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ARTICLE

The Pretreatment Neutrophil-to-Lymphocyte Ratio as a Near-Term Prognostic Indicator in Patients with Locally Advanced Hepatocellular Carcinoma Treated with Hepatic Arterial Infusion Chemotherapy: A Propensity Score Matching Cohort Study

Weifu Liu[1,2], Kongzhi Zhang[1,2], Shiguang Chen[1,2], Xiaolong Wang[1,2], Wenchang Yu[1,2,*]

[1]Department of Interventional Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China
[2]Fujian Provincial Key Laboratory of Tumor Biotherapy, Fuzhou, Fujian, China
*Correspondence: ywc21jy@163.com (Wenchang Yu)

Abstract

Aims/Background To investigate the predictive value of the pretreatment neutrophil-to-lymphocyte ratio (NLR) for estimating the near-term efficacy of hepatic arterial infusion chemotherapy (HAIC) in patients with locally advanced hepatocellular carcinoma (HCC).

Methods In this retrospective study, data were collected from patients with locally advanced HCC treated with HAIC between January 2018 and June 2022. Patients were categorized based on their pretreatment NLRs and analyzed using propensity score matching (PSM). The primary endpoints in this study were objective response rate (ORR), progression-free survival (PFS), and safety.

Results The optimal pretreatment NLR cutoff was 2.90 using the X-tile software (version 3.6.1; Yale Corp., New Haven, CT, USA), and 104 patients were included. These patients were divided into a high-NLR subgroup (>2.9; n = 44) and a low-NLR subgroup (≤2.9; n = 60). 43 matched pairs were analyzed following PSM. PFS (6.7 months vs. 3.8 months, $p = 0.007$) and ORR (69.8% vs. 37.2%, $p = 0.002$) were significantly higher in patients with a low pretreatment NLR than in patients with a high pretreatment NLR. Both univariate and multivariate regression analyses demonstrated that a high pretreatment NLR was an independent negative prognostic factor for ORR (hazard ratio [HR], 3.464; 95% CI, 1.383–8.678; $p = 0.008$) and PFS (HR, 1.634; 95% CI, 1.026–2.600; $p = 0.038$). No significant differences in the incidence of adverse events were observed between the groups.

Conclusion Pretreatment NLR is a readily obtainable and effective biomarker for predicting the near-term efficacy of HAIC in patients with locally advanced HCC.

Key words: hepatocellular carcinoma; hepatic arterial infusion chemotherapy; neutrophil-to-lymphocyte ratio; propensity score matching

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer in China. Unfortunately, the majority of patients with HCC are often diagnosed at advanced stages, where surgery is not feasible for treatment, while other effective treatment

options are lacking, making this cancer type one of the leading causes of cancer-related deaths in China (Han et al, 2024). Atezolizumab and bevacizumab therapies, as well as sorafenib and lenvatinib, are currently recognized as the standard first-line treatments for advanced HCC because they significantly improve the survival of patients with advanced HCC (Cheng et al, 2009; Finn et al, 2020; Kudo et al, 2018; Llovet et al, 2008). However, in China, hepatitis B virus (HBV) infection is the main etiological factor for HCC, presenting a markedly different pathogenic mechanism compared to the Western populations. Patients with advanced HCC have a significantly higher tumor burden as a result, as evidenced by a large tumor size, multiple tumors, tumors occupying more than 50% of the liver, and frequent invasion of major intrahepatic blood vessels (Chen et al, 2017). Consequently, this results in only modest survival benefits from the aforementioned systemic treatments in advanced HCC patients in China.

Hepatic arterial infusion chemotherapy (HAIC) is recognized as an effective alternative to systemic therapy for advanced HCC, especially in the Asia-Pacific region, because of its high local control rates and tolerable safety profile (General Office of National Health Commission, 2022; Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2022; Kudo et al, 2021). Several studies (Chen et al, 2020; Lyu et al, 2022) have demonstrated that HAIC, particularly when based on oxaliplatin, achieves an objective response rate (ORR) of 31.5–41.5% and a median progression-free survival (PFS) of 5.2–7.8 months in advanced HCC patients while maintaining manageable adverse reactions. Further research suggests that the survival benefits of HAIC and its combination therapies are particularly pronounced in patients who exhibit a positive response to HAIC (Fu et al, 2023; He et al, 2019b). However, given the huge heterogeneity of HCC, notable variations in sensitivity to chemotherapy have been observed. Thus, identifying patients with advanced HCC who are potential responders to HAIC and promptly switch to other treatment options is essential for those likely to be nonresponders, with the aim of maximizing overall survival benefits across the patient population.

The body's inflammatory response plays a pivotal role in the tumor microenvironment (TME) and significantly affects the occurrence, development, and prognosis of cancer. In HCC, inflammation driven by chronic liver disease, especially HBV infection, exacerbates tumor aggressiveness and affects treatment responses. The neutrophil-to-lymphocyte ratio (NLR), an indicator derivable fromindices based on the peripheral blood, represents a crucial measure of the body's inflammatory response and has emerged as an important prognostic factor for survival across patient populations affected by a diverse range of cancers (Shaul and Fridlender, 2018). Numerous studies have demonstrated that NLR is a valuable prognostic factor for HCC patients undergoing surgical resection, ablation, transarterial chemoembolization (TACE), or targeted immunotherapy or combination therapies (Chen et al, 2018; Chen et al, 2022; Chon et al, 2023; He et al, 2019a; Schobert et al, 2020). However, the prognostic significance of NLR in patients with advanced HCC receiving HAIC treatment has yet to be fully determined. To address this gap, we

conducted a propensity score matching analysis to investigate the predictive value of pretreatment NLR for estimating near-term efficacy in locally advanced HCC patients receiving HAIC treatment.

Methods

Study Design and Patient Selection

In this retrospective study, we gathered the data on patients diagnosed with locally advanced HCC who were treated with HAIC at Fujian Cancer Hospital from January 2018 to June 2022. The inclusion criteria included: (1) patients aged $\geq$18 and $\leq$75 years; (2) patients with histologically/cytologically confirmed HCC, or liver cirrhosis that fulfills the American Association for the Study of Liver Diseases (AASLD) clinical diagnostic criteria (Marrero et al, 2018) for HCC; (3) patients who were unsuitable for curative treatments such as surgical resection or radical ablation; (4) patients who were ineligible for TACE treatment or exhibited progression post-TACE; (5) patients with the Eastern Cooperative Oncology Group (ECOG) performance status (Oken et al, 1982) of 0–1; (6) patients with Child-Pugh class A or B; (7) patients with at least one measurable lesion; (8) patients with adequate organ and bone marrow function, defined as white blood cell count $\geq 3.0 \times 10^9$/L, neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, hemoglobin $\geq$85 g/L, alanine transaminase and aspartate transaminase $\leq 5\times$ upper limit of normal (ULN), serum creatinine $\leq 1.5\times$ ULN; (9) patients with a life expectancy of over 2 months; and (10) patients who had completed at least 2 cycles of HAIC treatment. The exclusion criteria of this study are as follows: (1) individuals with extrahepatic metastasis; (2) individuals with any HAIC contraindications, such as severe infection, significant coagulation dysfunction, liver or kidney insufficiency, or severe cardiopulmonary dysfunction; (3) individuals with concurrent diagnosis of other malignant tumors, except for treated basal cell carcinoma or *in situ* carcinoma; (4) individuals receiving any local treatment within 4 weeks before enrollment; (5) individuals receiving other local or systemic treatments concurrent with HAIC therapy; and (6) individuals with unassessable treatment efficacy or insufficient follow-up data.

The data of 178 consecutive patients with locally advanced HCC who received HAIC treatment were collected through the hospital's information system. Initially, 34 patients with extrahepatic metastasis were excluded; 40 patients were excluded, including 14 who received other treatments during HAIC, 13 who underwent only one cycle of treatment without efficacy analysis, 11 who were lost to follow-up after two cycles, and 2 afflicted with other malignancies. Finally, 104 patients were included in this study. The median follow-up interval was 32.1 months, with a cut-off date of 30 November 2022. Using the X-tile software (version 3.6.1; Yale Corp., New Haven, CT, USA) (Camp et al, 2004), the optimal pretreatment NLR cut-off value was determined to be 2.90, leading to the categorization of 44 patients into the high-NLR ($>$2.9) subgroup and 60 into the low-NLR ($\leq$2.9) subgroup.

Propensity Score Matching

Propensity score matching (PSM) was conducted using a 1:1 nearest-neighbor matching algorithm without replacement. The matched variables included age, sex, hepatitis B infection status, cirrhosis presence, Child-Pugh class, ECOG performance status, alpha-fetoprotein (AFP) level, maximum tumor size, tumor number, and portal vein tumor thrombosis (PVTT) status. The caliper width was set at 0.2 to ensure close matching between the groups. After PSM, 43 pairs of patients were successfully matched and analyzed (Fig. 1).

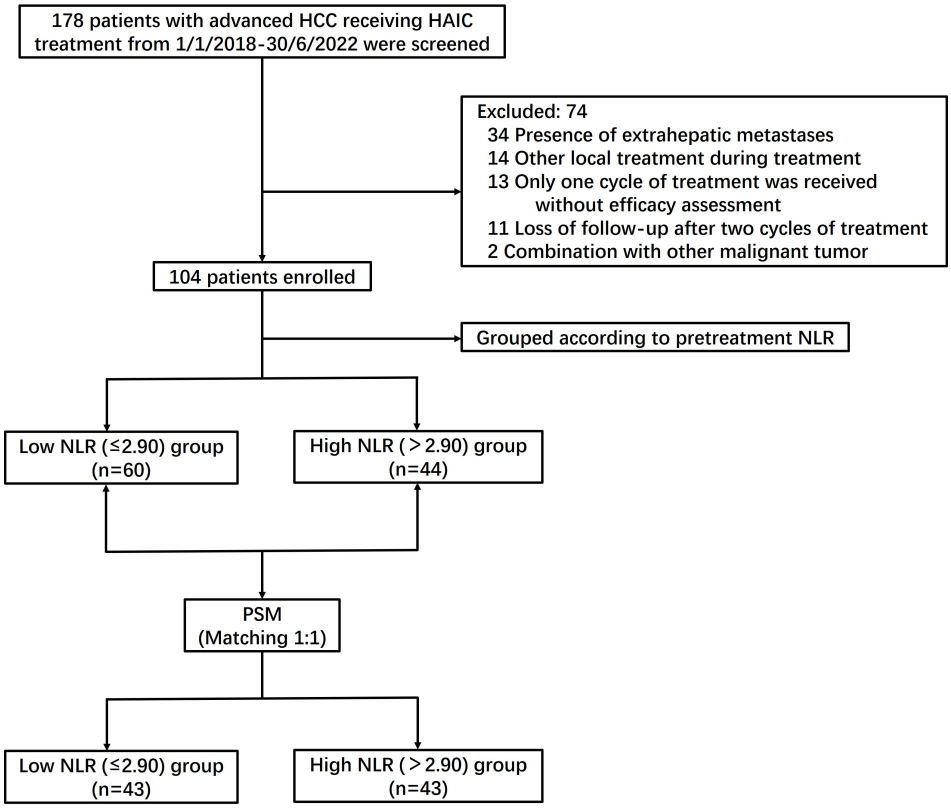

Fig. 1. A flowchart outlining patient selection and grouping. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; NLR, neutrophil-to-lymphocyte ratio; PSM, propensity score matching.

HAIC Treatment

In brief, following successful femoral artery puncture via the Seldinger technique, an angiographic catheter was introduced for celiac trunk and common hepatic artery angiography. Additionally, angiography of the superior mesenteric, phrenic, and right renal arteries was performed to precisely identify the feeding arteries of the tumor. A 2.7F coaxial microcatheter was then superselectively placed into the primary feeding artery of the tumor. After the catheter and sheath were stabilized, an infusion pump was connected to initiate HAIC treatment. The HAIC treatment regimen consisted of oxaliplatin (85 mg/m^2, administered continuously for 4 h) and raltitrexed (3 mg/m^2, administered continuously for 1 h). Upon completion of the

HAIC treatment, all related catheter components were removed. HAIC treatment was administered every three weeks for a maximum of six cycles. The criteria for terminating HAIC treatment included disease progression, intolerable toxicity, death, patient refusal to continue treatment, and tumor downstaging to allow curative resection or ablation. If grade 3 or 4 toxicity reactions occur during treatment, HAIC treatment should be discontinued until toxicity is reduced to grade 1. Upon resuming treatment, the dosage of both chemotherapeutic drugs was reduced by 25% compared to that in the previous cycle.

Patient Assessment and Follow-up

Each follow-up and assessment involved thorough history taking, physical examination, and a series of diagnostic tests, including laboratory investigations, electrocardiography, chest computed tomography (CT) scans, and contrast-enhanced abdominal CT or magnetic resonance imaging (MRI). Laboratory investigations included routine blood tests, liver and kidney function assessments, coagulation profile measurements, and AFP level measurements. The pretreatment NLR was calculated based on the neutrophil and lymphocyte counts derivable from the complete blood analysis results obtained within one week of the initial HAIC treatment. Tumor response evaluation was conducted every six weeks, beginning after the completion of every two HAIC cycles, for all participants. Tumor response, determined as the best response recorded at any time point, was independently verified by two experienced radiologists using radiological examinations in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al, 2009). The primary endpoints were objective response rate (ORR), progression-free survival (PFS), and safety. The ORR refers to the percentage of patients who achieved either complete response (CR) or partial response (PR). PFS is defined as the duration from the initiation of the initial treatment to disease progression or death due to any causes. Adverse events (AEs) were systematically assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (National Institutes of Health et al, 2017). In cases of disease progression, a multidisciplinary team convened to deliberate on and propose appropriate treatment strategies.

Statistical Analyses

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range. Comparisons of these variables were conducted using the Student's *t*-test or Mann-Whitney U test. Categorical variables are expressed as frequencies and percentages and were compared by using the chi-square test or Fisher's exact test. PSM was performed using a 1:1 nearest-neighbor matching algorithm, with the caliper width set to 0.2. Survival curves were generated using the Kaplan-Meier method, and differences in survival were evaluated using the log-rank test. For survival analysis, the Cox proportional hazards model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software (version 26.0; IBM Corp., Armonk, NY, USA).

Table 1. Baseline characteristics of the patients.

	Before PSM		χ^2/t	*p*-value	After PSM		χ^2/t	*p*-value
	High NLR (n = 44)	Low NLR (n = 60)			High NLR (n = 43)	Low NLR (n = 43)		
NLR, mean ± SD	4.55 ± 1.61	1.95 ± 0.56	–11.610	<0.01	4.56 ± 1.63	1.87 ± 0.54	–10.281	<0.01
Age (years), mean ± SD	54.0 ± 10.7	52.5 ± 10.1	–0.705	0.482	53.9 ± 10.8	54.3 ± 10.0	0.177	0.860
Gender				0.696*				0.676*
Male, n (%)	42 (95.5)	55 (91.7)			41 (95.3)	39 (90.7)		
Female, n (%)	2 (4.5)	5 (8.3)			2 (4.7)	4 (9.3)		
Hepatitis B infection				0.636*				0.616*
Yes, n (%)	43 (97.7)	57 (95.0)			42 (97.7)	40 (93.0)		
No, n (%)	1 (2.3)	3 (5.0)			1 (2.3)	3 (7.0)		
Liver cirrhosis			1.009	0.315			0.925	0.336
No, n (%)	10 (22.7)	19 (31.7)			10 (23.3)	14 (32.6)		
Yes, n (%)	34 (77.3)	41 (68.3)			33 (76.7)	29 (67.4)		
Child-Pugh class			4.384	0.036			1.350	0.245
A, n (%)	27 (61.4)	48 (80.0)			27 (62.8)	32 (74.4)		
B, n (%)	17 (38.6)	12 (20.0)			16 (37.2)	11 (25.6)		
ECOG PS			3.438	0.064			0.454	0.500
0, n (%)	14 (31.8)	30 (50.0)			14 (32.6)	17 (39.5)		
1, n (%)	30 (68.2)	30 (50.0)			29 (67.4)	26 (60.5)		
AFP (ng/mL)			0.316	0.547			0.059	0.808
>400, n (%)	33 (75.0)	42 (70.0)			32 (74.4)	31 (72.1)		
≤400, n (%)	11 (25.0)	18 (30.0)			11 (25.6)	12 (27.9)		
Maximum tumor size (cm)			4.162	0.041			2.991	0.084
>10, n (%)	25 (56.8)	22 (36.7)			24 (55.8)	16 (37.2)		
≤10, n (%)	19 (43.2)	38 (63.3)			19 (44.2)	27 (62.8)		
Tumor number			0.295	0.587			0.068	0.795
>3, n (%)	35 (79.5)	45 (75.0)			34 (79.1)	33 (76.7)		
≤3, n (%)	9 (20.5)	15 (25.0)			9 (20.9)	10 (23.3)		

Table 1. Continued.

	Before PSM		χ^2/t	*p*-value	After PSM		χ^2/t	*p*-value
	High NLR (n = 44)	Low NLR (n = 60)			High NLR (n = 43)	Low NLR (n = 43)		
PVTT			1.211	0.271			1.261	0.261
Positive, n (%)	31 (70.5)	36 (60.0)			30 (69.8)	25 (58.1)		
Negative, n (%)	13 (29.5)	24 (40.0)			13 (30.2)	18 (41.9)		
PVTT type			2.798	0.424			3.006	0.391
Negative, n (%)	13 (29.5)	24 (40.0)			13 (30.2)	18 (41.9)		
Vp1-2, n (%)	4 (9.1)	9 (15.0)			4 (9.3)	6 (14.0)		
Vp3, n (%)	17 (38.6)	17 (28.3)			16 (37.2)	14 (32.6)		
Vp4, n (%)	10 (22.7)	10 (16.7)			10 (23.3)	5 (11.6)		
Cycles of HAIC, mean ± SD	3.3 ± 1.4	3.7 ± 1.5	1.282	0.203	3.3 ± 1.4	3.6 ± 1.6	0.921	0.360
Previous therapy								
Locoregional treatments, n (%)	17 (38.6)	34 (56.7)	3.302	0.069	17 (39.5)	23 (53.5)	1.683	0.195
Resection†	3	6			3	4		
Ablation†	2	8			2	6		
Radiotherapy†	2	5			2	2		
TACE†	16	33			15	20		
Systemic treatments, n (%)	8 (18.0)	16 (26.7)	1.029	0.310	8 (18.6)	6 (14.0)	0.341	0.559

PSM, propensity score matching; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombosis; HAIC, hepatic arterial infusion chemotherapy; TACE, transhepatic arterial chemoembolization.

* Fisher's exact test was performed.

† Number of times patients received this treatment.

Table 2. Tumor responses assessed as per the RECIST 1.1 criteria.

Treatment group	CR	PR	SD	PD	ORR (%)	χ^2	*p*-value
High NLR (n = 43)	0	16	15	12	16/43 (37.2)	9.161	0.002
Low NLR (n = 43)	2	28	8	5	30/43 (69.8)		

RECIST, Response Evaluation Criteria in Solid Tumors; NLR, neutrophil-to-lymphocyte ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

Results

Patient Characteristics

Table 1 presents the baseline characteristics of both the high- and low-NLR subgroups before and after PSM. Notably, before PSM, significant differences were observed between the two subgroups in terms of Child-Pugh class and maximum tumor size ($p < 0.05$). After PSM, the baseline characteristics were not statistically different between the two subgroups.

Tumor Response

Table 2 presents the best tumor response as evaluated using the RECIST v1.1 criteria. Notably, the ORR was significantly greater in the low-NLR subgroup than in the high-NLR subgroup (30/43 [69.8%] vs. 16/43 [37.2%], $p = 0.002$), with two patients in the low-NLR subgroup achieving CR. Tables 3,4 detail the outcomes of both the univariate and multivariate logistic regression analyses conducted on the entire patient cohort. These analyses confirmed that a high pretreatment NLR was an independent adverse prognostic factor for the ORR, with an HR of 3.464 (95% CI, 1.383–8.678; $p = 0.008$).

Survival Analyses

As shown in Fig. 2, the median PFS was 6.7 months (95% CI, 5.4–8.0) for the low-NLR subgroup and 3.8 months (95% CI, 2.1–5.5) for the high-NLR subgroup. The log-rank test results substantiated a significantly longer median PFS in the low-NLR subgroup than in the high-NLR subgroup ($p = 0.007$). As shown in Tables 5,6, univariate and multivariate Cox regression analyses revealed that high pretreatment NLR was an independent adverse prognostic factor for PFS, with an HR of 1.634 (95% CI, 1.026–2.600; $p = 0.038$).

Adverse Events

Table 7 shows the AEs observed during and after treatment in both subgroups. There was no statistically significant difference in the frequency of any level of AEs between the two subgroups (all $p > 0.05$). In the high-NLR group, the most common grade 1–2 AEs were elevated alanine transaminase (ALT; 69.1%) and aspartate transaminase (AST; 44.2%), with the most frequent grade 3 AE being elevated AST (9.3%). Similarly, increased ALT and AST levels were the most common grade 1–2 AEs in the low-NLR group, standing at 67.4% and 46.5%, respectively, with the elevated AST levels (7.0%) being the most frequent grade 3 AE. Gastrointestinal

Table 3. Univariate analyses of prognostic factors for objective response rate.

Univariate analysis	n	ORR (%)	B	S.E.	Wald	*p*-value	HR (95% CI)
NLR (≤2.9/>2.9)	43/43	69.8/37.2	1.359	0.458	8.810	0.003	3.894 (1.587–9.557)
Age, years (≤50/>50)	33/53	48.5/56.6	–0.326	0.445	0.537	0.463	0.772 (0.302–1.727)
Gender (male/female)	80/6	55.0/33.3	0.894	0.895	0.998	0.318	2.444 (0.423–14.118)
Hepatitis B infection (no/yes)	4/82	50.0/53.7	–0.147	1.024	0.020	0.886	0.864 (0.116–6.429)
Liver cirrhosis (no/yes)	24/62	62.5/50.0	0.511	0.492	1.077	0.299	1.667 (0.635–4.374)
Child-Pugh class (A/B)	59/27	59.3/40.7	0.752	0.473	2.528	0.112	2.121 (0.840–5.360)
ECOG PS (0/1)	31/55	61.3/49.1	0.496	0.457	1.178	0.278	1.642 (0.671–4.020)
AFP, ng/mL (≤400/>400)	23/63	52.2/54.0	–0.072	0.488	0.022	0.883	0.930 (0.358–2.422)
Maximum tumor size, cm (≤10/>10)	46/40	63.0/42.5	0.836	0.442	3.576	0.059	2.308 (0.970–5.492)
Tumor number (≤3/>3)	19/67	63.2/50.7	0.509	0.535	0.907	0.341	1.664 (0.583–4.745)
PVTT (negative/positive)	31/55	58.1/50.9	0.289	0.453	0.407	0.523	1.335 (0.594–3.245)

ORR, objective response rate; S.E., standard error; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombosis.

Table 4. Multivariate analyses of prognostic factors for objective response rate.

Multivariate analysis	B	S.E.	Wald	*p*-value	HR (95% CI)
NLR (≤2.9/>2.9)	1.242	0.469	7.033	0.008	3.464 (1.383–8.678)
Child-Pugh class (A/B)	0.529	0.512	1.067	0.302	1.697 (0.622–4.627)
Maximum tumor size, cm (≤10/>10)	0.572	0.476	1.446	0.229	1.773 (0.697–4.507)

S.E., standard error; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

reactions, including nausea and vomiting, and hematological disorders, including leukopenia and thrombocytopenia, were also common AEs in both subgroups. No grade 4–5 AEs were observed in either of the subgroups.

Discussion

Hepatic arterial infusion chemotherapy is recognized as a potent treatment for locally advanced HCC in the Asia-Pacific region (General Office of National Health Commission, 2022; Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), 2022; Kudo et al, 2021). However, studies have indicated that the ORR for HAIC in patients with advanced HCC seldom surpasses 50% (Chen et al, 2020; Lyu et al, 2022), suggesting that a significant proportion of these patients do not derive substantial benefits from HAIC. Despite the recent advancements in terms of notable efficacy achieved by HAIC combined with systemic therapy in advanced HCC, the near-term effectiveness of HAIC largely depends on the initial response (Liang et al, 2021). We undertook this retrospective study to identify prognostic factors influencing the near-term efficacy of HAIC in patients with advanced HCC. Our PSM findings revealed that patients with locally advanced HCC who received HAIC and exhibited a low pretreatment NLR had a higher ORR

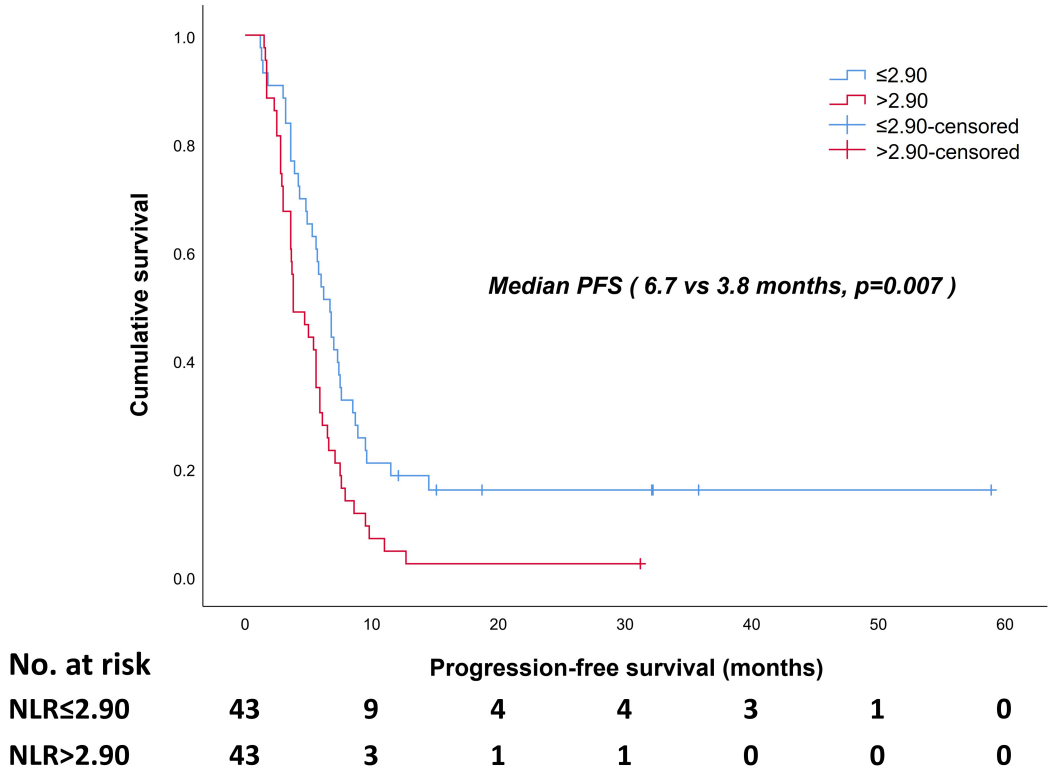

Fig. 2. Kaplan-Meier curves for comparing progression-free survival (PFS) among patients grouped according to neutrophil-to-lymphocyte ratio (NLR) values.

and longer PFS than those with a high pretreatment NLR. Prognostic analyses further confirmed that a high pretreatment NLR (>2.90) was a negative prognostic indicator for both ORR and PFS.

Several studies have confirmed the significant influence of the tumor microenvironment on the occurrence, progression, and prognosis of liver cancer (D'Alessio and Pinato, 2022; Liu et al, 2021; Wang et al, 2021; Zhang et al, 2022). Lyu et al (2022) performed tumor biopsies and corresponding liver tissue analyses, in addition to genomic profiling, in patients with advanced HCC undergoing HAIC treatment. They developed a predictive model based on mutated genes and demonstrated its effectiveness in identifying potential HAIC responders. However, according to the Chinese guidelines for diagnosing primary liver cancer, most cases of HCC are clinically diagnosed based on the presence of hepatitis, tumor markers, and radiological findings. This approach obviates the need to perform tissue biopsies, as they are deemed non-compliant with these guidelines. Thus, histopathological analysis is challenging for the prognostication of patients with advanced HCC in the Chinese clinical setting.

The NLR is typically regarded as a marker of systemic inflammatory activity. Neutrophils can promote tumor growth and metastasis by secreting pro-inflammatory cytokines and proteases, thereby fortifying the tumor-supportive microenvironment. Conversely, lymphocytes, particularly T-cells, play a crucial role in antitumor immunity. A high NLR indicates a relative increase in neutrophils and a decrease in lymphocytes, suggesting a shift towards a pro-tumor inflammatory milieu and

Table 5. Univariate analyses of prognostic factors for progression-free survival.

Univariate analysis	n	PFS (months)	B	S.E.	Wald	*p*-value	HR (95% CI)
NLR (≤2.9/>2.9)	43/43	6.7/3.8	0.605	0.231	6.892	0.009	1.832 (1.166–2.878)
Age, years (≤50/>50)	33/53	5.9/5.6	–0.256	0.232	1.215	0.270	0.774 (0.491–1.221)
Gender (male/female)	80/6	5.6/5.6	0.238	0.431	0.305	0.581	1.269 (0.545–2.953)
Hepatitis B infection (no/yes)	4/82	3.6/5.6	–0.322	0.517	0.387	0.534	0.725 (0.263–1.996)
Liver cirrhosis (no/yes)	24/62	5.6/5.6	0.136	0.256	0.281	0.596	1.145 (0.694–1.890)
Child-Pugh class (A/B)	59/27	5.9/3.6	0.412	0.241	2.907	0.088	1.509 (0.940–2.423)
ECOG PS (0/1)	31/55	5.7/5.6	0.460	0.245	3.528	0.060	1.584 (0.980–2.561)
AFP, ng/mL (≤400/>400)	23/63	5.4/5.6	0.037	0.257	0.021	0.884	1.038 (0.627–1.719)
Maximum tumor size, cm (≤10/>10)	46/40	5.7/4.9	0.490	0.232	4.449	0.035	1.633 (1.035–2.575)
Tumor number (≤3/>3)	19/67	5.9/5.0	0.082	0.269	0.094	0.760	1.086 (0.640–1.841)
PVTT (negative/positive)	31/55	5.7/5.6	0.066	0.238	0.076	0.783	1.068 (0.669–1.704)

PFS, progression-free survival; S.E., standard error; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombosis.

Table 6. Multivariate analyses of prognostic factors for progression-free survival.

Multivariate analysis	B	S.E.	Wald	*p*-value	HR (95% CI)
NLR (≤2.9/>2.9)	0.491	0.237	4.285	0.038	1.634 (1.026–2.600)
Child-Pugh class (A/B)	0.232	0.249	0.871	0.351	1.261 (0.775–2.053)
ECOG PS (0/1)	0.332	0.250	1.765	0.184	1.394 (0.854–2.276)
Maximum tumor size, cm (≤10/>10)	0.321	0.239	1.800	0.180	1.378 (0.863–2.202)

S.E., standard error; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group performance status.

weakened immune surveillance. This imbalance can lead to accelerated tumor progression and reduced responsiveness to antitumor therapies (Crusz and Balkwill, 2015; SenGupta et al, 2019). By virtue of the straightforward measurement, the NLR has become a widely utilized prognostic indicator for patients with HCC (Martin et al, 2018; Najjar et al, 2018). In a retrospective study, Qu et al (2022) analyzed the clinical data of 215 patients who underwent curative resection for HCC. Their findings revealed an independent correlation of enhanced overall survival with a lower NLR, rather than a higher NLR. Similarly, Cho et al (2022) investigated 605 patients treated with TACE and confirmed that NLR can independently predict disease progression and survival outcomes, with a higher NLR indicating a poorer prognosis.

In the present study, which focused on tumor response rate, we noted a significantly higher ORR in the low-NLR subgroup than in the high-NLR subgroup. This ORR also surpasses the previously reported range of 31.5–41.5% (Chen et al, 2020; Lyu et al, 2022). Furthermore, our prognostic analysis established that NLR was independently associated with ORR, indicating that locally advanced HCC patients with a lower NLR are more likely to respond favorably to HAIC. This finding is par-

Table 7. Treatment-related adverse events in patients.

Adverse events	High NLR (n = 43)			Low NLR (n = 43)			*p*-value*
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	
Leukopenia, n (%)	5 (11.6)	4 (9.3)	1 (2.3)	2 (4.7)	4 (9.3)	1 (2.3)	0.788
Thrombocytopenia, n (%)	5 (11.6)	7 (16.3)	2 (4.7)	4 (9.3)	7 (16.3)	2 (4.7)	1.000
Elevated ALT, n (%)	18 (41.9)	12 (27.2)	2 (4.7)	16 (37.2)	13 (30.2)	1 (2.3)	0.915
Elevated AST, n (%)	10 (23.3)	9 (20.9)	4 (9.3)	12 (27.9)	8 (18.6)	3 (7.0)	0.951
Hyperbilirubinemia, n (%)	5 (11.6)	5 (11.6)	1 (2.3)	3 (7.0)	3 (7.0)	1 (2.3)	0.774
Nausea/Vomiting, n (%)	13 (30.2)	4 (9.3)	0 (0)	10 (23.3)	3 (7.0)	0 (0)	0.697
Fever, n (%)	4 (9.3)	1 (2.3)	0 (0)	6 (14.0)	1 (2.3)	0 (0)	0.867
Diarrhea, n (%)	8 (18.6)	2 (4.7)	1 (2.3)	6 (14.0)	1 (2.3)	1 (2.3)	0.834
Abdominal pain, n (%)	6 (14.0)	4 (9.3)	0 (0)	7 (16.3)	2 (4.7)	0 (0)	0.853

NLR, neutrophil-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Fisher's exact test was performed.

ticularly relevant for HCC patients in need of rapid disease control in the short term, such as those receiving HAIC as a bridging therapy or those requiring urgent liver function improvement due to high tumor burden and major portal vein thrombosis. Regarding near-term survival outcomes, our study revealed that the median PFS in the high-NLR subgroup was not only lower than that in the low-NLR subgroup but also lower than the previously documented range of 5.2–7.8 months. This finding suggests that patients with locally advanced HCC having a higher NLR might benefit from HAIC combined with other local or systemic treatments to increase survival. Additionally, significant differences in baseline liver function and maximum tumor size were observed between the two subgroups prior to PSM, implying that patients with a higher NLR presented with more severe baseline tumor conditions. This observation aligns with the findings reported by Wang et al (2018).

Regarding safety, there were no treatment-related fatalities and no statistically significant differences in the incidence of AEs between the two groups in our study. The most prevalent AE observed in both subgroups was an increase in transaminase levels, which is consistent with previous studies (Chen et al, 2020; Lyu et al, 2022). This increase is likely brought on by the cytotoxic effects of chemotherapeutic agents. It can generally be managed through dosage adjustments or temporary treatment discontinuation, although this may affect treatment efficacy. Gastrointestinal reactions such as nausea and vomiting are other common AEs that can lead to poor nutritional status and reduced treatment adherence. Therefore, understanding and effectively managing these reactions are critical for optimizing treatment outcomes and improving patients' quality of life. Overall, our findings confirmed that HAIC treatment for advanced HCC is safe and tolerable.

Several limitations of the current study warrant our attention. First, as a retrospective study, this research is vulnerable to an inherent risk of selection bias, on account of the study being conducted at a single center, incomplete data collection, and non-randomized grouping. Nevertheless, the application of PSM to equalize the baseline characteristics between the two subgroups may have mitigated some

of these biases, thus adding scientific robustness to our results. Additionally, considering different populations, particularly patients with HCC of varying etiologies, may respond variably to HAIC, the relatively small cohort of patients in our study, which encompasses a high proportion of HBV-associated HCC cases, could potentially limit the generalizability of our results to populations with HCC of other etiologies. Consequently, larger-scale, prospective, multicenter cohort studies are warranted to further corroborate our observations and conclusions.

Conclusion

In conclusion, our study demonstrated that the pretreatment NLR, a readily obtainable biomarker, can effectively predict the near-term efficacy of HAIC treatment in patients with locally advanced HCC. Further large-scale studies are needed to confirm our findings.

Key Points

- Our study investigates the prognostic value of the pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with locally advanced hepatocellular carcinoma (HCC) treated with hepatic arterial infusion chemotherapy (HAIC).
- A low pretreatment NLR ($\leq$2.9) is associated with a higher objective response rate (ORR) and longer progression-free survival (PFS), compared to a high pretreatment NLR ($>$2.9).
- High NLR is an independent negative prognostic factor for both ORR and PFS.
- Pretreatment NLR can serve as a readily obtainable and effective biomarker for predicting the near-term efficacy of HAIC in locally advanced HCC patients.
- The NLR holds potential in guiding treatment decisions and improving outcomes in patients with advanced HCC.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available because of privacy or ethical restrictions but are available from the corresponding author upon reasonable request.

Author Contributions

WL and WY conceived the idea, designed the research and wrote manuscript. WL, KZ, SC, and XW collected clinical samples, analyzed the data. WL and WY were responsible for the final modified version. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This single-center retrospective study was approved by the Ethics Committee of Fujian Cancer Hospital (Ethical code: K2022-197-01), and the study was conducted in adherence to the Declaration of Helsinki and the ethical standards established by the Institutional Research Committee. Informed consent was obtained from all the participating patients.

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Conflict of Interest

The authors declare no conflict of interest.

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