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ORIGINAL RESEARCH

The Prognostic Value of Neutrophil-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio in Patients with Hepatocellular Carcinoma Receiving HAIC-Based Conversion Hepatectomy: A Dual-Center Retrospective Cohort Study

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Background: Clinical tools for predicting prognosis are limited for patients with hepatocellular carcinoma (HCC) undergoing hepatic arterial infusion chemotherapy (HAIC)-based hepatectomy. This study evaluated the prognostic significance of neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) in patients with HCC who received HAIC-based hepatectomy.

Methods: This dual-center retrospective study included 390 patients who received HAIC-based conversion resection to investigate the relationship of NLR and LMR with survival outcomes, adverse events, and risk factors.

Results: A total of 390 patients with HCC who received HAIC-based conversion liver resection were included. Patients with NLR ≥ 5 exhibited a significantly shorter overall survival (OS) and recurrence-free survival (RFS) compared to those with NLR < 5 ($P = 0.0181$ and $P = 0.0164$, respectively). Patients with LMR ≥ 3 exhibited favorable OS and RFS rates compared to those with LMR < 3 ($P = 0.0195$ and $P = 0.0225$, respectively). Similar results were observed in patients who achieved an objective response. NLR ≥ 5 and LMR < 3 were significantly associated with decreased OS and RFS compared to NLR < 5 and LMR ≥ 3 ($P = 0.0131$, $P = 0.0104$, $P = 0.0055$, and $P = 0.0329$, respectively).

Conclusion: NLR and LMR have an effective predictive capability in prognosis for patients with HCC who received HAIC-based conversion surgery. These findings may help surgeons and patients make decisions regarding HAIC-based conversion hepatectomy.

Plain Language Summary: Patients with NLR ≥ 5 and LMR < 3 exhibited a significantly shorter OS and RFS than those with NLR < 5 and LMR ≥ 3. NLR$\geq$5 and LMR<3 were significantly associated with decreased OS and RFS compared to NLR < 5 and LMR ≥ 3 for patients who achieved an objective response. Our findings may be useful in guiding surgeons and patients in decision-making regarding HAIC-based conversion hepatectomy.

Keywords: hepatic arterial infusion chemotherapy, conversion, hepatocellular carcinoma, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio

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Introduction

Hepatocellular carcinoma (HCC) is the most common malignant liver tumor with high incidence and mortality rates.[1,2] Hepatectomy remains one of the most effective treatments for long-term survival in patients with HCC.[3] For patients initially diagnosed with unresectable tumors, conversion therapy plays a crucial role in downstaging, enabling some patients to undergo conversion hepatectomy and achieve improved prognosis.[4,5]

Hepatic arterial infusion chemotherapy (HAIC) has recently made significant advancements in treating HCC.[6,7] HAIC plays a vital anti-tumor role in treating advanced HCC and serves as adjuvant therapy for patients with high postoperative recurrence rates. Additionally, HAIC demonstrates promising conversion efficacy in patients with unresectable HCC via HAIC-based conversion therapy.[7–9] Despite these advancements, tumor heterogeneity and variable treatment responses often result in a high recurrence rate following partial resection, leading to unsatisfactory survival outcomes for these patients.[10,11] Current predictive models for HAIC efficacy lack integration of immune-inflammatory biomarkers and face limitations in clinical accessibility for routine assessment.[12,13] Therefore, identifying reliable biomarkers to predict the efficacy of conversion resection is of significant clinical importance.

The neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) are easily accessible in clinical practice and can serve as effective prognostic indicators for patients with cancer.[14–17] Currently, an increasing number of studies are investigating the predictive value of these two indicators in cancer treatment, particularly for colorectal cancer, lung cancer, melanoma, and other types of cancer.[18–21] These inflammatory indicators have demonstrated good prognostic predictive value. As an immune organ, the liver is often involved in the immune responses during the treatment of HCC.[22] Immune cells, such as lymphocytes, neutrophils, and monocytes, are central to immune inflammation, and their influence on the tumor varies within the immune microenvironment of HCC under different conditions.[23]

Reports indicate that NLR and LMR exhibit significant predictive value in various treatments for HCC.[24,25] These two indicators can predict recurrence-free survival (RFS) and overall survival (OS) following liver cancer resection and forecast the prognosis for patients undergoing transarterial chemoembolization (TACE) and radiofrequency ablation as local treatments.[26,27] Furthermore, NLR and LMR can predict the prognosis of patients with unresectable HCC undergoing systemic treatments, such as tyrosine kinase inhibitor (TKI) and programmed death 1 (PD-1) monoclonal antibodies.[14,28] As a result, this study aimed to investigate the prognostic value of NLR and LMR in patients with HCC who underwent HAIC-based conversion liver resection.

Methods

Patient Population

The study included patients from two institutions who received HAIC-based conversion hepatectomy between January 1, 2016, and December 31, 2023. Patients with HCC were considered unsuitable for radical hepatectomy due to multiple tumors, vascular invasion, or insufficient future liver remnants. Only those with preserved hepatic function (Child-Pugh grade A/B) and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 were eligible for HAIC-based conversion treatment. These patients did not receive any anti-tumor treatments before HAIC.

Patients who underwent conversion surgery were selected according to the following criteria: (1) their conversion therapy included HAIC, (2) their intrahepatic lesions were effectively managed following HAIC-based conversion treatment, (3) the tumors were entirely excised (R0 resection), (4) hepatic function was well-preserved (Child-Pugh grade A/B), and (5) ECOG score was ≤ 1. Those excluded from the study had (1) a history of other concurrent malignancies, (2) organ insufficiency during treatment (such as pulmonary, cardiocirculatory, or renal insufficiency), or (3) incomplete information or follow-up data.

Clinicopathological data for patients with HCC were retrieved from their medical records. Routine preoperative assessments included liver and renal function tests, complete blood count, coagulation profiles, and tumor markers. Other preoperative examinations before surgery included computed tomography (CT), abdominal imaging using magnetic resonance imaging (MRI), ultrasound, cardiopulmonary function tests, and ECOG scores. This study is reported in accordance with REMARK.[29]

HAIC and Hepatectomy

The HAIC protocol was based on a previously reported regimen using modified FOLFOX.[30] It included oxaliplatin (130 mg/m^2), leucovorin (400 mg/m^2), and fluorouracil (400 mg/m^2) administered on day 1, followed by a 23 or 46 hours infusion of fluorouracil (2400 mg/m^2). Treatment with HAIC was repeated every three weeks, with patients receiving the same protocol and dosage regimen at each center. The treatment response was evaluated using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST), with MRI or CT scans performed after every two HAIC treatment cycles. It is recommended that no patient receive more than six cycles of HAIC.

Two senior consultant surgeons specializing in hepatobiliary surgery performed or supervised surgical procedures, typically 4–8 weeks following the final HAIC treatment. During surgery, ultrasound was routinely used to confirm the number, size, and location of tumors and to assess their relationship between tumors and major vasculobiliary structures. The extent of hepatectomy was determined using preoperative imaging and intraoperative ultrasound examination. The choice of liver transection instruments depends on the surgeon's preference. Inflow occlusion was conducted using an extrahepatic Glissonian approach based on intraoperative conditions. The objective of liver resection was to achieve margin-negative resection (R0) and to place a drainage tube near the resection surface.

Outcomes and Follow-Up

Patients were followed up regularly every 1–2 months for the first two years following surgery and subsequently every 3–6 months afterward. Patients were routinely examined during each follow-up, including assessments of hepatic function, tumor marker, complete blood count, coagulation tests, and imaging examinations (CT, MRI, or ultrasonography). The primary outcomes were OS and RFS. OS was defined as the time interval between conversion treatment and death or last follow-up. In contrast, RFS was defined as the interval between conversion resection and recurrence or last follow-up. Secondary outcomes included tumor response rate and adverse events (AEs).

Inflammatory-Based Scores

Routine blood tests were conducted within one week before the initiation of HAIC and conversion hepatectomy, and NLR and LMR were calculated using the following formulas: NLR = neutrophil count/lymphocyte count; LMR = lymphocyte count/monocyte count. Based on previous studies, NLR and LMR scores were divided into two cohorts.[8,31]

Statistical Analysis

Categorical variables between groups were compared using the Chi-square, Fisher's exact, or Kruskal–Wallis tests. Continuous variables were compared using the Student's *t*-test or Mann–Whitney *U*-test. The fully conditional specification discriminant and fully conditional specification regression functions were used to impute missing categorical and continuous values, respectively. The Kaplan–Meier curves were generated to calculate survival rates, and the Log rank test was used to compare differences among groups. Univariate and multivariate analyses based on Cox regression models were performed to identify potential independent risk factors associated with OS or RFS. A P-value of < 0.05 was considered statistically significant. All data analyses were conducted using the IBM Statistical Package for the Social Sciences software (version 26.0; SPSS Inc., Armonk, NY, USA).

Results

Patient Characteristics

This study included 390 patients treated with HAIC-based conversion resection between January 2016 and December 2023. The study inclusion criteria are illustrated in Figure 1, and the baseline characteristics of the patients are summarized in Table 1. Among the whole cohort, 286 (73.3%) patients achieved complete response (CR)/partial response (PR), while 104 (26.7%) patients experienced stable disease (SD)/ progressive disease (PD). Patients were divided into two groups based on NLR (NLR < 5 and NLR ≥ 5) and LMR (LMR < 3 and LMR ≥ 3). Statistically, non-significant differences were observed in age, gender, liver function, tumor stage, microvascular invasion (MVI) status, and ECOG scores when stratified using NLR and LMR levels. The temporal evolution of NLR and LMR across three critical therapeutic phases - pre-HAIC therapy

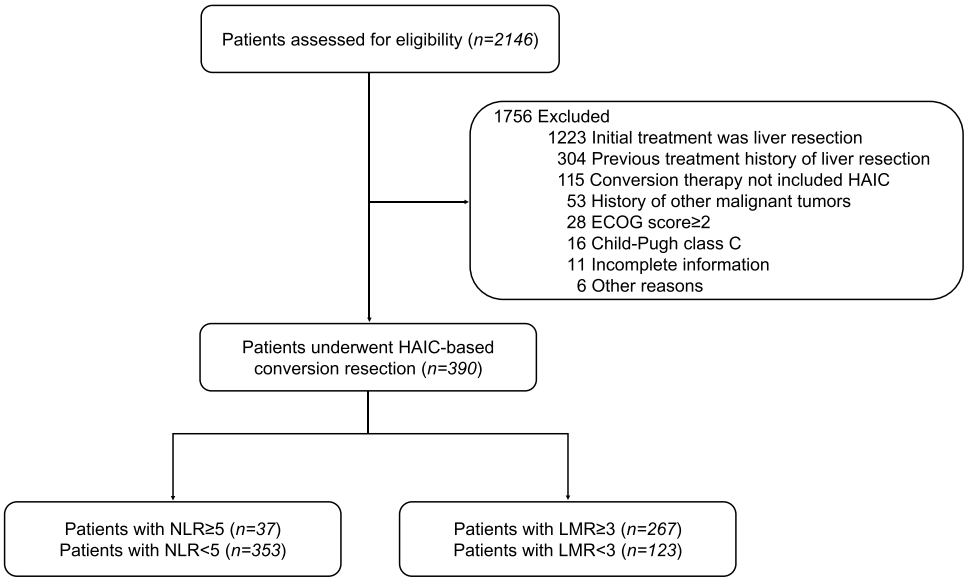

Figure 1 Flowchart of patient enrollment in the study.

baseline, pre-conversion hepatectomy dynamic phase, and post-conversion hepatectomy inflammatory resolution window - was presented in Supplementary Figure S1 and Supplementary Figure S2. Most of these patients with HCC exhibited preserved underlying hepatic function, viral etiology, larger tumor size, and elevated pre-HAIC tumor marker levels.

Table 1 Baseline Characteristics of Patients

Variable	NLR<5 (n=353)	NLR≥5 (n=37)	*P*-Value	LMR<3 (n=123)	LMR≥3 (n=267)	*P*-Value
Age, years, median (range)	53 (16–82)	51 (26–78)	0.350	52 (26–78)	53 (16–82)	0.694
Gender (male/female)	294/59 (83.3/16.7)	31/6 (83.8/16.2)	0.499	113/10 (91.9/8.1)	212/55 (79.4/20.6)	0.102
Child-Pugh Class (Class A/Class B)	350/3 (99.2/0.8)	37/0 (100.0/0.0)	0.573	122/1 (99.2/0.8)	265/2 (99.3/0.7)	0.946
ECOG PS (0/1)	270/83 (76.5/23.5)	27/10 (73.0/27.0)	0.633	97/26 (78.9/21.1)	200/67 (74.9/25.1)	0.394
Hepatitis B infection (yes/no)	324/29 (91.8/8.2)	37/0 (100.0/0.0)	0.138	116/7 (94.3/5.7)	245/22 (91.8/8.2)	0.373
Tumor number (solitary/multiple)	195/158 (55.2/44.8)	22/15 (59.5/40.5)	0.623	67/56 (54.5/45.5)	150/117 (56.2/43.8)	0.752
Tumor size			0.796			**0.009**
≤ 3 cm	11 (3.1)	1 (2.7)		2 (1.6)	11 (4.1)	
3–5 cm	30 (8.5)	2 (5.4)		3 (2.4)	28 (10.5)	
≥ 5 cm	312 (88.4)	34 (91.9)		118 (96.0)	228 (85.4)	
HAIC cycles (≤ 2/3-4/ > 4)	190/136/27 (53.8/38.6/7.6)	17/12/8 (45.9/32.4/21.7)	**0.018**	53/53/17 (43.1/43.1/13.8)	154/95/18 (57.7/35.6/6.7)	**0.009**
MVI (absent/present)			0.429			0.199
0	276 (78.2)	31 (83.8)		92 (74.8)	215 (80.5)	
1	77 (21.8)	6 (16.2)		31 (25.2)	52 (19.5)	
BCLC stage			0.644			0.175
A	136 (38.5)	17 (45.9)		44 (35.8)	109 (40.8)	
B	89 (25.2)	9 (24.4)		27 (22.0)	71 (26.6)	
C	128 (36.3)	11 (29.7)		52 (42.2)	87 (32.6)	

(*Continued*)

Table 1 (Continued).

Variable	NLR<5 (n=353)	NLR≥5 (n=37)	*P*-Value	LMR<3 (n=123)	LMR≥3 (n=267)	*P*-Value
CNLC stage			0.703			0.201
I	131 (37.1)	16 (43.2)		44 (35.8)	103 (38.6)	
II	95 (26.9)	10 (27.1)		28 (22.8)	77 (28.8)	
III	127 (36.0)	11 (29.7)		51 (41.4)	87 (32.6)	
Pre-HAIC serum tests						
AFP, ng/mL (< 400/≥ 400)	181/172 (51.3/48.7)	15/22 (40.5/59.5)	0.214	53/70 (43.1/56.9)	143/124 (53.6/46.4)	0.055
PIVKA-II, mAU/mL (< 40/≥ 40)	24/329 (6.8/93.2)	2/35 (5.4/94.6)	0.746	8/115 (93.5/6.5)	18/249 (6.7/93.3)	0.930
TBIL, μmol/L (≤ 20.5/> 20.5)	307/46 (87.0/13.0)	29/8 (78.4/21.6)	0.150	103/20 (83.7/16.3)	233/34 (87.3/12.7)	0.349
ALB, g/L (≤ 35/> 35)	17/336 (4.8/95.2)	6/31 (16.2/83.8)	**0.015**	14/109 (11.4/88.6)	9/258 (3.4/96.6)	**0.002**
PT (≤ 13.5/> 13.5)	331/22 (93.8/6.2)	32/5 (86.5/13.5)	0.187	108/15 (87.8/12.2)	255/12 (95.5/4.5)	**0.005**
Platelets, $\times 10^3/\mu L$ (< 100/≥ 100)	8/345 (2.3/97.7)	2/35 (5.4/94.6)	0.547	3/120 (2.4/97.6)	7/260 (2.6/97.4)	0.916
Preoperative serum tests						
AFP, ng/mL (< 400/≥ 400)	256/97 (72.5/27.5)	21/16 (56.8/43.2)	**0.044**	82/41 (66.7/33.3)	195/72 (73.0/27.0)	0.198
PIVKA-II, mAU/mL (< 40/≥ 40)	88/265 (24.9/75.1)	14/23 (37.8/62.2)	0.110	27/96 (22.0/78.0)	75/192 (28.1/71.9)	0.200
TBIL, μmol/L (≤ 20.5/> 20.5)	264/48 (74.8/25.2)	37/0 (100.0/0.0)	**0.010**	112/11 (91.1/8.9)	254/13 (95.1/4.9)	0.120
ALB, g/L (≤ 35/> 35)	25/328 (7.1/92.9)	3/34 (8.1/91.9)	0.818	11/112 (8.9/91.1)	17/250 (6.3/93.6)	0.360
PT (≤ 13.5/> 13.5)	341/12 (96.6/3.4)	35/2 (94.6/5.4)	0.873	118/3 (95.9/4.1)	258/9 (96.6/3.7)	0.638
Platelets, $\times 10^3/\mu L$ (< 100/≥ 100)	41/312 (11.6/88.4)	4/33 (10.8/89.2)	0.884	11/112 (8.9/91.1)	34/233 (12.7/87.3)	0.276
Postoperative serum tests						
AFP, ng/mL (≤ 25/> 25)	273/80 (77.3/22.7)	23/14 (62.2/37.8)	**0.040**	87/36 (70.7/29.3)	209/58 (78.3/21.7)	0.105
PIVKA-II, mAU/mL (< 40/≥ 40)	262/91 (74.2/25.8)	28/9 (75.7/24.3)	0.847	87/36 (70.7/29.3)	203/64 (76.0/24.0)	0.266
TBIL, μmol/L (≤ 20.5/> 20.5)	324/29 (96.9/3.1)	36/1 (97.3/2.7)	0.383	108/15 (87.8/12.2)	252/15 (94.4/5.6)	**0.024**
ALB, g/L (≤ 35/> 35)	23/330 (6.5/93.5)	37/0 (100.0/0.0)	**<0.001**	10/113 (8.1/91.9)	13/254 (4.9/95.1)	0.204

Note: Bold font indicates a *P*-value < 0.05.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; BCLC, Barcelona-Clinic Liver Cancer; CNLC, The China liver cancer; ECOG PS, Eastern Cooperative Oncology Group performance score; HAIC, hepatic artery infusion chemotherapy; LMR, lymphocyte-to-monocyte ratio; MVI, microvascular invasion; NLR, neutrophil-to-lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PT, prothrombin time; TBIL, total bilirubin.

Efficacy and Survival Outcomes

Investigators assessed tumor response according to the mRECIST criteria. Statistically, non-significant differences were observed in tumor response, objective response rate (ORR), and disease control rate (DCR) between different NLR and LMR groups (Table 2).

The median follow-up period for the entire cohort was 29.0 months (range: 2.9–89.9 months). The median OS for the whole cohort was 70.1 months (95% confidence interval (CI): 61.421–81.045, with 1-, 3-, and 5-year survival rates of 96.5%, 77.1%, and 62.1%, respectively. The median RFS was 15.0 months (95% CI: 10.805–19.129) in the whole cohort, with corresponding 1-, 3-, and 5-year survival rates of 55.6%, 36.8%, and 33.3%, respectively. Additionally, the median OS for the NLR < 5 group was 71.2 months (95% CI: 61.421–81.045), which was significantly better compared to the NLR ≥ 5 groups, whose median OS of 46.9 months (95% CI: 38.397–55.470, $P = 0.0181$, hazard ratio (HR):

Table 2 Tumor Response and Survival According to the Treatments in the Whole Cohort

Tumour Response (mRECIST)	Whole Group (n=390)	NLR<5 (n=353)	NLR≥5 (n=37)	*P*-Value	LMR<3 (n=123)	LMR≥3 (n=267)	*P*-Value
Complete response (CR)	51 (13.1%)	46 (13.0%)	5 (13.5%)	0.924	17 (13.8%)	34 (12.7%)	0.982
Partial response (PR)	235 (60.3%)	212 (60.1%)	23 (62.2%)		74 (60.2%)	161 (60.3%)	
Stable disease (SD)	100 (25.6%)	91 (25.8%)	9 (24.3%)		31 (25.2%)	69 (25.8%)	
Progressive disease (PD)	4 (1.0%)	4 (1.1%)	0 (0%)		1 (0.8%)	3 (1.1%)	
Objective response rate (CR+PR)	286 (73.3%)	258 (73.1%)	28 (75.7%)	0.735	91 (74.0%)	195 (73.0%)	0.844
Disease control rate (CR+PR+SD)	386 (99.0%)	349 (98.9%)	37 (100.0%)	0.670	121 (98.4%)	264 (98.9%)	0.682
RFS, median (95% CI)	15.0 (10.805–19.129)	15.8 (11.374–20.226)	9.6 (6.833–12.300)	**0.0164**	10.300 (8.010–12.590)	16.433 (11.296–21.571)	**0.0195**
OS, median (95% CI)	70.1 (63.778–76.422)	71.2 (61.421–81.045)	46.9 (38.397–55.470)	**0.0181**	62.267 (50.634–73.899)	71.233 (59.314–83.152)	**0.0225**

Note: Bold font indicates a *P*-value < 0.05.
Abbreviations: mRECIST, modified Response Evaluation Criteria in Solid Tumours; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; RFS, recurrence-free survival; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

2.438, 95% CI: 1.164–5.105; Figure 2A). The 1-, 3-, and 5-year OS rates were 96.4%, 78.3%, and 64.4% for patients with NLR < 5 compared to 97.3%, 65.5%, and 38.2% for patients with NLR ≥ 5, respectively. The median RFS was 15.8 months (95% CI: 11.374–20.226) for the low-NLR group and 9.6 months (95% CI: 6.833–12.300) for the high-NLR

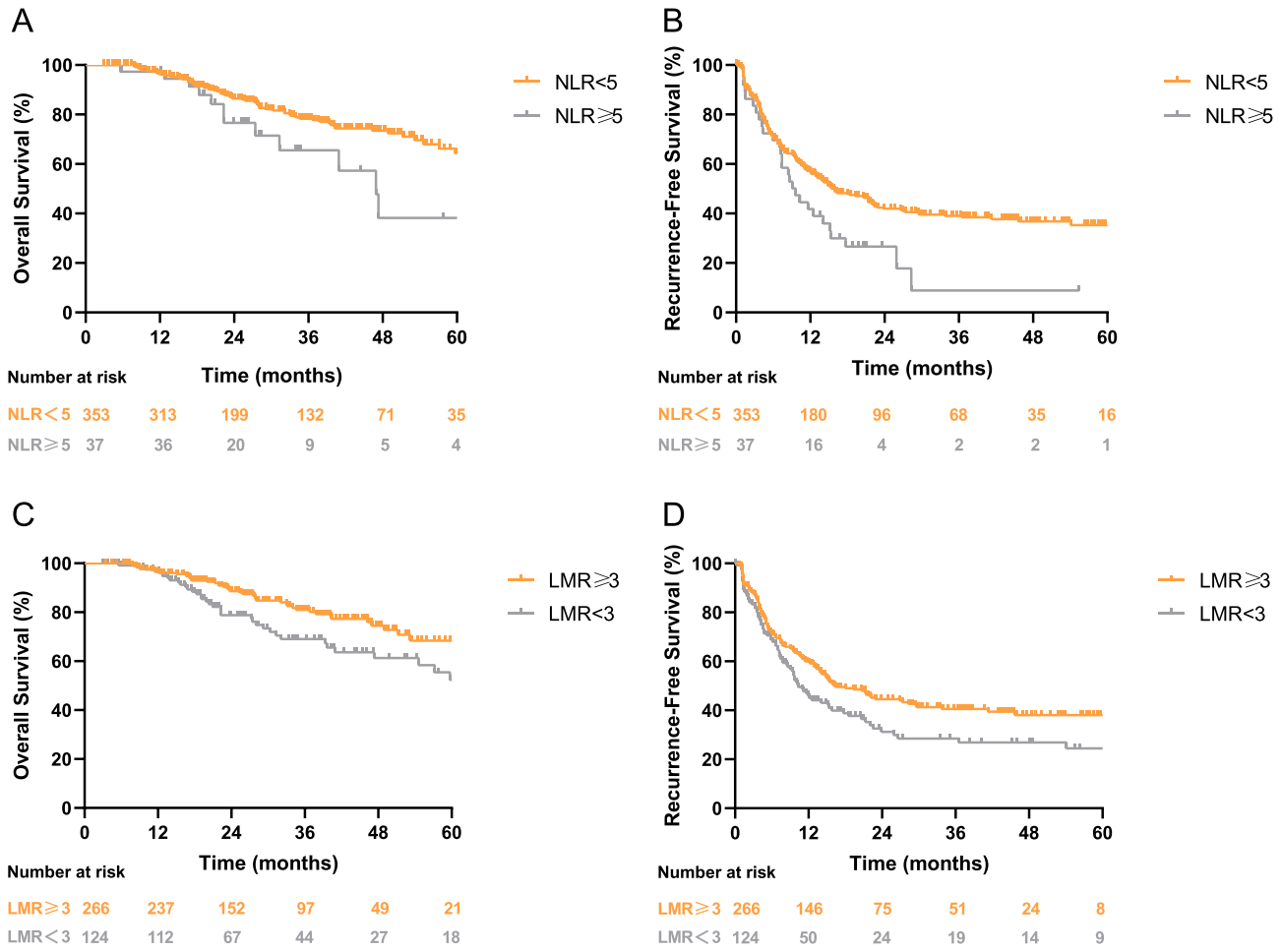

Figure 2 OS and RFS in patients with HCC receiving HAIC-based conversion hepatectomy were stratified by NLR and LMR. (**A**) OS according to NLR (*P*=0.0181, HR=2.438 (1.164–5.105)); (**B**) RFS according to NLR (*P*=0.0164, HR=1.804 (1.114–2.921)); (**C**) OS according to LMR (*P*=0.0195, HR=1.613 (1.046–2.490)); (**D**) RFS according to LMR (*P*=0.0225, HR=1.370 (1.026–1.830)).

group (P = 0.0164, HR: 1.804, 95% CI: 1.114–2.921; Figure 2B). The RFS rates at 1-, 3-, and 5-year were 56.9%, 39.0%, and 35.3% for patients with NLR < 5 and 41.8%, 8.9%, and 8.9% for patients with NLR ≥ 5, respectively. Moreover, the LMR < 3 group exhibited a low median OS of 62.3 months (95% CI: 50.634–73.899) and RFS of 10.3 months (95% CI: 8.010–12.590), which were inferior to the median OS of 71.2 months (95% CI: 59.314–83.152) and 16.4 months (95% CI: 11.296–21.571) observed in the LMR ≥ 3 groups (P = 0.0195, HR: 1.613, 95% CI: 1.046–2.490; P = 0.0225, HR: 1.370, 95% CI: 1.026–1.830; Figure 2C and D). The 1-, 3-, and 5-year OS rates were 96.6%, 69.1%, and 52.4% for patients with LMR ≥ 3 compared to 93.3%, 81.0%, and 68.4% for patients with LMR < 3, respectively. Similarly, the 1-, 3-, and 5-year RFS rates were 46.0%, 28.5%, and 24.5% for patients with LMR ≥ 3, and 60.0%, 40.6%, and 38.0% for patients with LMR < 3, respectively.

The associations between NLR, LMR, and survival outcomes were analyzed for 286 patients who achieved an objective response (CR or PR). The median OS was 75.2 months (95% CI: 66.976–83.515) for the low-NLR group and 47.3 months (95% CI: 26.533–68.000) for the high-NLR group (P = 0.0131, HR: 3.289, 95% CI: 1.284–8.424; Figure 3A). The median RFS was 21.3 months (95% CI: 13.843–28.757) for the low-NLR group and 10.3 months (95% CI: 5.041–15.559) for the high-NLR group (P = 0.0104, HR: 2.146, 95% CI: 1.197–3.849; Figure 3B). Besides, the low-LMR group had a median OS of 70.1 months (95% CI: 53.863–86.337) and RFS of 11.6 months (95% CI: 6.107–17.160), which were worse than the 75.2 (95% CI: 63.051–87.440) and 22.2 (95% CI: 2.627–41.840) for the high-LMR group (P = 0.0055, HR: 2.276, 95% CI: 1.273–4.068; P = 0.0329, HR: 1.470, 95% CI: 1.032–2.095; Figure 3C and D).

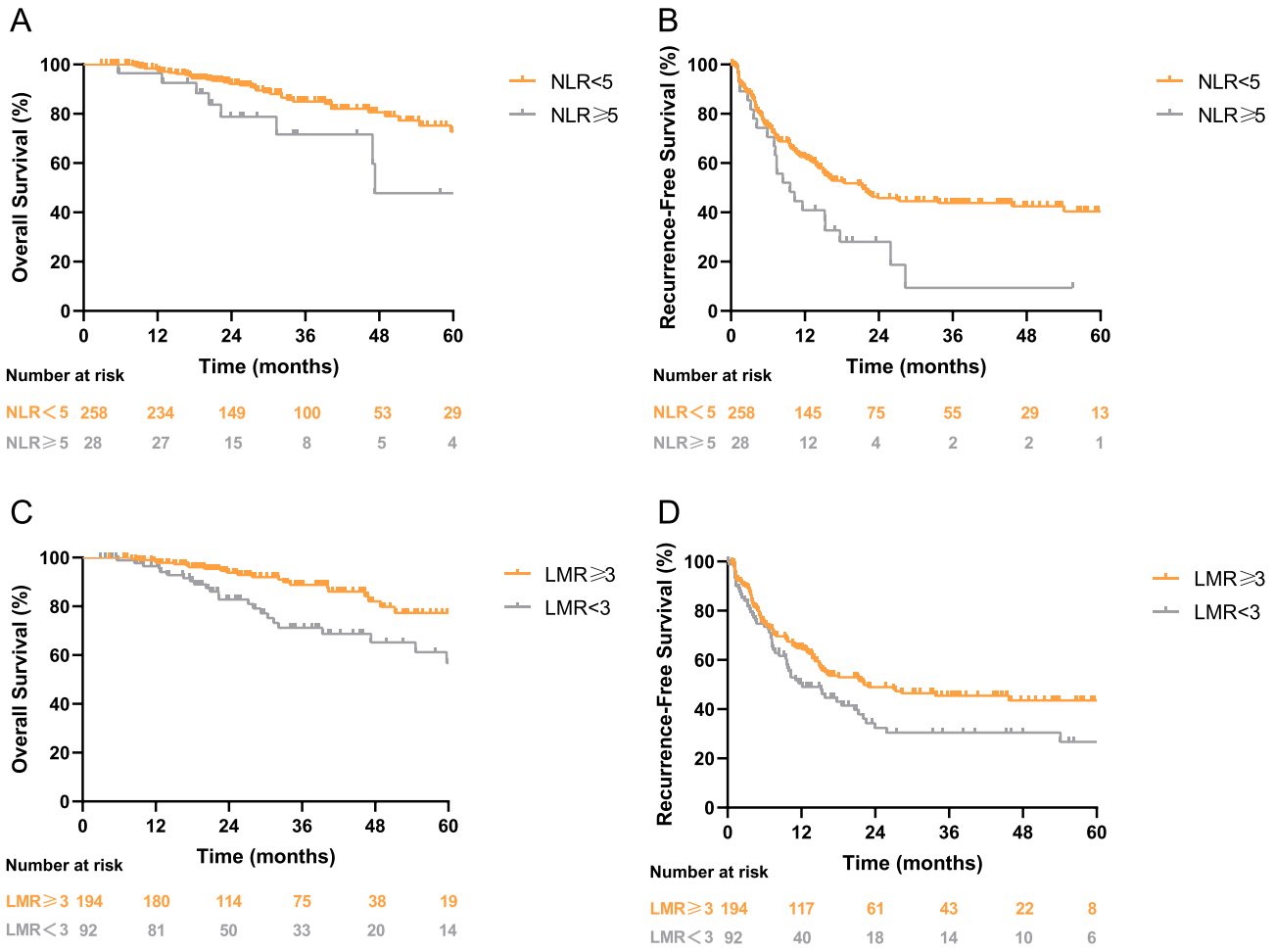

Figure 3 OS and RFS in the tumor response cohort (CR or PR) of patients with HCC receiving HAIC-based conversion hepatectomy were stratified based on NLR and LMR. (**A**) OS according to NLR (P=0.0131, HR=3.289 (1.284–8.424)); (**B**) RFS according to NLR (P=0.0104, HR=2.146 (1.197–3.849)); (**C**) OS according to LMR (P=0.0055, HR=2.276 (1.273–4.068)); (**D**) RFS according to LMR (P=0.0329, HR=1.470 (1.032–2.095)).

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Risk Factors Analysis

A univariate analysis was conducted to identify factors influencing OS and RFS, followed by a multivariate analysis to account for potential risk factors. The multivariate analysis identified the following independent risk factors for poor OS: limited tumor response (HR: 1.693; 95% CI: 1.080–2.653), poorer tumor differentiation (HR: 1.280; 95% CI: 1.020–1.606), presence of MVI (HR: 1.687; 95% CI: 1.056–2.696), high postoperative alpha-fetoprotein (AFP, HR: 2.372; 95% CI: 1.242–4.530), and elevated postoperative protein induced by vitamin K absence or antagonist-II levels (PIVKA-II, HR: 1.744; 95% CI: 1.103–2.756). Similarly, the multivariate analysis identified the following independent risk factors for RFS: age at diagnosis (HR: 1.249; 95% CI: 1.010–1.545), multiple tumors (HR: 1.567; 95% CI: 1.197–2.052), poorer differentiation (HR: 1.119; 95% CI: 1.051–1.367), presence of MVI (HR: 1.924; 95% CI: 1.393–2.656), pre-HAIC NLR (HR: 1.612; 95% CI: 1.012–2.567), high postoperative AFP (HR: 2.286; 95% CI: 1.522–3.436), elevated postoperative PIVKA-II (HR: 2.458; 95% CI: 1.825–3.311), and ECOG score (HR: 1.604; 95% CI: 1.170–2.199). The results are presented in Supplementary Table 1 and Supplementary Table 2.

AEs

AEs were assessed using the Common Terminology Criteria for Adverse Events (version 5.0). The incidence of AEs and their associations with NLR and LMR were analyzed across the whole cohort, as summarized in Table 3. Most AEs were mild to moderate in severity (grades 1 or 2) and did not disrupt the planned treatment regimen. No treatment-related deaths were reported following the initial treatment.

Discussion

Studies have demonstrated that approximately 50–70% of patients are unsuitable for radical hepatectomy at the time of initial diagnosis due to factors such as large tumor size, vascular invasion, and metastasis. Comprehensive treatment based on HAIC has recently made significant progress in HCC, resulting in prolonged patient survival. Some patients who responded well to the treatment underwent subsequent conversion liver resection, leading to long-term survival. Inflammatory factors, such as NLR and LMR, have recently been identified as the prognostic indicators in patients with malignancies. However, the prognostic value of these two indicators for patients with HCC undergoing HAIC-based conversion hepatectomy remains unclear. This study retrospectively analyzed the medical records of patients with HCC receiving HAIC-based liver resection and found that patients with NLR $\geq$ 5 and LMR < 3 exhibited poorer OS and RFS.

HAIC-based comprehensive therapy has recently made significant advancements in HCC treatment.[6–9] He et al demonstrated that the combination of HAIC and TKI significantly prolonged the survival in patients with portal vein invasion.[6] For patients with MVI, postoperative adjuvant HAIC can substantially reduce tumor recurrence and improve prognosis.[7] Specifically, for patients with large HCC, HAIC provides a higher ORR and a more favorable conversion rate compared to TACE.[8,9] Deng et al conducted a retrospective analysis of patients who received HAIC-based conversion hepatectomy, revealing that immune and inflammatory factors, such as NLR, serve as independent risk factors.[31] HAIC often triggers immune and inflammatory responses, resulting in strong anti-tumor immunity.[32]

Effective conversion therapy can enhance tumor remission, enabling many patients to undergo subsequent conversion liver resection and achieve long-term survival.[8] However, due to tumor heterogeneity and the presence of high recurrence risk factors before initial treatment, many patients still experience early postoperative recurrence, which results in a lack of survival benefits from conversion treatments and surgery.[4] Consequently, identifying effective predictive markers for conversion resection is crucial to improving the outcomes of these patients. This study analyzed NLR and LMR, two easily accessible indicators in clinical practice, and found that these markers have good predictive value for patients with HCC treated with HAIC-based conversion hepatectomy.

NLR and LMR, as indicators of tumor inflammation, have been proven to serve as reliable prognostic markers in various cancers.[14,33–35] Margetts et al demonstrated that patients with HCC and NLR > 3.15 exhibited unfavorable outcomes, suggesting that high NLR is a significant prognostic biomarker.[33] For unresectable HCC, high NLR is associated with poor tumor response and short progression-free survival (PFS) for patients treated with atezolizumab plus bevacizumab and drug-eluting bead transarterial chemoembolization.[26,35] In addition, Wu et al revealed that patients

Table 3 Adverse Events

	Whole Cohort (n=390)			NLR<5 (n=353)		NLR≥5 (n=37)			LMR<3 (n=123)		LMR≥3 (n=267)		
	Grade 1 to 2	Grade 3 to 4	Total	Grade 1 to 2	Grade 3 to 4	Grade 1 to 2	Grade 3 to 4	*P*-value	Grade 1 to 2	Grade 3 to 4	Grade 1 to 2	Grade 3 to 4	*P*-value
Hematologic toxicity													
White blood cell	53 (13.6%)	0 (0%)	53 (13.6%)	50 (14.2%)	0 (0%)	3 (8.1%)	0 (0%)	0.306	14 (11.4%)	0 (0%)	39 (14.6%)	0 (0%)	0.388
Neutrophils	47 (12.1%)	3 (0.8%)	50 (12.8%)	47 (13.3%)	3 (0.8%)	0 (0%)	0 (0%)	**0.028**	9 (7.3%)	0 (0%)	38 (14.2%)	3 (1.1%)	**0.027**
Lymphocytes	5 (1.3%)	1 (0.3%)	6 (1.5%)	5 (1.4%)	1 (0.3%)	0 (0%)	0 (0%)	0.548	3 (2.4%)	0 (0%)	2 (0.7%)	1 (0.4%)	0.591
Haemoglobin	36 (9.2%)	1 (0.3%)	37 (9.5%)	29 (8.2%)	1 (0.3%)	7 (18.9%)	0 (0%)	0.078	13 (10.6%)	0 (0%)	23 (8.6%)	1 (0.4%)	0.621
Platelets	44 (11.3%)	1 (0.3%)	45 (11.5%)	40 (11.3%)	1 (0.3%)	4 (10.8%)	0 (0%)	0.884	10 (8.1%)	1 (0.8%)	34 (12.7%)	0 (0%)	0.276
Nonhematologic toxicity													
Fever	21 (5.4%)	0 (0%)	21 (5.4%)	19 (5.4%)	0 (0%)	2 (5.4%)	0 (0%)	0.995	8 (6.5%)	0 (0%)	13 (4.9%)	0 (0%)	0.506
Malaise	58 (14.9%)	0 (0%)	58 (14.9%)	54 (15.3%)	0 (0%)	4 (10.8%)	0 (0%)	0.466	14 (11.4%)	0 (0%)	44 (16.5%)	0 (0%)	0.189
Dizziness	19 (4.9%)	0 (0%)	19 (4.9%)	17 (4.8%)	0 (0%)	2 (5.4%)	0 (0%)	0.874	6 (4.9%)	0 (0%)	13 (4.9%)	0 (0%)	0.997
Cough	3 (0.8%)	0 (0%)	3 (0.8%)	3 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0.741	1 (0.8%)	0 (0%)	2 (0.7%)	0 (0%)	0.680
Nausea	37 (9.5%)	0 (0%)	37 (9.5%)	34 (9.6%)	0 (0%)	3 (8.1%)	0 (0%)	0.995	10 (8.1%)	0 (0%)	27 (10.1%)	0 (0%)	0.535
Vomiting	41 (10.5%)	0 (0%)	41 (10.5%)	37 (10.5%)	0 (0%)	4 (10.8%)	0 (0%)	0.950	12 (9.8%)	0 (0%)	29 (10.9%)	0 (0%)	0.741
Constipation	7 (1.8%)	0 (0%)	7 (1.8%)	7 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0.495	3 (2.4%)	0 (0%)	4 (1.5%)	0 (0%)	0.810
Abdominal pain	128 (32.8%)	23 (5.9%)	151 (38.7%)	113 (32.0%)	21 (5.9%)	15 (40.5%)	2 (5.4%)	0.343	45 (36.6%)	10 (8.1%)	83 (31.1%)	13 (4.9%)	0.099
Abdominal distension	24 (6.2%)	0 (0%)	24 (6.2%)	19 (5.4%)	0 (0%)	5 (13.5%)	0 (0%)	0.110	8 (6.5%)	0 (0%)	16 (6.0%)	0 (0%)	0.845
Back pain	5 (1.3%)	0 (0%)	5 (1.3%)	5 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0.606	1 0.8%)	0 (0%)	4 (1.5%)	0 (0%)	0.941
Pruritus	7 (1.8%)	0 (0%)	7 (1.8%)	6 (1.7%)	0 (0%)	1 (2.7%)	0 (0%)	0.505	2 (1.6%)	0 (0%)	5 (1.9%)	0 (0%)	0.865
Gastrointestinal haemorrhage	5 (1.3%)	0 (0%)	5 (1.3%)	5 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0.606	1 (0.8%)	0 (0%)	4 (1.5%)	0 (0%)	0.941
Immune-related pneumonia	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0.905	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0.685
Hypothyroidism	2 (0.5%)	0 (0%)	2 (0.5%)	1 (0.3%)	0 (0%)	1 (2.7%)	0 (0%)	0.181	1 (0.8%)	0 (0%)	1 (0.4%)	0 (0%)	0.532
Hand-foot syndrome	3 (0.8%)	1 (0.3%)	4 (1.0%)	3 (0.8%)	1 (0.3%)	0 (0%)	0 (0%)	0.670	1 (0.8%)	0 (0%)	2 (0.7%)	1 (0.4%)	0.777
Rash	4 (1.0%)	0 (0%)	4 (1.0%)	4 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0.670	1 (0.8%)	0 (0%)	3 (1.1%)	0 (0%)	0.777
ALT	4 (1.0%)	2 (0.5%)	6 (1.5%)	4 (1.1%)	2 (0.6%)	0 (0%)	0 (0%)	0.548	1 (0.8%)	0 (0%)	3 (1.1%)	2 (0.7%)	0.728

(*Continued*)

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Table 3 (Continued).

	Whole Cohort (n=390)			NLR<5 (n=353)		NLR≥5 (n=37)			LMR<3 (n=123)		LMR≥3 (n=267)		
	Grade 1 to 2	**Grade 3 to 4**	**Total**	**Grade 1 to 2**	**Grade 3 to 4**	**Grade 1 to 2**	**Grade 3 to 4**	***P*-value**	**Grade 1 to 2**	**Grade 3 to 4**	**Grade 1 to 2**	**Grade 3 to 4**	***P*-value**
AST	1 (0.3%)	2 (0.5%)	3 (0.8%)	1 (0.3%)	2 (0.6%)	0 (0%)	0 (0%)	0.741	0 (0%)	0 (0%)	1 (0.4%)	2 (0.7%)	0.555
TBIL	2 (0.5%)	0 (0%)	2 (0.5%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0.819	2 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0.099
Hypoalbuminemia	26 (6.7%)	0 (0%)	26 (6.7%)	25 (7.1%)	0 (0%)	1 (2.7%)	0 (0%)	0.503	11 (8.9%)	0 (0%)	15 (5.6%)	0 (0%)	0.221
Creatinine	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0.905	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0.315

Note: Bold font indicates a *P*-value < 0.05.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

with NLR ≥ 5 exhibited inferior OS and PFS compared to those with an NLR < 5 in HCC.[14] These findings are consistent with the above-mentioned studies. Furthermore, a prognostic model incorporating NLR has demonstrated high efficacy in predicting outcomes for patients undergoing liver resection.[34] These studies collectively highlight NLR as an effective prognostic marker for resectable and unresectable patients with HCC. Conversely, high LMR is associated with a better prognosis for patients with malignancies.[36–39] For patients with malignant tumors undergoing chemotherapy or TKI therapies, those with high LMR before treatment exhibited better OS.[16] In patients with resectable tumors, LMR can predict the early recurrence rate of HCC following hepatectomy and the postoperative survival rate for patients with hilar cholangiocarcinoma (HCCA).[15,40] Moreover, high LMR correlated with an increase in $CD3^+$ T-cells within the HCCA,[15] indicating that high LMR is associated with the tumor immune microenvironment and may serve as a potential factor for predicting the efficacy of immunotherapy. Mei et al found that anti-PD-1 treatment improved OS in patients with HCC and high LMR.[41] Mano et al reported that LMR reflected the immune status in the tumor microenvironment and serves as an independent survival predictor in patients with HCC who were treated with liver transplantation.[17] Moreover, the prognostic model, combining LMR with another immune-inflammatory factor, such as NLR, demonstrated good predictive ability for OS in untreated patients with HCC.[42] This study used the threshold (LMR ≥ 3) as most of the aforementioned studies, achieving consistent results.

Systemic alterations in neutrophil, lymphocyte, and monocyte absolute counts, along with their ratio imbalances, serve as critical indicators of tumor immune microenvironment dysregulation in HCC. Neutrophils play a vital role in tumor resistance and immune evasion.[43–45] Research indicates that the recruitment of neutrophils and their reprogramming into immunosuppressive phenotypes are key mechanisms by which tumor-infiltrating neutrophils promote tumor progression.[46] Elevated peripheral neutrophil counts correlate with advanced disease and poor prognosis, driven by expansion of pro-tumorigenic neutrophil subsets that enhance extracellular matrix degradation via MMP-9 secretion and facilitate metastatic spread through NET formation.[47] Suppressing the activation of tumor-infiltrating neutrophils can enhance T cells' immune activity and improve the effectiveness of immune checkpoint blockade.[44,45] Conversely, lymphopenia (particularly $CD8^+$ T/NK cell depletion) reflects antitumor immune exhaustion, linked to Treg-mediated immunosuppression through upregulated CTLA-4/PD-1 expression and IL-10/TGF-β secretion.[48,49] The body activates peripheral or paratumoral T cells to infiltrate the tumor tissues, exerting cytotoxic effects and achieving significant anti-tumor immunity.[50] Existing studies have confirmed that following HAIC treatment, the infiltration of $CD8^+$ T cells in HCC tissue significantly increases, with a high level of $CD8^+$ T cells exhibiting better anti-tumor efficacy than that of a low $CD8^+$ T cell count.[32,51] The key drug in FOLFOX-HAIC), oxaliplatin, induced pyroptosis in hepatoma cells by activating caspase-3-mediated cleavage of GSDME, which enhanced the cytotoxicity of $CD8^+$ T cells by regulating the p38/MAPK signaling pathway.[32] Monocytes are associated with M2-polarized TAMs, which promote angiogenesis/fibrosis via VEGF/PDGF release and impair T-cell mitochondrial function through arginase-1-mediated L-arginine depletion.[52,53] Notably, NLR and LMR fluctuations not only predict HCC outcomes but directly mirror tumor-induced systemic immune reprogramming. NLR and LMR, two inflammatory indicators, encompass counts of neutrophils and lymphocytes. A high NLR indicates an increase in the number of neutrophils or/and a decrease in lymphocyte counts, indicating more pronounced immunosuppression and potentially worse prognosis. Conversely, a high LMR indicates an increase in lymphocyte counts and is associated with a stronger anti-tumor immune response and a potentially better prognosis. This study revealed that NLR and LMR can stratify the survival outcome of patients undergoing HAIC-based conversion hepatectomy, consistent with previous research findings.

The anti-tumor immunity and local inflammation induced by comprehensive treatment may also be associated with certain side effects. In this study, for example, the incidence of hypoproteinemia following conversion therapy was higher in the low NLR and high LMR groups. Prolongation prothrombin time (PT) was observed in the high LMR group. For patients with good therapeutic response, it is essential to periodically monitor vital organs, including liver and cardiopulmonary function, during the treatment process. In adverse reactions, timely intervention should be implemented to prevent more serious complications. Notably, in this study, following conversion treatment, the decrease in neutrophil count was more pronounced in the group with a better prognosis (LMR ≥ 3) compared to the group with a worse prognosis (LMR < 3), with a statistically significant difference. This result suggests that neutrophils and lymphocytes may engage in a competitive relationship, potentially influencing subsequent anti-tumor immune responses.

This study has some limitations. First, as a retrospective study, it is subject to inherent bias, highlighting the need for future multicenter prospective randomized controlled trials to validate these findings. Second, regarding the threshold value determination for NLR and LMR, while NLR ≥ 5 and LMR ≥ 3 have demonstrated promising results in our study and others, various thresholds are used in different studies. The optimal thresholds need further investigation. Third, this study's comprehensive treatment based on HAIC includes various TKIs, bevacizumab, and PD-1 inhibitors. The differential impact of these regimens on immunity and inflammatory factors is still unclear and warrants further in-depth exploration research.

Conclusions

NLR and LMR are easily accessible in clinical practice and have been demonstrated to effectively predict survival outcomes in patients with HCC who underwent HAIC-based conversion resection. These markers are essential in customizing personalized postoperative adjuvant therapy and determining the appropriate follow-up duration for these patients.

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 (Prof. Di Tang).

Ethical Approval and Consent to Participate

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. This research was approved by the institutional review board of Sun Yat-sen University Cancer Center (No. B202031801). The study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment.

Consent for Publication

All authors have reviewed the final version of the manuscript and are in agreement its content and submission.

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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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