib-resistant HCC patients. We also identified that prognostic factors (ECOG PS and AFP) were key indicators affecting survival time in our study based on the length of follow-up.

There are a number of underlying restrictions in this study. First, this was a single-center retrospective study and may have been affected by specific treatment practices. Second, the number of patients included in the study was too small to detect relevant differences. As no randomized controlled studies have been conducted, caution should be exercised when interpreting these findings. Finally, because the enrolled patients used various combination therapeutic regimens, there was a certain bias in the process of selecting patients and evaluating treatment efficacy.

In summary, our study suggests that the LP group had a trend of higher tumor response and better disease control rate than the R group; nevertheless, their PFS and OS did not demonstrate the possibility of benefits. Future research on second-line treatments for HCC patients is needed and should be conducted with a larger sample, particularly in those who have previously received treatment with ICIs. Let us look forward to more and better drugs in the future and better guidance for clinical diagnosis and treatment so that more patients can benefit.

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Disclosure

The authors state that there are no potential conflicts of interest in this article.

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