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Prognosis of Neoadjuvant HAIC and Lenvatinib Followed by Surgery versus Direct Resection for Resectable or Borderline Resectable Hepatocellular Carcinoma: A Real-World Study

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Purpose: This research aims to compare the efficacy of neoadjuvant hepatic arterial infusion chemotherapy (HAIC) combined with Lenvatinib (Len) to direct liver resection (LR) in patients with resectable or borderline resectable hepatocellular carcinoma (HCC).

Methods: This retrospective study included 154 patients with hepatocellular carcinoma (HCC) treated at the a large-scale hepatocellular carcinoma Research Center between March 2019 and June 2023. Patients were assigned to one of two groups: 63 received neoadjuvant hepatic arterial infusion chemotherapy (HAIC) combined with Lenvatinib followed by liver resection (HAIC+Len→LR), while 91 received direct liver resection (LR). The primary outcomes assessed were median overall survival (mOS), median progression-free survival (mPFS), median duration of response (mDOR), and adverse events (AEs).

Results: Patients in the HAIC+Len→LR group demonstrated significantly longer median overall survival (mOS) (40.1 months vs 35.9 months, P=0.001) and median progression-free survival (mPFS) (32.8 months vs 23.8 months, P=0.0023) compared to the LR group. Preoperative complete response (CR) to HAIC was associated with better median duration of response (mDOR) and mOS compared to partial response (PR) (not reached vs 28.9 months, P=0.006; 40.0 vs 29.1 months, P=0.037). Subgroup analysis revealed no significant difference in OS or PFS between the HAIC+Len→LR and LR groups in early Barcelona Clinic Liver Cancer (BCLC) stages. However, in late BCLC stages, the HAIC+Len→LR group exhibited significantly improved OS and PFS (HR 0.471, P=0.016; HR 0.551, P=0.022). Treatment-related grade ≥3 adverse events were comparable between the two groups.

Conclusion: For patients with resectable or marginally resectable HCC in the intermediate to advanced stages of BCLC, surgery after neoadjuvant HAIC+Len may offer improved long-term prognosis.

Keywords: hepatic arterial infusion chemotherapy, lenvatinib, progression-free survival, overall survival, resectable or borderline resectable hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer and the second leading cause of cancer death in China.,[1] It is the sixth most common cancer worldwide and the third leading cause of cancer deaths.[2,3] Approximately half of the global HCC cases occur in China, with over 90% of these cases diagnosed as hepatocellular carcinoma.[4] Surgery is the most effective treatment for HCC, with liver transplantation and resection as complementary options. However, due to limited donor livers, resection is the preferred choice for long-term survival. Despite this, HCC prognosis remains poor, with only a small percentage of patients eligible for surgery and a 5-year survival rate of 10–18%.[5] Even for those HCC patients who undergo surgery, the 5-year OS ranges from 33.6% to 76.4%, with long-term outcomes often falling short of satisfaction due to high recurrence and metastasis rates.[6,7] Hepatic resection can be curative for extensive or multifocal HCC, provided adequate liver function and physical condition. However,

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postoperative adjuvant therapy is often needed to prevent recurrence, especially in patients with microvascular invasion (MVI). MVI is a significant independent risk factor for early recurrence after surgery, with an incidence of 20–60% depending on the staging and diagnostic criteria. Notably, MVI can be present even in early stages of HCC.[8] Numerous researches have indicated that postoperative adjuvant therapy can mitigate recurrence, thus improving long-term prognosis.[9,10]

Some researches have demonstrated that neoadjuvant chemotherapy combined with tyrosine kinase inhibitors (TKIs) can promote tumor necrosis and shrinkage, reduce the incidence of postoperative MVI, thereby improving the prognosis following curative resection.[11–13] Preoperative transarterial chemoembolization (TACE) has been shown to decrease the occurrence of MVI and has been applied for many years in resectable and borderline resectable HCC. However, its effect on prognosis improvement is contentious.[14,15] Combined hepatic arterial infusion chemotherapy (HAIC) with systemic therapy has become a standard treatment for advanced HCC, leading to significant improvements in prognosis. Studies suggest that HAIC, compared to transarterial chemoembolization (TACE) with targeted or immunotherapy, offers better survival outcomes and fewer side effects.[16,17] Lenvatinib has proven effective as a first-line treatment for advanced HCC in numerous studies. However, some research indicates that lenvatinib and other TKIs can increase tumor cell resistance to oxaliplatin and 5-FU. HAIC can rapidly reduce tumor size, improving patients' tolerance to TKIs. This allows for greater tumor shrinkage and potentially easier surgical procedures.[18–20] Lenvatinib is a feasible and cost-effective option for preoperative adjuvant therapy in HCC. However, no studies have explored the combination of HAIC with tyrosine kinase inhibitors (TKIs) as neoadjuvant therapy for borderline resectable or partially resectable HCC. This retrospective study aimed to evaluate the safety and efficacy of neoadjuvant HAIC combined with lenvatinib followed by hepatic resection for resectable or borderline resectable HCC.

Materials and Methods

Patient Selection

This retrospective analysis was conducted at the First Affiliated Hospital of Chongqing Medical University, encompassing patients with HCC who underwent either neoadjuvant HAIC combined with lenvatinib (HAIC+Len→LR group) or direct hepatic resection (LR group) from March 2019 to June 2023. The screening process is depicted in Figure 1. A total of 154 patients, deemed resectable or borderline resectable, were ultimately enrolled.

Inclusion criteria for both groups included: 1. clinical diagnosis of HCC without prior systemic therapy; 2. age over 18 years; 3. resectable or borderline resectable disease; 4. Child-Pugh classification A; 5. ECOG performance score of 0–2; 6. for the HAIC+Len→LR group: pre-operative HAIC+Len achieving at least PR or CR according to mRECIST; 7. for both groups: R0 resection achieved during curative hepatic resection. For the HAIC+Len→LR group, complete outcome records post HAIC treatment, including treatment cycles and total duration, were retained.

Exclusion criteria included: 1. prior anticancer therapies other than HAIC+Len, TKIs, anti-PD1 immunotherapy, and hepatic resection; 2. contraindications for angiography or arterial puncture, uncontrolled perilesional or systemic infections, severe hepatic, renal, cardiac, or pulmonary dysfunction, history of other malignancies, known HIV infection, or inability to tolerate or comply with treatment; 3. non-performance of hepatic resection or receipt of non-R0 hepatic resection.

All patients were stratified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Clinical data were retrospectively extracted from our electronic medical records, and written informed consent for data use was obtained from all patients. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Research Ethics No: K2024-191-01) and conducted in accordance with the Helsinki Declaration.[21]

Treatment Methods

The HAIC+Len therapy was administered as follows: All HAIC procedures were performed by an experienced interventional radiologist using the modified Seldinger technique for femoral artery puncture. For tumors supplied solely by the left or right hepatic artery, a microcatheter was placed into the corresponding artery. For tumors supplied by both hepatic arteries, the microcatheter was inserted into the hepatic artery proper. If tumors were supplied by both hepatic

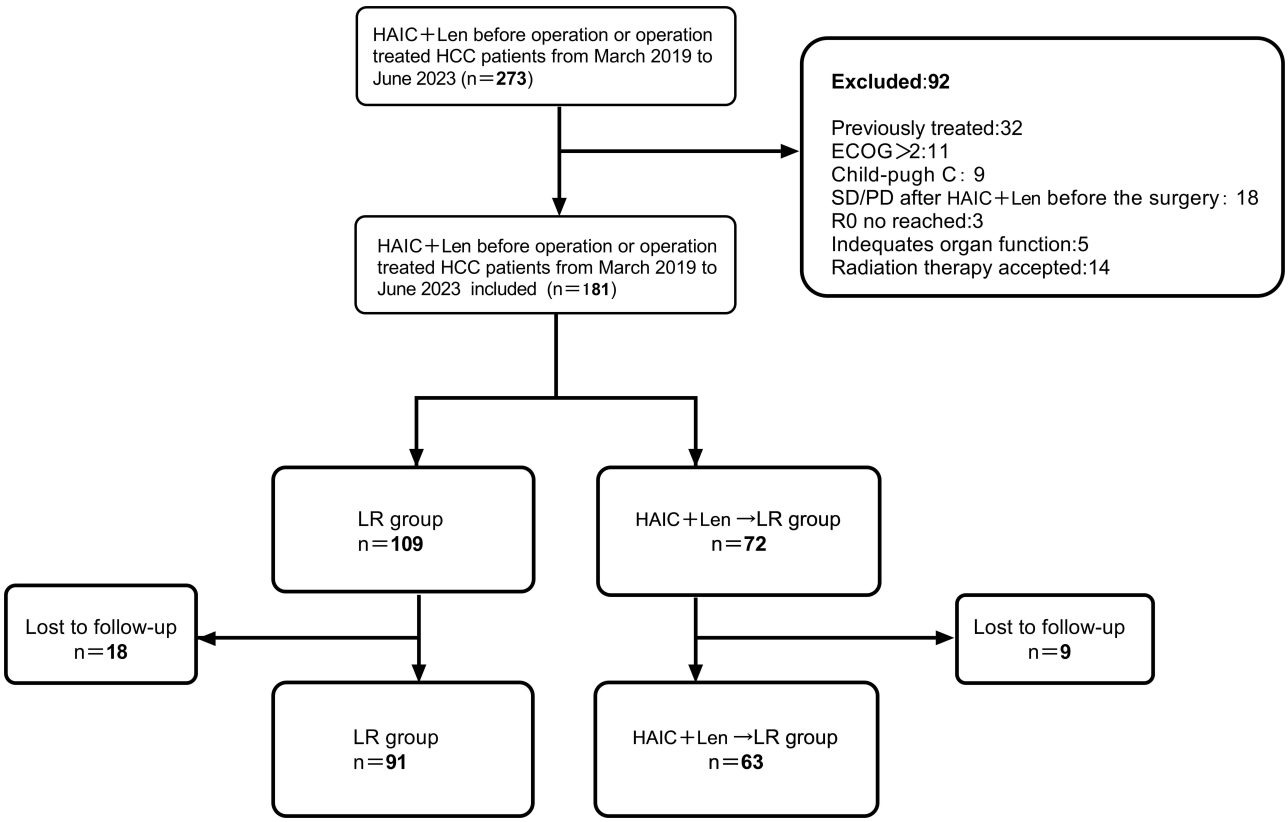

Figure 1 Flowchart of HCC patients treated with neoadjuvant HAIC and Lenvatinib followed by surgery and direct surgical resection.
Abbreviations: HAIC + Len, Hepatic Arterial Infusion Chemotherapy (HAIC) and Lenvatinib; HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Group performance status score; SD/PD, as evaluated based on the modified Response Evaluation Criteria in Solid Tumors22 (mRECIST), stable disease (SD), or progressive disease (PD); LR, liver resection.

arteries and the gastroduodenal artery could not be avoided, coil embolization of the gastroduodenal artery was performed before inserting the microcatheter into the hepatic artery proper. Chemotherapy Infusion (FOLFOX regimen):

Oxaliplatin: 85 mg/m² via arterial infusion over 2 hours. Calcium folinate: 400 mg/m² via intravenous infusion over 1 hour. Fluorouracil: 400 mg/m² via arterial infusion over 1 hour, followed by 2400 mg/m² via arterial infusion over 23 hours. This regimen was repeated every 4 weeks based on imaging reassessment showing partial or complete response. Patients also received lenvatinib at 8 mg orally daily (or 12 mg daily for weight ≥60 kg). Dosage adjustments were made for significant tumor reduction. Postoperative Adjuvant Therapy: Began 4 weeks after surgery, with continued lenvatinib administration at 8 mg (or 12 mg for weight ≥60 kg) until disease progression or unacceptable toxicity.

Treatment efficacy was evaluated by experienced radiologists using RECIST 1.1 and mRECIST criteria, with results reported based on mRECIST.[22,23]

Patients eligible for surgery were determined by a multidisciplinary team (MDT) comprising surgeons, radiologists, interventional radiologists, ultrasonographers, oncologists, and pathologists. Surgical procedures for enrolled patients were performed by the same surgical team at the ethics-reviewed hospital, with tumor resectability determined based on preoperative imaging and adequate residual liver volume. Borderline resectable HCC was defined as tumors presenting: 1. excessive volume, 2. close proximity to major vessels, 3. high-risk individuals for post-hepatectomy liver failure and/or advanced disease, and 4. indistinct tumor margins.[11,24] Patients undergoing HAIC+Len regimen were all subjected to assess resectability prior to hepatectomy, which was conducted by two senior imaging technicians following the mRECIST criteria. Determination of achieving PR/CR after neoadjuvant therapy was made through consensus in case of discordant views. All enrolled patients underwent laparoscopic partial hepatectomy under general anesthesia, with intraoperative margins maintained at least >1cm.

Study Endpoints

The primary endpoint of this study was overall survival (OS), with secondary endpoints including progression-free survival (PFS) and duration of response (DOR). Tumor responses were independently assessed by two experienced radiologists, reaching consensus in case of disagreement. DOR, as defined by mRECIST, was the time from the first documented complete (CR) or partial response (PR) to disease progression or death, whichever occurred first. OS was measured from hepatectomy to death from any cause or the last follow-up. PFS was defined as the time from hepatectomy to hepatocellular carcinoma (HCC) recurrence. Cirrhosis was diagnosed histopathologically based on resected liver specimens. Treatment-related adverse events (TRAEs) during follow-up were recorded and assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, categorized as follows: Grade 1: Mild; asymptomatic or mild symptoms; no intervention needed. Grade 2: Moderate; requires minimal, local, or non-invasive intervention; limits some daily activities. Grade 3: Severe; medically significant but not immediately life-threatening; hospitalization may be needed. Grade 4: Life-threatening; requires urgent intervention. Grade 5: Death related to adverse event.[25]

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 for Windows (SPSS, Inc., Armonk, NY, USA) and R 4.3.1 for Windows. P-value < 0.05 was considered to indicate statistical significance. Categorical variables were reported as numbers (N) or proportions (%). Student's *t*-test was employed for comparison of continuous variables where applicable. Otherwise, the Mann–Whitney *U*-test was applied. Comparison of categorical variables was conducted using the χ^2-test, with Yates correction or Fisher's exact test employed as appropriate. Kaplan-Meier curves comparing PFS and OS of patients receiving preoperative HAIC+Len versus those who did not were generated using the Log rank test. Subsequently, univariate and multivariate Cox proportional hazards regression analyses were conducted to identify additional prognostic factors associated with PFS and OS. The results of Cox proportional hazards analysis were represented using forest plots. Differences were considered statistically significant at $P < 0.05$.

Result

Baseline Characteristics

Baseline characteristics of the two patient groups included gender, age, presence of ascites, alpha-fetoprotein (AFP) levels, ECOG performance status, presence of hepatitis B virus infection, maximum tumor diameter, number of tumors, presence of major vascular invasion, presence of microvascular invasion, presence of distant metastasis, and cirrhosis. The median follow-up time was 30.60 months for patients in the HAIC+Len→LR group and 38.50 months for patients in the LR group (Table 1).

OS, PFS, DOR

At the conclusion of follow-up, the median overall survival (mOS) for the HAIC+Len→LR group and the LR group was 40.1 months (95% CI 32.2–47.8) and 35.9 months (95% CI 29.3–42.7), respectively, with a statistically significant difference (P=0.001) (Figure 2A). The median progression-free survival (mPFS) for the HAIC+Len→LR group and the LR group was 32.80 months (95% CI not reached) and 23.8 months (95% CI 18.2–29.4), respectively, with a statistically significant difference (P=0.0023) (Figure 2B). According to mRECIST assessment, the mOS for the complete response (CR) group and the partial response (PR) group was 40.0 months (95% CI not reached) and 29.1 months (95% CI 26.9–31.0), respectively, with a statistically significant difference (P=0.037) (Figure 2C). The median duration of response (mDOR) was not reached and 28.9 months (95% CI 25.1–32.7), respectively, with a statistically significant difference (P=0.006) (Figure 2D).

Univariable and Multivariable Analyses of OS and PFS

In the single-variable and multivariable analyses of factors influencing OS, ascites (HR 7.322, 95% CI 2.776–19.313, P=0.001), major vascular invasion (HR 2.501, 95% CI 1.309–4.779, P=0.006), cirrhosis (HR 1.782, 95% CI

Table 1 Baseline Characteristics

Characteristics	HAIC + Len→LR (n = 63)	LR (n = 91)	X^2 value X	p Value
Age			0.137	0.712
<65y	49 (77.77%)	54 (59.34%)		
≥65y	14 (22.23%)	37 (40.66%)		
Sex			5.713	0.017
Female	9 (14.28%)	15 (16.48%)		
Male	54 (87.72%)	76 (83.52%)		
Ascites			0.742	0.389
Absence	60 (95.24%)	82 (90.11%)		
Presence	3 (4.76%)	9 (9.89%)		
AFP			0.19	0.663
≤400 ng/mL	49 (77.78%)	68 (74.72%)		
>400 ng/mL	14 (22.22%)	23 (25.28%)		
ECOG			2.457	0.117
0–1	42 (66.66%)	71 (78.02%)		
2	21 (33.34%)	20 (21.98%)		
HBV			3.8	0.051
Absence	13 (20.63%)	32 (35.16%)		
Presence	50 (79.37%)	59 (64.84%)		
Tumor size			1.803	0.179
≤7cm	37 (58.73%)	63 (69.23%)		
>7cm	26 (41.27%)	28 (30.77%)		
Tumor number			7.083	0.008
1–3	51 (80.95%)	87 (95.60%)		
>3	12 (19.05%)	4 (4.40%)		
Macrovascular invasion			0.359	0.549
Absence	48 (76.19%)	73 (80.22%)		
Presence	15 (20.81%)	18 (19.78%)		
MVI			0.896	0.344
Absence	48 (70.19%)	63 (69.23%)		
Presence	15 (23.81%)	28 (30.77%)		
Metastasis			0.007	0.935
Absence	53 (84.12%)	77 (84.61%)		
Presence	10 (15.87%)	14 (15.39%)		
BCLC			3.583	0.058
Early	7 (11.10%)	21 (23.10%)		
Intermediate-Advanced	56 (88.90%)	70 (76.90%)		
Cirrhosis			0.539	0.463
Absence	37 (58.73%)	48 (52.75%)		
Presence	26 (41.27%)	43 (47.25%)		

Abbreviations: MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer stage; ECOG, Eastern Cooperative Group performance status score.

1.007–3.152, P=0.047), and preoperative treatment (HR 0.256, 95% CI 0.128–0.513, P=0.001) were identified as independent risk factors. In the single-variable and multivariable analyses of factors influencing PFS, ascites (HR 4.576, 95% CI 1.95–10.736, P=0.001), major vascular invasion (HR 2.682, 95% CI 1.538–4.677, P=0.001), and preoperative treatment (HR 0.31, 95% CI 0.172–0.559, P=0.001) were identified as independent risk factors (Table 2).

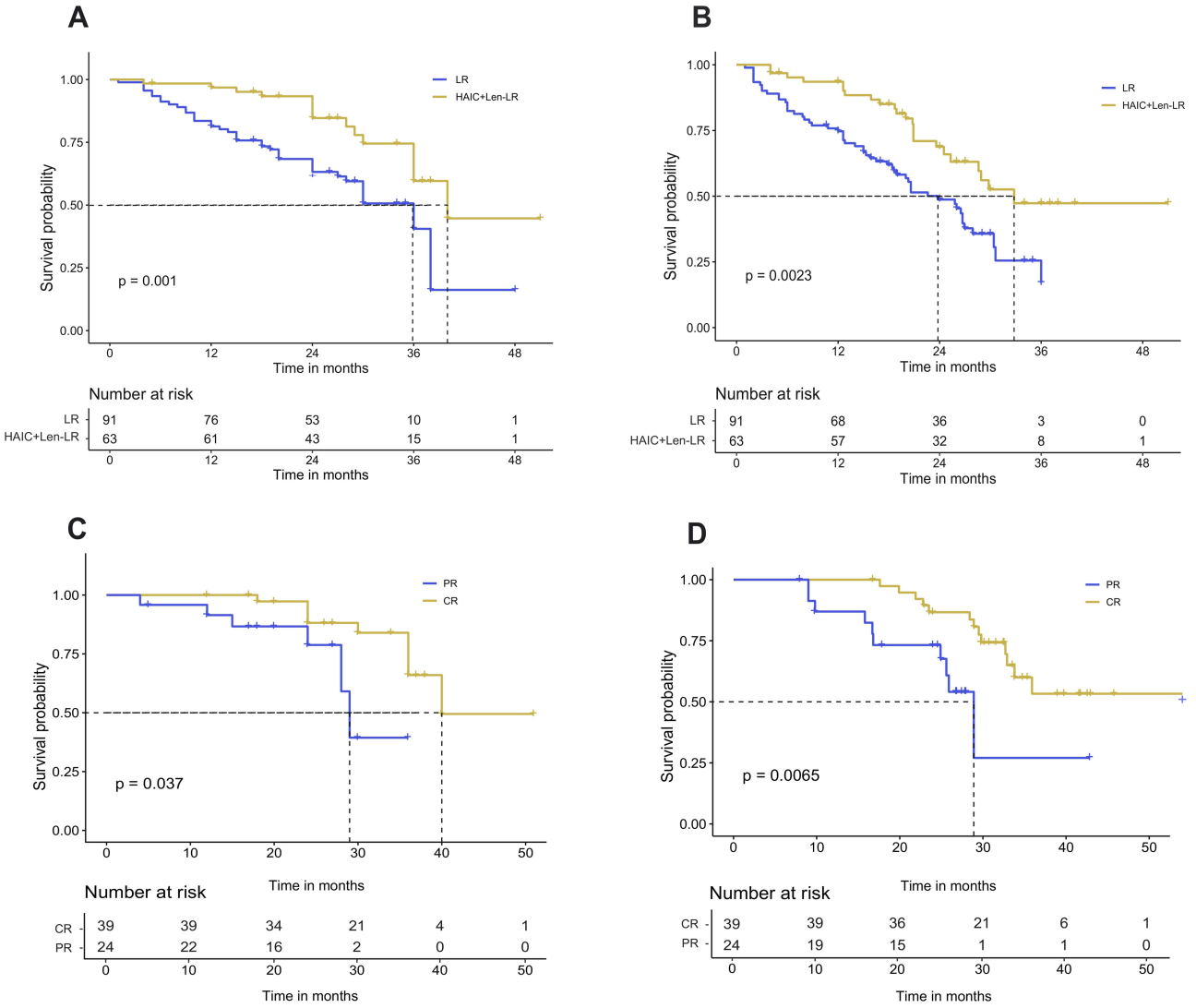

Figure 2 (**A–D**) The Kaplan–Meier survival curves by Log rank test for HAIC + Len-LR group and the LR group, CR group and PR group. (**A**) The mOS was 40.1 (95% CI 32.23–47.76) and 35.9 (95% CI 29.3–42.7) months; (**B**). The PFS was 32.8 (95% CI not reached) and 23.8 (95% CI 18.2–29.4) months; (**C**) The mOS was 40.0 (95% CI not reached) and 29.1 (95% CI 26.9–31.0) months; (**D**) The mDOR (mRecist) was not reached and 28.9 (95% CI 25.1–32.7) months.
Abbreviations: mOS, mean overall survival; mPFS, median progression-free survival; mDOR, median duration of response; CR, complete response; PR, partial response.

Subgroup Analysis

In addressing common factors influencing HCC recurrence and long-term survival, such as tumor size, number of tumors, BCLC staging, presence of cirrhosis, microvascular invasion, major vascular invasion, and distant metastasis, subgroup analyses were conducted regarding OS and PFS (Figures 3 and 4).

Adverse Events

In this research, the most common adverse events included anorexia (19% vs 23.1%, P=0.549), abdominal pain (12.7% vs 23.1%, P=0.105), and elevated AST (22.2% vs 24.2%, P=0.778), with no significant differences observed between the two groups. Short-term postoperative common complications such as liver failure (4.8% vs 5.5%, P=1.00), bleeding (9.5% vs 6.5%, P=0.34), bile duct fistula (9.5% vs 2.2%, P=0.100), and infection (4.8% vs 8.8%, P=0.525) did not exhibit notable differences in this study. The incidence rates of grade 3 adverse events were 15.9% and 6.6% in the two groups, with no statistically significant difference (P=0.064). No patients experienced treatment-related grade 4 or 5 AEs, and all patients underwent successful surgery without any surgeries being canceled due to tumor progression or

Table 2 Univariate and Multivariate Analyses of Predictors of Survival After Treatment

	Overall Survival				Progression-Free Survival			
		Multivariate Analysis				Multivariate Analysis		
Factors	**Univariate Analysis p Value**	**HR**	**95% CI**	**p Value**	**Univariate Analysis p Value**	**HR**	**95% CI**	**p Value**
Age	0.416				0.709			
<65y								
≥65y								
Sex	0.862				0.883			
Female								
Male								
Ascites	0.001	7.322	2.776,19.313	0.001	0.001	4.576	1.95,10.736	0.001
Absence								
Presence								
AFP	0.261				0.066			
≤400 ng/mL								
>400 ng/mL								
ECOG	0.225				0.054			
0–1								
2								
HBV	0.107				0.488			
Absence								
Presence								
Tumor size	0.001				0.009			
≤7cm								
>7cm								
Tumor number	0.219				0.797			
1–3								
>3								
Macrovascular invasion	0.001	2.501	1.309,4.779	0.006	0.001	2.682	1.538, 4.677	0.001
Absence								
Presence								
MVI	0.128				0.21			
Absence								
Presence								
Metastasis	0.001				0.016			
Absence								
Presence								

(*Continued*)

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Table 2 (Continued).

	Overall Survival				**Progression-Free Survival**			
		Multivariate Analysis				**Multivariate Analysis**		
Factors	**Univariate Analysis p Value**	**HR**	**95% CI**	**p Value**	**Univariate Analysis p Value**	**HR**	**95% CI**	**p Value**
BCLC	0.841				0.468			
Early								
Intermediate-Advanced								
Cirrhosis	0.015	1.782	1.007,3.152	0.047	0.113			
Absence								
Presence								
Preoperative treatment	0.002	0.256	0.128,0.513	0.001	0.003	0.31	0.172,0.559	0.001
Absence								
Presence								

Abbreviations: MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer stage; ECOG, Eastern Cooperative Group performance status score.

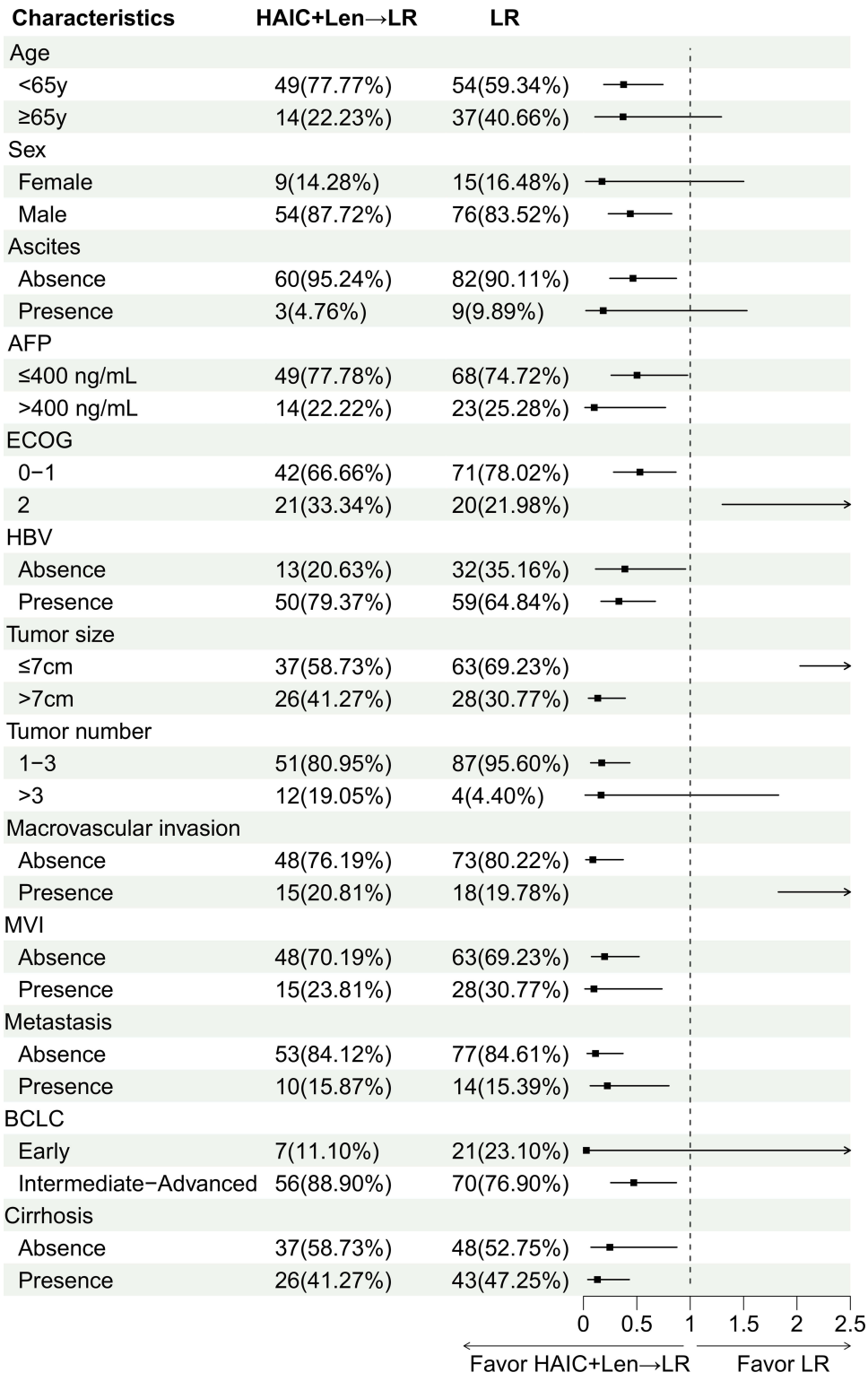

Figure 3 Forest plot of OS for subgroups in patients of HAIC + Len-LR group and the LR group.
Abbreviations: MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer stage; ECOG, Eastern Cooperative Group performance status score.

intolerable adverse events. The rates of postoperative complications were comparable between the neoadjuvant therapy group and the surgery group (P> 0.05) (Table 3).

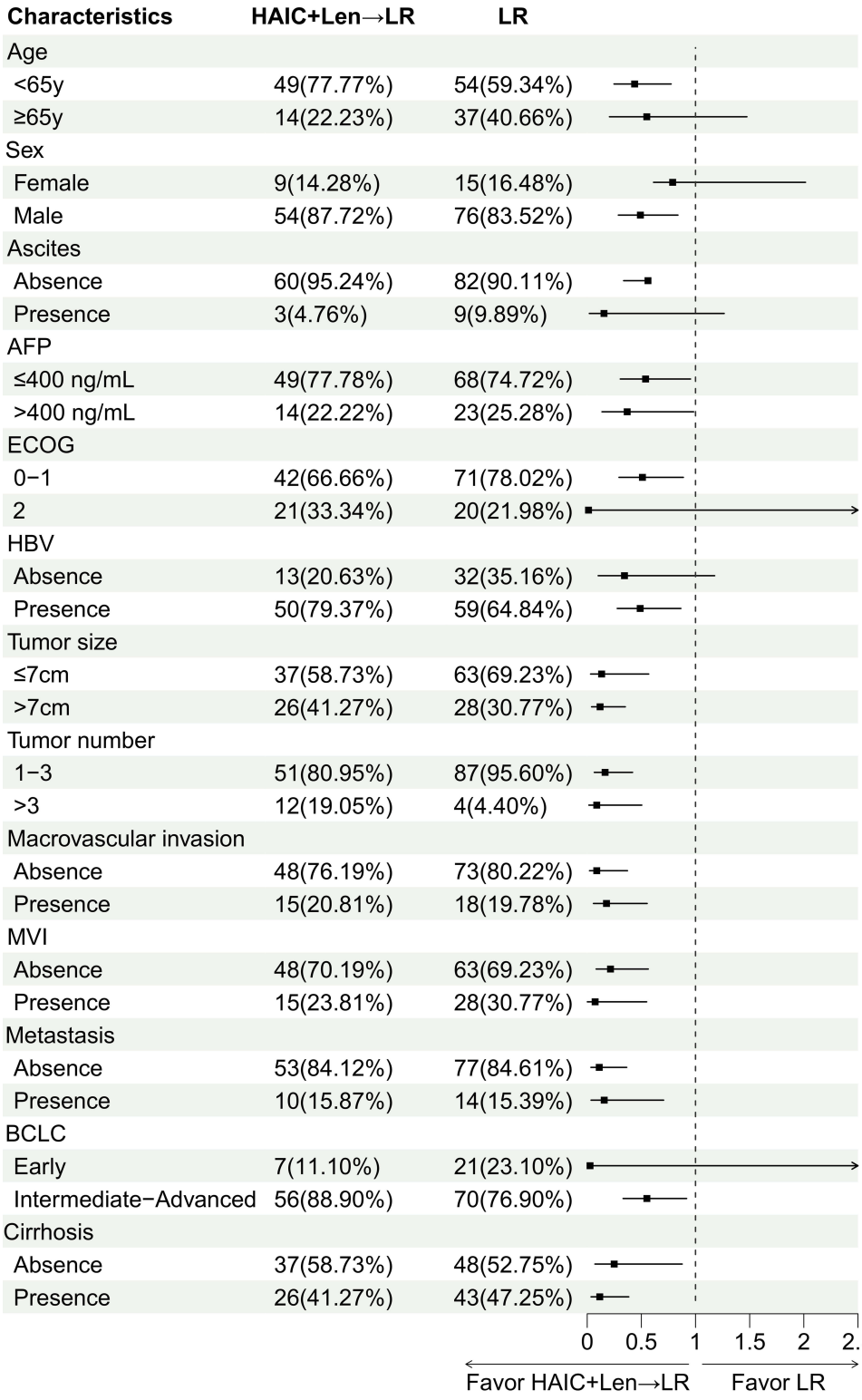

Figure 4 Forest plot of PFS for subgroups in patients of HAIC + Len-LR group and the LR group.
Abbreviations: MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer stage; ECOG, Eastern Cooperative Group performance status score.

Discussion

A nationwide cohort study in Japan found that patients undergoing liver resection (LR) had a median survival time 1.77 years longer than those who did not undergo surgery [2.87 years (95% CI, 2.60–3.37) vs 1.10 years (95% CI, 1.03–1.17);

Table 3 Adverse Events

Adverse Events	Any Grade			Grade 3/4		
	HAIC + Len→LR (n = 63)	LR (n = 91)	p Value	HAIC + Len→LR (n = 63)	LR (n = 91)	P Value
Treatment-related AEs, n (%)				10(15.9)	6(6.6)	0.064
Gastrointestinal events						
Diarrhea	13(20.6)	14(15.4)	0.4	0	0	1
Vomiting	13(20.6)	15(16.5)	0.511	0	0	1
Inappetence	12(19.0)	21(23.1)	0.549	0	0	1
Abdominal pain	8(12.7)	21(23.1)	0.105	0	0	1
Surgical-related complications						
Liver failure	3(4.8)	5(5.5)	1	2(3.2)	1(1.1)	0.359
Hemorrhage	6(9.5)	5(5.5)	0.34	3(4.8)	1(1.1)	0.16
Bile duct fistula	6(9.5)	2(2.2)	0.1	4(6.3)	1(1.1)	0.071
infection	3(4.8)	8(8.8)	0.525	1(1.6)	3(3.3)	0.512
Laboratory-related AEs, n (%)				1(1.6)	3(3.3)	0.512
Anemia	8(12.7)	6(6.6)	0.195	0	0	1
Leukopenia	7(11.1)	7(7.7)	0.468	0	0	1
Elevated ALT	13(20.6)	13(14.3)	0.301	0	1(1.1)	1
Elevated AST	14(22.2)	22(24.2)	0.778	0	0	1
Hypoalbuminemia	18(28.6)	28(30.8)	0.770	0	0	1
Hyperbilirubinemia	14(22.2)	19(20.9)	0.842	1(1.6)	2(2.2)	0.788

Notes: Patient treatment-related and laboratory-related adverse events.
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate transaminase.

P < 0.001]. Despite this, survival rates for LR patients remain suboptimal, with 1-year, 3-year, and 5-year survival rates of 74.8%, 49.1%, and 39.1%, respectively.[26] Adjuvant therapy is therefore recommended to address postoperative complications and improve long-term survival.[27] HAIC is a minimally invasive, safe, and effective treatment for liver cancer, particularly in East Asia.[28,29] While studies comparing HAIC to standard treatments show mixed results, preliminary evidence supports its feasibility and survival benefits for hepatocellular carcinoma (HCC).[30,31] HAIC has a high response rate and manageable toxicity, proving effective for liver cancer management.[32–35] Furthermore, HAIC demonstrates substantive benefits in certain patients, such as those with portal vein thrombosis or high intrahepatic tumor burden. When combined with tyrosine kinase inhibitors (TKIs) or PD-1 inhibitors, HAIC has shown promise in improving patient outcomes.[28,35] Despite ongoing debate about survival benefits, particularly for overall survival (OS), most combination therapies show higher objective response rates compared to hepatic arterial infusion chemotherapy (HAIC) alone. Recent data from a randomized trial indicate that combining sorafenib with FOLFOX extends overall survival by 6.24 months in patients with portal vein invasion.[35] This improved efficacy is likely due to chemotherapy agents inducing apoptosis and enhancing anti-tumor immune responses, TKIs increasing PD-L1 expression and facilitating immune cell infiltration, and TKIs inhibiting tumor angiogenesis.[18–20]

We have identified several factors worthy of further investigation. Tumor response to chemotherapy and targeted therapy is critical, as achieving greater tumor burden relief after combined therapies often results in better long-term prognosis.[20,34] In this study, 59.2% of patients had a complete (CR) or partial response (PR) to HAIC+Len. The CR group showed significantly longer median duration of response (28.9 months, P=0.006) and overall survival (40.0 months, P=0.037) compared to the PR group. A recent study reported that CR or PR after HAIC+Len was associated with median overall survival and progression-free survival of 40.1 and 32.8 months, respectively, outperforming the surgery-only group, indicating enhanced benefits of neoadjuvant therapy.[36] Furthermore, Cox regression analysis in this study identified ascites and macrovascular invasion as significant independent risk factors affecting PFS and OS. Addressing these through early intervention and tailored therapies is vital for improving survival and quality of life.[37,38]

In subgroup analysis, no significant difference in long-term survival was observed between early BCLC stage patients undergoing preoperative HAIC + Len and those undergoing direct surgery (HR=0.027, P=0.213 for OS; HR=0.026, P=0.176 for PFS). Additionally, the HAIC + Len group had higher rates of postoperative bile duct fistula and bleeding compared to direct surgery. Previous studies suggest that preoperative intervention with targeted immunotherapy may increase perioperative complications.[39,40] And some studies suggest that local chemotherapy for patients in early BCLC stage is not superior to direct surgery.[41,42] Taken together, for patients in early BCLC stage who are resectable or borderline resectable, direct surgical resection may be a preferable option. However, for patients with resectable or borderline resectable HCC in intermediate to advanced BCLC stages (HR = 0.471, P = 0.016 in OS and HR = 0.551, P = 0.022 in PFS), surgery following neoadjuvant HAIC + Len may offer better long-term prognosis, a notion supported by recent studies.[43,44]

Adverse events in this study were acceptable Postoperative bleeding and bile duct fistula rates were higher in the HAIC+Len→LR group compared to the LR group (bleeding: 9.5% vs 5.5%, P=0.34; bile duct fistula: 9.5% vs 2.2%, P=0.100). Some studies have suggested that HAIC-related neoadjuvant therapy may increase the incidence of perioperative complications after liver resection.[39,40] Although HAIC-related neoadjuvant therapy may increase perioperative complications, proper management and close follow-up can effectively address.[45] In this study, all patients who developed bile duct fistulas were managed with abdominal drainage tubes. Only one patient experienced hyperbilirubinemia post-removal of the drainage tube, which resolved within a month following appropriate liver and gastric protective treatments. This outcome underscores the importance of proper perioperative management and close monitoring, which can significantly manage and resolve complications such as bile duct fistulas.

This study has several limitations: selection bias due to physician and patient preferences, being a single-center retrospective study, small sample size, relatively short average follow-up time, and a need for further analysis of additional laboratory indicators. Future studies with larger sample sizes and longer follow-up are necessary to validate the benefits of neoadjuvant HAIC+Len.

Conclusion

In conclusion, the combination of neoadjuvant HAIC and lenvatinib (HAIC+Len) demonstrates manageable adverse events and shows promise for patients with resectable or marginally resectable HCC at intermediate to advanced BCLC stages. Incorporating HAIC+Len before surgery may enhance long-term prognosis and could be considered a viable strategy to improve outcomes in this patient population. Future research should focus on optimizing this approach and validating its benefits in larger, multicenter trials.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Research Ethics No: K2024-191-01). The study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment.

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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Disclosure

The authors report no conflicts of interest in this work.

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