

Preoperative lymphocyte-to-C-reactive protein ratio predicts hepatocellular carcinoma recurrence after surgery

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Purpose: This study was performed to determine the prognostic value of lymphocyte-to-CRP ratio after curative resection for hepatocellular carcinoma.

Methods: Between July 2010 and October 2021, 173 consecutive patients (144 male, 29 female) who underwent surgical resection for pathologically confirmed hepatocellular carcinoma were included in this retrospective study. Cox regression analysis was used to evaluate the relationship between clinicopathological characteristics and recurrence-free survival (RFS) and overall survival (OS). A P-value of <0.05 was considered statistically significant.

Results: The patients (mean age, 71 years) were stratified into high ($\geq 9,500$, $n = 108$) and low ($< 9,500$, $n = 65$) lymphocyte-to-CRP ratio groups. The low lymphocyte-to-CRP ratio group had significantly worse RFS and OS. Low lymphocyte-to-CRP ratio [hazard ratio (HR), 1.865; 95% confidence interval (CI), 1.176–2.960; $P = 0.008$], multiple tumors (HR, 3.333; 95% CI, 2.042–5.343; $P < 0.001$), and microvascular invasion (HR, 1.934; 95% CI, 1.178–3.184; $P = 0.009$) were independently associated with RFS, whereas low albumin-to-globulin ratio (HR, 2.270; 95% CI, 1.074–4.868; $P = 0.032$), α -FP of ≥ 25 ng/mL (HR, 2.187; 95% CI, 1.115–4.259; $P = 0.023$), and poor tumor differentiation (HR, 2.781; 95% CI, 1.041–6.692; $P = 0.042$) were independently associated with OS. Lymphocyte-to-CRP ratio had a higher area under the curve (0.635) than other inflammation-based markers (0.51–0.63).

Conclusion: Lymphocyte-to-CRP ratio is superior to other inflammation-based markers as a predictor of RFS in patients with surgically resected hepatocellular carcinoma.

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Key Words: Biomarkers, Hepatocellular carcinoma, Prognosis, Regression analysis, Survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 6th most common cancer, with increasing incidence, and the third leading cause of cancer-related death worldwide [1]. Curative resection is the optimal treatment for patients with well-preserved liver function [2]. However, most patients fail to undergo curative resection, owing to the clinical characteristics of HCC (local invasion, distant metastasis, and the absence of symptoms

in the early stages) [3,4]. Despite improved diagnosis and treatment, prognosis remains poor. Therefore, more attention should be paid to the investigation of prognostic factors [5].

The presence of a systemic inflammatory response is associated with poor survival in various malignancies [6,7]. Albumin-to-globulin ratio (AGR) has previously been identified as an independent prognostic factor for overall survival (OS) in patients with HCC [8]. Additional prognostic markers include CRP-to-albumin ratio (CAR) [9], neutrophil-to-lymphocyte

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ratio (NLR) [10], prognostic nutritional index (PNI) [11], and platelet-to-lymphocyte ratio (PLR) [12]. Despite evidence that these markers predict prognosis, optimal predictors of HCC recurrence remain unclear.

Lymphocyte-to-CRP ratio (LCR) is a novel prognostic biomarker in colorectal cancer that has proved useful for perioperative management and postoperative follow-up [13,14]. LCR has also been shown to be an independent prognostic marker in patients with surgically resected HCC [15-17]. However, data on its ability to predict recurrence are lacking. Therefore, we explored the clinical significance of LCR as a prognostic marker, especially for recurrence, in patients with surgically resected HCC.

METHODS

Patients

Between July 2010 and October 2021, 173 consecutive patients who underwent surgical resection for pathologically confirmed HCC at our institution were analyzed. All data were blinded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design was approved by the Ethical Review Board of the National Hospital Organization Fukuyama Medical Center (No. R2-34). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Data collection

The following clinicopathological characteristics were obtained from medical records: demographic data (sex, age at surgery, and body mass index), laboratory data (CRP, lymphocyte count, neutrophil count, platelet count, total bilirubin, ALT, γ -GT, albumin, globulin, total protein, α -FP, and HBV/HCV status), LCR, AGR, CAR, PLR, NLR, PNI, comorbidities (hypertension, diabetes mellitus, cardiac disease, and stroke), operative data (type of resection, blood loss, surgical duration, and blood transfusion), and tumor characteristics, including stage (American Joint Committee on Cancer/Union for International Cancer Control, 8th ed) [18], number, size, microvascular invasion, and differentiation. Liver function was assessed using the Child-Pugh classification. LCR was calculated as lymphocyte count (number/mL) / CRP (mg/dL) [17]. AGR was calculated as albumin / (total protein – albumin). CAR was calculated as the ratio of CRP to albumin [19]. NLR and PLR were calculated as the neutrophil and platelet counts divided by the lymphocyte count, respectively [20,21]. PNI was calculated as $10 \times \text{albumin (g/dL)} + 0.05 \times \text{total lymphocyte count (/mm}^3\text{)}$ [22]. Postoperative complications were defined as complications of

Clavien-Dindo grade of \geq III [23].

Follow-up

All patients were followed up until October 2021. Postoperative follow-up included laboratory and imaging studies every 3–6 months for \geq 5 years. Recurrence-free survival (RFS) and OS were defined as the time from the date of surgery to the date of recurrence or the date of death or last follow-up, respectively.

Statistical analyses

Data are presented as mean \pm standard deviation. Univariate analysis was performed using the chi-square test and Mann-Whitney U-test. Diagnostic accuracy was evaluated using the area under the receiver operating characteristic curve (AUC). The optimal cutoff value of each inflammation-based marker was determined by maximizing the Youden index (sensitivity + specificity – 1) [24]. RFS and OS curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Prognostic factors for RFS and OS were determined using Cox regression. Variables that were significant in the univariate analysis were entered into the multivariate analysis. All statistical analyses were conducted using JMP ver. 11 (SAS Institute, Cary, NC, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The patients' baseline characteristics are shown in Table 1. The study population comprised 144 male and 29 female patients (mean age, 71 years). Sixty-six patients had HBV; 60, HCV; 21, neither HBV nor HCV; 20, alcoholic hepatitis; 5, non-alcoholic fatty liver disease; and 1, autoimmune hepatitis. Most patients (95.9%) were Child-Pugh class A. The mean tumor diameter was 4.1 ± 3.3 cm. Multiple tumors were found in 37 patients. The mean operative time was 402.2 ± 143.1 minutes (mean blood loss, 912.7 ± 139.5 mL). Forty-seven patients required blood transfusion. Partial hepatectomy was performed in 8 patients, subsegmentectomy in 84, sectionectomy in 51, hemihepatectomy in 28, and trisectionectomy in 2. Tumors were well-differentiated in 46 patients, moderately differentiated in 102, poorly differentiated in 14, and unknown in 46. Twenty-nine patients had postoperative complications of Clavien-Dindo grade \geq IIIa. The mean postoperative hospital stay was 15.9 days.

Receiver operating characteristic curve analysis

The cutoff value of LCR was 9,500 (sensitivity, 62.5%; specificity, 69.2%; AUC, 0.643) (Fig. 1). Based on the cutoff value, patients were stratified into high (\geq 9,500, n = 108) and low

Table 1. Patient demographic and clinical characteristics

Characteristic	Data
No. of patients	173
Age (yr)	71.0 ± 9.8 (36–89)
Sex, male:female	144:29
Body mass index (kg/m ²)	23.1 ± 3.5 (15.6–40.9)
Etiology	
HBV	66 (38.2)
HCV	60 (34.7)
Non-HBV/HCV	21 (12.1)
Alcoholic hepatitis	20 (11.6)
NASH	5 (2.9)
Autoimmune hepatitis	1 (0.6)
Preoperative laboratory data	
CRP (mg/dL)	0.38 ± 1.08 (0.01–11.90)
Lymphocytes (×10 ³ /mm ³)	1.47 ± 0.55 (0.37–53.31)
Platelet count (×10 ⁴ /mm ³)	16.93 ± 6.31 (6.30–46.70)
Serum albumin (g/dL)	4.09 ± 5.01 (2.6–5.2)
Total bilirubin (mg/dL)	– (0.30–3.50)
ALT (U/L)	31.8 ± 24.8 (6–156)
γ-GT (U/L)	83.9 ± 106.6 (8–764)
α-FP (ng/mL)	863 ± 3,188 (0.97–26,748)
LCR	31,372 ± 44,770 (84–279,300)
AGR	1.33 ± 0.32 (0.54–2.33)
CAR	0.11 ± 0.37 (0.002–4.407)
NLR	2.67 ± 1.89 (0.12–16.60)
PLR	0.130 ± 0.069 (0.036–0.504)
PNI	48.24 ± 5.75 (29.05–61.33)
Child-Pugh score, 5/6/7/8	153/13/5/2–
Comorbidities	145 (83.8)
Type of liver resection	
Partial hepatectomy	8 (4.6)
Subsegmentectomy	84 (48.6)
Sectionectomy	51 (29.5)
Hemihepatectomy	28 (16.2)
Trisectionectomy	2 (1.2)
Surgical duration (min)	402.2 ± 143.1 (152–958)
Blood loss (mL)	912.7 ± 1,39.5 (0.0–13,000.0)
Blood transfusion	47 (27.2)
Stage ^{a)}	
IA/IB/II/IIIA/IIIB	37/50/69/5/12
Tumor size (cm)	4.1 ± 3.3 (0.5–18.0)
No. of tumor	
1/2/3/4/5/10	136/25/9/1/1/1
Microvascular invasion	69 (39.9)
Tumor differentiation	
Well	46 (26.6)
Moderate	102 (60.0)
Poor	14 (8.1)
Unknown	11 (6.3)

(<9,500, n = 65) LCR groups. The AUC values for the other inflammation-based markers were as follows: AGR, 0.631; CAR, 0.632; NLR, 0.590; PLR, 0.506; and PNI, 0.611.

Table 1. Continued

Characteristic	Data
Mortality	0 (0)
Postoperative hospital stay (day)	15.9 ± 10.8 (4–78)
Postoperative complications ^{b)}	29 (16.8)

Values are presented as number only, mean ± standard deviation (range), or number (%).

NASH, non-alcoholic fatty liver disease; AGR, albumin-to-globulin ratio; AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; CAR, CRP-to-albumin ratio; LCR, lymphocyte-to-CRP ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

^{a)}According to AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control), 8th ed. ^{b)}Clavien-Dindo grade of ≥IIIa.

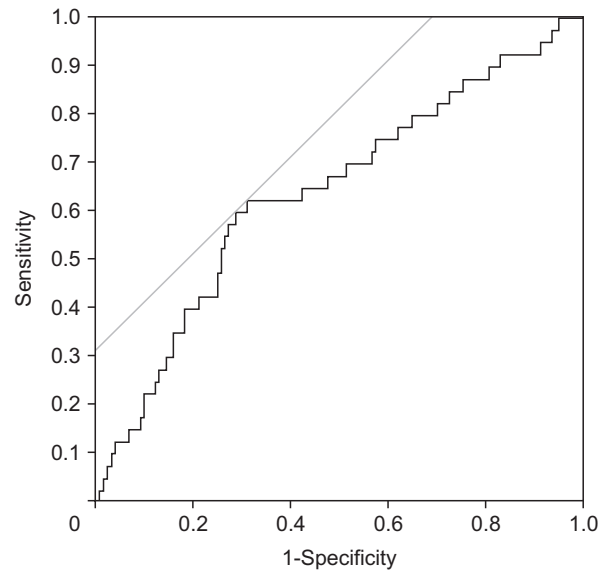


Fig. 1. Receiver operating characteristic curve determining the optimal cutoff value of the lymphocyte-to-CRP for predicting recurrence-free survival after surgery in patients with hepatocellular carcinoma.

Association between clinicopathological characteristics and lymphocyte-to-CRP ratio

The association between clinicopathological characteristics and LCR is shown in Table 2. Compared with the high LCR group, the low LCR group had significantly higher serum ALT and γ-GT levels, more microvascular invasion, and a larger tumor size.

Univariate and multivariate analysis of survival

The median RFS and OS were 24.5 months (range, 1.0–122.4 months) and 124.9 months (range, 1.0–130.6 months), respectively. The 1-, 3-, and 5-year RFS and OS rates were 73.6%, 50.1%, and 40.3% and 90.8%, 80.5%, and 68.2%, respectively.

Table 2. Clinicopathological characteristics according to the LCR

Characteristic	High LCR ($\geq 9,500$) group (n = 108)	Low LCR ($< 9,500$) group (n = 65)	P-value
Age, ≥ 75 yr	47 (43.5)	25 (38.5)	0.513
Male sex	89 (82.4)	55 (84.6)	0.705
Body mass index, ≥ 22 kg/m ²	70 (64.8)	36 (55.4)	0.219
Etiology, HBV	48 (44.4)	14 (21.5)	0.107
Preoperative laboratory data			
Total bilirubin, ≥ 1.2 mg/dL	25 (23.1)	14 (21.5)	0.806
ALT, ≥ 40 U/L	15 (13.9)	25 (38.5)	$< 0.001^{***}$
γ -GT, ≥ 65 U/L	21 (19.4)	39 (60.0)	$< 0.001^{***}$
α -FP, ≥ 25 ng/mL	29 (26.9)	22 (33.8)	0.331
Child-Pugh class A	106 (98.1)	60 (92.3)	0.064
Comorbidities	90 (83.3)	55 (84.6)	0.824
Surgical duration, ≥ 360 min	65 (60.2)	33 (50.8)	0.226
Blood loss, ≥ 300 mL	72 (66.7)	48 (73.8)	0.318
Blood transfusion	29 (26.9)	18 (27.7)	0.904
Tumor size, ≥ 3.5 cm	30 (27.8)	41 (63.8)	$< 0.001^{***}$
Tumor number, solitary	88 (81.5)	48 (73.8)	0.239
Microvascular invasion	36 (33.3)	33 (50.8)	0.024*
Tumor differentiation, poor	6 (5.6)	8 (12.3)	0.122
Postoperative complications ^{a)}	17 (15.7)	12 (18.5)	0.644

Values are presented as number (%).

LCR, lymphocyte-to-CRP.

^{a)}Clavien-Dindo grade of \geq IIIa.

*P < 0.05, ***P < 0.001.

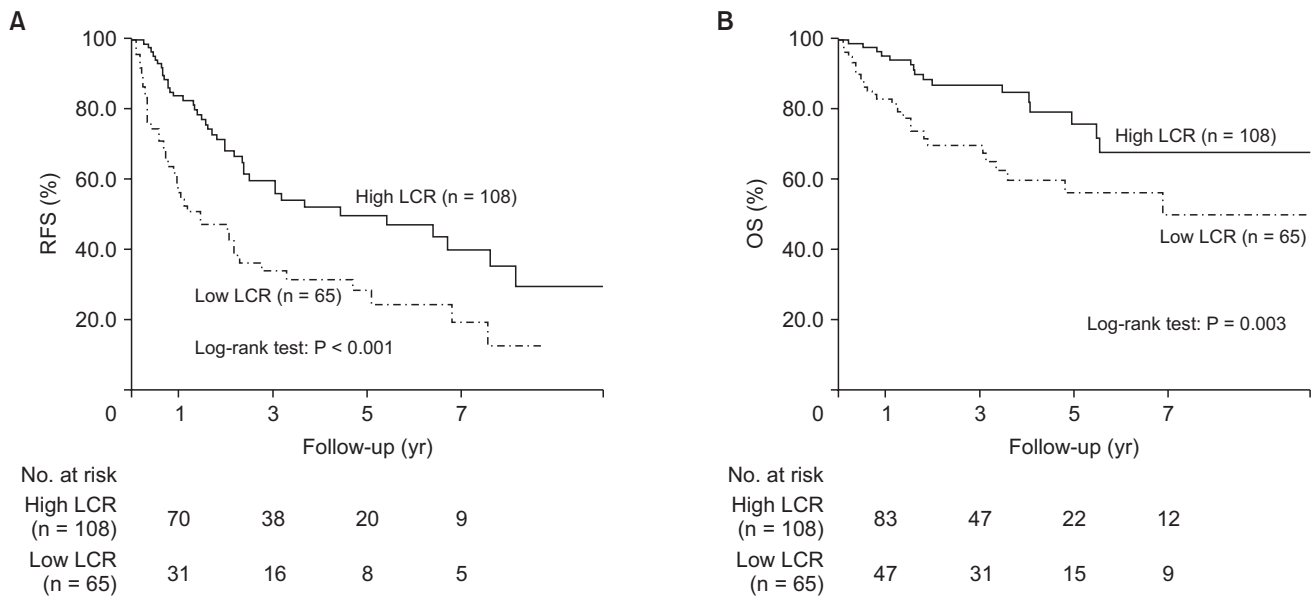


Fig. 2. Kaplan-Meier curves of (A) recurrence-free survival (RFS) and (B) overall survival (OS) in the high and low lymphocyte-to-CRP ratio (LCR) groups. The high ($\geq 9,500$) and low ($< 9,500$) LCR groups are represented by solid and dashed lines, respectively.

Patients in the high LCR group had longer RFS and OS than those in the low LCR group (Fig. 2). Tables 3 and 4 show the relationships between clinicopathological characteristics and RFS and OS after surgery. In univariate analysis, low LCR, ALT of ≥ 40 U/L, tumor size of ≥ 3.5 cm, multiple tumors, and

microvascular invasion were significantly associated with poor RFS, whereas low LCR, low AGR, α -FP of ≥ 25 ng/mL, tumor size of ≥ 3.5 cm, microvascular invasion, and poor tumor differentiation were significantly associated with poor OS. In multivariate analysis, low LCR (hazard ratio [HR], 1.865;

Table 3. Univariate and multivariate analyses of clinicopathological factors affecting recurrence-free survival

Characteristic	Univariate analysis		Multivariate analysis	
	Number	P-value	HR (95% CI)	P-value
Age (yr)		0.203		-
≥75	72		-	
<75	101		-	
Sex		0.069		-
Male	144		-	
Female	29		-	
Body mass index (kg/m ²)		0.239		-
≥22	106		-	
<22	67		-	
Etiology		0.250		-
HBV	66		-	
Others	107		-	
LCR		<0.001***		0.008**
≥9,500	108		1.865 (1.176–2.960)	
<9,500	65			
AGR		0.101		-
≥1.16	122		-	
<1.16	51		-	
Total bilirubin (mg/dL)		0.681		-
≥1.2	39		-	
<1.2	134		-	
ALT (U/L)		0.014*		0.499
≥40	40		1.194 (0.707–1.969)	
<40	133			
γ-GT (U/L)		0.157		-
≥65	60		-	
<65	113		-	
α-FP (ng/mL)				
≥25	51	0.051	-	-
<25	122		-	
Comorbidities		0.623		-
Absent	28		-	
Present	145		-	
Surgical duration (min)		0.080		-
≥360	98		-	
<360	75		-	
Blood loss (mL)		0.336		-
≥300	120		-	
<300	53		-	
Blood transfusion		0.648		-
Absent	47		-	
Present	126		-	
Tumor size (cm)		0.002**		0.597
≥3.5	71		1.150 (0.685–1.930)	
<3.5	102			
Tumor number		<0.001*		<0.001***
Solitary	136		3.333 (2.042–5.343)	
Multiple	37			
Microvascular invasion		<0.001*		0.009*
Absent	104		1.934 (1.178–3.184)	
Present	69			
Tumor differentiation		0.168		-
Poor	14		-	
Others	159		-	

Table 3. Continued

Characteristic	Univariate analysis		Multivariate analysis	
	Number	P-value	HR (95% CI)	P-value
Postoperative complications ^{a)}				
Absent	144	0.836	-	-
Present	29		-	

HR, hazard ratio; CI, confidence interval; LCR, lymphocyte-to-C-reactive protein ratio; AGR, albumin-to-globulin ratio.

^{a)}Clavien-Dindo grade of \geq IIIa.

*P < 0.05, **P < 0.01, ***P < 0.001.

Table 4. Univariate and multivariate analyses of clinicopathological factors affecting overall survival

Characteristic	Univariate analysis		Multivariate analysis	
	Number	P-value	HR (95% CI)	P-value
Age (yr)		0.710		
≥75	72		-	-
<75	102		-	
Sex		0.340		-
Male	144		-	-
Female	29		-	
Body mass index (kg/m ²)		0.104		
≥22	106		-	-
<22	67		-	
Etiology		0.580		
HBV	66		-	-
Others	107		-	
LCR		0.003**	1.45 (0.691–3.087)	0.325
≥9,500	108			
<9,500	65			
AGR		0.001**	2.27 (1.074–4.868)	0.032*
≥1.16	51			
<1.16	122			
Total bilirubin (mg/dL)		0.549		
≥1.2	39		-	-
<1.2	144		-	
ALT (U/L)		0.080		
≥40	40		-	-
<40	133		-	
γ-GT (U/L)		0.217		
≥65	60		-	-
<65	113		-	
α-FP (ng/mL)				
≥25	51	0.001**	2.187 (1.115–4.259)	0.023*
<25	122			
Child-Pugh class		0.115		
A	166		-	-
B	7		-	
Comorbidities				
Absent	28	0.701	-	-
Present	145		-	
Surgical duration (min)				
≥360	98	0.436	-	-
<360	75		-	
Blood loss (mL)		0.095		
≥300	120		-	-
<300	53		-	

Table 4. Continued

Characteristic	Univariate analysis		Multivariate analysis	
	Number	P-value	HR (95% CI)	P-value
Blood transfusion		0.110		
Absent	126		-	-
Present	47		-	-
Tumor size (cm)		0.003**		0.482
≥3.5	71		1.317 (0.612–2.870)	
<3.5	102			
Tumor number		0.097		
Solitary	136		-	-
Multiple	37		-	-
Microvascular invasion		0.026*		0.189
Absent	104		1.608 (0.789–3.302)	
Present	69			
Tumor differentiation		0.003**		0.042*
Poor	14		2.781 (1.041–6.692)	
Others	159			
Postoperative complications ^{a)}				
Absent	144	0.063	-	-
Present	29		-	-

HR, hazard ratio; CI, confidence interval; LCR, lymphocyte-to-C-reactive protein ratio; AGR, albumin-to-globulin ratio.

^{a)}Clavien-Dindo grade of ≥IIIa.

*P < 0.05, **P < 0.01.

95% confidence interval [CI], 1.176–2.960; P = 0.008), multiple tumors (HR, 3.333; 95% CI, 2.042–5.343; P < 0.001), and microvascular invasion (HR, 1.934; 95% CI, 1.178–3.184; P = 0.009) were independent predictors of RFS, whereas low AGR (HR, 2.270; 95% CI, 1.074–4.868; P = 0.032), α -FP \geq 25 ng/mL (HR, 2.187; 95% CI, 1.115–4.259; P = 0.023), and poor tumor differentiation (HR, 2.781; 95% CI, 1.041–6.692; P = 0.042) were independent predictors of OS.

DISCUSSION

This study explored the prognostic value of LCR in patients with surgically resected HCC. We showed that low LCR was an independent risk factor for recurrence and that the AUC was higher for LCR than for other inflammation-based markers, suggesting that LCR was a superior predictor of RFS.

LCR has been shown to predict recurrence, prognosis, and postoperative morbidity in various malignancies [18,25]. It has also been shown to be superior to other inflammation-based markers for predicting the prognosis of patients with surgically resected HCC [14-16]. However, in the aforementioned studies, the AUC analysis of LCR showed poor prognostic performance, and AGR was not considered as a potential prognostic marker. AGR was previously reported to be an independent predictor of OS, but not RFS, in patients with surgically resected HCC [8]. In this study, LCR, which was not investigated previously, was found to be an independent predictor of RFS. To our knowledge, this is the first study to report the effectiveness of

LCR in predicting HCC recurrence in an analysis including AGR.

The mechanism underlying the association between LCR and surgical outcomes in patients with HCC has not been fully elucidated. Tumor growth and metastasis result from interactions between tumor cells and the tumor immune microenvironment (TIME) [26]. Tumor-infiltrating lymphocytes are indicators of the cytotoxic immune response [27]. Lymphopenia is associated with poor host immunological competence in malignant disease and predicts oncologic outcomes [28]. Iseda et al. [15] showed that patients with high LCR had fewer vessels encapsulating tumor clusters and higher intratumoral CD8⁺ T-cell counts than those with low LCR, suggesting that LCR is associated with TIME status. Conversely, serum CRP reflects a systemic inflammatory response. High CRP is associated with early recurrence and poor survival after liver resection [29]. High CRP is also associated with reduced infiltration of CD4⁺ tumor-infiltrating lymphocytes, which correlates with cancer-specific survival [30]. Therefore, LCR may reflect the antitumor cytotoxicity of the intratumoral immune response in the TIME and affect tumor progression and survival after recurrence. This evidence supports our main finding that low LCR status is an independent prognostic factor for RFS but not OS.

We revealed significant associations between low LCR and impaired liver function and tumor progression. Low LCR was significantly associated with high ALT and γ -GT levels. Child-Pugh scores in the low LCR group were higher than those in the high LCR group, although not significant. These findings

may reflect liver inflammation and poor liver function. Low LCR was also significantly associated with larger tumor size and more microvascular invasion than high LCR, suggesting that low LCR is associated with a more aggressive and invasive phenotype than high LCR. LCR reflects the inflammatory and immune status and may be a more sensitive indicator of recurrence. Thus, LCR may better reflect the intrinsic malignant properties of tumor cells.

In multivariate analysis, LCR did not remain an independent predictor of OS in patients with surgically resected HCC. We showed that low AGR (which may reflect nutritional status), α -FP of ≥ 25 ng/mL, and poor tumor differentiation were independent predictors of OS, as previously reported [8]. Nutritional status and the malignant properties of tumor cells may affect OS more sensitively than RFS.

We consider that LCR, which is accessible, objective, and noninvasive, may be a preferable prognostic factor. It has the potential to assist treatment stratification and guide the management of patients with surgically resected HCC.

There are some limitations to this study. First, it was a small retrospective study at a single institution. Second, our cohort included patients treated with postoperative ablation, endovascular treatment, and molecularly-targeted drugs, which may have influenced the prognosis of these patients. Finally, the AUC value of LCR was not high enough to predict prognosis. Larger multicenter prospective studies are needed to confirm our findings.

In conclusion, preoperative LCR is an independent predictor of RFS in patients with surgically resected HCC. It is superior to other inflammation-based prognostic markers, including AGR. LCR-based risk stratification can be performed before surgery using a standard blood sample for perioperative management.

Therefore, LCR could benefit treatment decision-making.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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