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Preoperative Ratio of Neutrophils to Lymphocytes Predicts Postresection Survival in Selected Patients With Early or Intermediate Stage Hepatocellular Carcinoma

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Abstract: This study aims to clarify the prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR) for patients with hepatocellular carcinoma (HCC) after potentially curative hepatic resection (HR). The prognostic value of the NLR for HCC patients has not been definitely reviewed by large studies, especially for those with different Barcelona Clinic Liver Cancer (BCLC) stages.

A consecutive sample of 963 HCC patients who underwent potentially curative HR was classified as having low or high NLR using a cut-off value of 2.81. Overall survival (OS) and tumor recurrence were compared for patients with low or high NLR across the total population, as well as in subgroups of patients in BCLC stages 0/A, B, or C. Clinicopathological parameters, including NLR, were evaluated to identify risk factors of OS and tumor recurrence after potentially curative hepatic resection. Multivariate analyses were performed using the Cox proportional hazards model or subdistribution hazard regression model.

Multivariate analyses showed that NLR (>2.81), tumor number (>3), incomplete capsule, serum albumin (≤35 g/L), alanine transaminase activity (>40 U/L), and macrovascular invasion were risk factors for low OS, whereas NLR (>2.81), tumor size (>5 cm), alpha fetal protein concentration (>400 ng/L), and macrovascular invasion were risk factors for low tumor recurrence. NLR > 2.81 was significantly associated with poor OS and tumor recurrence in the total patient population (both $P < 0.001$), as well as in the subgroups of patients in BCLC stages 0/A or B (all $P < 0.05$). Moreover, those with high NLR were associated with low OS ($P = 0.027$), and also with slightly higher tumor recurrence than those with low NLR for the subgroups in BCLC stage B ($P = 0.058$). Neither association, however, was observed among patients with BCLC stage C disease.

NLR may be an independent predictor of low OS and tumor recurrence after potentially curative HR in HCC patients in BCLC stages 0/A or B.

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Abbreviations: AFP = alpha-fetoprotein, ALB = serum albumin, ALT = alanine transaminase, BCLC = Barcelona Liver Cancer, HbsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hepatic resection, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, RFS = recurrence-free survival.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, and China accounts for ~50% of HCC cases and HCC-related deaths worldwide.[1] Various treatments against HCC are commonly used and their efficacy has improved in recent decades; among them, hepatic resection (HR) is the most frequently used treatment in Asia for patients with resectable cancer,[2] which the Barcelona Liver Cancer (BCLC) staging system defines as stage 0/A disease.[3,4] In fact, HR is often used to treat patients in later stages of HCC, especially in Asia, and work from our research group and others argues strongly that the surgery technique can be safe and effective for patients in BCLC stages B or C.[5–8] Nevertheless, the prognosis of patients with HCC after HR remains unsatisfactory: disease recurs in up to 74% of patients with intermediate or advanced HCC within 5 years of surgery,[8] and patients with advanced disease show hospital mortality up to 2.3% and overall morbidity up to 31.3%.[6] This highlights the need to identify risk factors of poor prognosis and HCC recurrence after HR in patients at any BCLC stage of disease, in order to inform cancer treatment and management.

Several studies have established a significant correlation between systemic inflammation and poor survival in lung cancer, breast cancer, soft-tissue sarcoma, and renal cell carcinoma.[9–12] The mechanisms underlying this correlation remain unclear. It has been suggested that cytokines and inflammatory mediators are upregulated in the inflammatory state, leading to repair of DNA damage, inhibition of apoptosis, and promotion of angiogenesis, all of which facilitate the proliferation and metastasis of malignant cells.[13,14] The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation that has been linked to poor survival of HCC patients after liver transplantation, transarterial chemoembolization, radiofrequency ablation, treatment with sorafenib,[15–18] and HR.[19–21] On the other hand, 1 study failed to find an

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association of NLR with poor overall survival (OS) or recurrence-free survival (RFS) after liver transplantation,[22] another study found no association of NLR with OS or RFS of HCC patients after curative HR in BCLC stage 0/A,[23] and a third study recommended against using NLR to guide HCC treatment decisions.[24]

The present study aimed to help resolve the lack of consensus on whether NLR is a risk factor of low OS and/or high tumor recurrence in HCC patients after potentially curative HR in a relatively large sample size. We used subgroup analysis to examine these possible relationships separately in patients in BCLC stages 0/A, B, or C. The patients in this study were treated at a single large medical center in Guangxi Province (China), which has the highest incidence of HCC in the world.[25–27]

METHODS

Ethics Statements

This retrospectively study was approved by the Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University; it was performed according to the Declaration of Helsinki 2013 edition. Written informed consent was obtained from patients, and patient records or information was anonymized before analysis.

Patients

This retrospective study examined a consecutive sample of HCC patients who underwent potentially curative HR at the Affiliated Tumor Hospital of Guangxi Medical University between January 2004 and December 2011. Clinicopathological baseline data and outcomes had been prospectively collected in the hospital's central database. Patients were included in the study if they (1) had primary HCC with no prior treatment, such as transarterial chemoembolization, radiofrequency ablation, or percutaneous ethanol injection; and (2) had preserved liver function (Child Pugh class A or B). Patients were excluded if their medical records were insufficient or if the records showed evidence of immunodeficiency, hematological disease, or bacterial infection.

Definitions

Potentially curative HR for HCC was defined as complete surgical removal of macroscopic tumor tissues. Incomplete capsule was defined as incomplete or absent of tumor capsule. Macrovascular invasion was defined as the presence of invasion in 1 or more of the following vessels, based on imaging and histology: main portal vein and its right/left branches, hepatic vein and its branches, superior mesenteric vein, or inferior vena cava. Tumor recurrence was defined based on histopathology or, in the absence of such evidence, on HCC diagnostic criteria used by the European Association for the Study of the Liver.[8] HCC was staged according to the most recent reviews by the main authors of the BCLC system.[28,29] The censoring criteria of OS was defined as patients loss to follow up and those still live in March 2015, and tumor recurrence was defined as those without tumor recurrence when they died and those without recurrence in March 2015.

Patients were defined as having high or low NLR depending on whether the ratio at admission was higher or lower than 2.81. Even though several cut-off values (5.00, 2.81, 2.00, and 2.31) of NLR for OS and/or RFS after HR in HCC patients was used,[19–21,30] we selected the cut-off point of 2.81 from the study by Mano and coworkers.[19] That study comprised 958 patients with the cut-off value derived from a time-dependent receiver-operating characteristic curve analysis, which can take full advantage of censored survival data for a diagnostic maker to assess prognosis.[31]

Continuous variables were categorized by the threshold with significant clinical value. For example, the patient with serum albumin (ALB) <35 g/L might be considered to have hypoproteinemia. Patient with alanine transaminase (ALT) >40 g/L might suffer from hepatic injury. Patient with alpha-fetoprotein (AFP) >400 ng/mL might have poor OS and high recurrence rate.

Outcomes and Subgroup Analysis

Outcomes were OS and tumor recurrence. These outcomes were compared for patients with low or high NLR across all patients in the study population, as well as in 3 subgroups of patients with HCC in different BCLC stages: 0/A, B, or C.

Follow-Up

During the first year after HR, patients were followed up 4 to 6 times and then 2 times each year. At each follow-up time, patients were received blood examination including levels of serum markers of hepatitis B virus (HBV) infection, liver function testing, serum AFP concentration, and imageological examination such as abdominal ultrasonography, enhanced computed tomography and/or magnetic resonance imaging, and chest radiography.[32]

Statistical Analysis

Data were analyzed using SPSS19.0 (IBM, Chicago, IL) and R 3.2.2 (R Development Core Team) using a significance threshold of $P < 0.05$. Differences between patients with low or high NLR across all patients were assessed for significance using the Pearson χ^2 test or Fisher's exact test. Survival curves of OS were estimated across the entire population and in subgroups using Kaplan–Meier analysis and compared to each other using the log-rank test. Multivariate analyses to identify risk factors for low OS were performed using the Cox proportional hazards model. Competing risk (Gray Test) model was used for univariate analyses, whereas subdistribution hazard regression (Fine and Gray) model was used for multivariate analyses to identify risk factors of tumor recurrence.

RESULTS

During the study period, 1057 patients with HCC underwent potentially curative HR at our hospital. Of these, 94 were excluded because they underwent only palliative HR (n = 55), they were died of other diseases (n = 27), or baseline data in their medical records were incomplete (n = 12). In the end, 963 patients were included in the study (Table 1), of whom 227 (23.6%) had high preoperative NLR (> 2.81) and the remaining 736 (76.4%) had low NLR (≤ 2.81). Of all included patients, 18 were with BCLC stage 0 HCC, 593 with BCLC stage A HCC, 211 with BCLC stage B HCC, and 141 with BCLC stage C HCC. The median survival time was 49 months for OS among total population.

Preoperative NLR correlated significantly with cirrhosis ($P = 0.003$), tumor size > 5 cm ($P < 0.001$), incomplete capsule ($P = 0.017$), macrovascular invasion ($P < 0.001$), hepatitis B surface antigen (HbsAg; $P = 0.033$), ALB ≤ 40 g/L ($P = 0.041$), and ALT > 40 U/L ($P = 0.006$). NLR did not, however, correlate significantly with tumor number, age, gender, or AFP > 400 ng/mL (Table 1).

Risk Factors for Low OS or Tumor Recurrence

Multivariate analyses by the Cox proportional hazards model identified the following independent risk factors for low OS: NLR > 2.81, tumor number > 3, incomplete capsule,

TABLE 1. Association of Clinicopathological Characteristics With Low or High Preoperative Neutrophil-to-Lymphocyte Ratio

			No. Patients (%) With NLR		
Characteristic	**Category**	**No. Patients**	**≤ 2.81**	**> 2.81**	***P***
NLR	≤ 2.81	736			
	> 2.81	227			
Gender	Male	830	635 (77)	195 (23)	0.912
	Female	133	101 (76)	32 (24)	
Age, y	≤ 60	828	638 (77)	190 (23)	0.274
	> 60	135	98 (73)	37 (27)	
Cirrhosis	No	160	107 (67)	53 (33)	0.003
	Yes	803	629 (78)	174 (22)	
Tumor number	≤ 3	850	654 (77)	196 (23)	0.303
	> 3	113	82 (73)	31 (27)	
Tumor size, cm	≤ 5	403	355 (88)	48 (12)	<0.001
	> 5	560	381 (68)	179 (32)	
Capsule	Complete	339	286 (84)	53 (16)	<0.001
	Incomplete	624	450 (72)	174 (28)	
HBsAg	Negative	143	99 (69)	44 (31)	0.033
	Positive	820	637 (78)	183 (22)	
ALB, g/L	≤ 35	108	75 (69)	33 (31)	0.070
	> 35	855	661 (77)	194 (23)	
ALT, U/L	≤ 40	486	382 (79)	104 (21)	0.109
	> 40	477	354 (74)	123 (26)	
AFP, ng/mL	≤ 400	593	463 (78)	130 (22)	0.127
	> 400	370	273 (74)	97 (26)	
Macrovascular invasion	Absent	822	650 (79)	172 (21)	<0.001
	Present	141	86 (61)	55 (39)	

AFP = alpha fetal protein; ALB = serum albumin; ALT = alanine transaminase; HBsAg = hepatitis B surface antigen; NLR = neutrophil-to-lymphocyte ratio.

ALB ≤ 35 g/L, ALT > 40 U/L, and macrovascular invasion (Table 2). Multivariate analyses by subdistribution hazard regression (Fine and Gray) model found NLR > 2.81, tumor size > 5 cm, AFP > 400 ng/mL, and macrovascular invasion were risk factors of tumor recurrence (Table 3).

Comparison of Prognosis Between Patients With Low or High NLR, Regardless of BCLC Stage

OS was significantly higher among patients with low preoperative NLR than among those with high NLR at 1 year (90.1% vs 78.8%), 3 years (65.3% vs 45.0%), and 5 years

TABLE 2. Univariate and Multivariate Analyses of Factors Predicting Overall Survival of Patients With Hepatocellular Carcinoma After Potentially Curative Resection

	Univariate			Multivariate		
Factor	**Hazard Ratio**	**95% CI**	***P***	**Hazard Ratio**	**95% CI**	***P***
NLR > 2.81	1.590	1.332–1.899	< 0.001	1.296	1.074–1.563	0.007
Male	0.922	0.731–1.162	0.490			
Age > 60 y	0.991	0.789–1.245	0.941			
Cirrhosis	1.051	0.846–1.306	0.650			
Tumor no. > 3	2.416	1.936–3.016	< 0.001	1.934	1.538–2.432	< 0.001
Tumor size > 5 cm	1.410	1.197–1.660	< 0.001	1.154	0.968–1.375	0.109
Incomplete capsule	1.559	1.311–1.855	< 0.001	1.265	1.054–1.519	0.011
HBsAg (+)	1.123	0.893–1.412	0.323			
ALB ≤ 35 g/L	1.305	1.028–1.658	0.029	1.355	1.065–1.724	0.014
ALT > 40 U/L	1.414	1.050–1.544	< 0.001	1.458	1.41–1.714	< 0.001
AFP > 400 ng/mL	1.239	1.053–1.458	0.010	1.107	0.936–1.309	0.236
Macrovascular invasion	3.282	2.662–4.045	< 0.001	2.603	2.085–3.250	< 0.001

AFP = alpha fetal protein; ALB = serum albumin; ALT = alanine transaminase; CI = confidence interval; HBsAg = hepatitis B surface antigen; NLR = neutrophil-to-lymphocyte ratio.

TABLE 3. Factors Predicting Recurrence-Free Survival of Patients With Hepatocellular Carcinoma After Potentially Curative Resection, Univariate Analyses Using Competing Risk (Gray Test) Model and Multivariate Analyses Using Subdistribution Hazard Regression (Fine and Gray) Model

	Univariate		Multivariate			
Factor	**CIF for Followed up 5 Y**	***P***	**Coefficient**	**Hazard Ratio**	**95% CI**	***P***
NLR > 2.81	0.838	< 0.001	0.279	1.32	1.06–1.65	0.014
NLR ≤ 2.81	0.765					
Female	0.814	0.938				
Male	0.782					
Age ≤ 60 y	0.849	0.304				
Age > 60 y	0.834					
Cirrhosis (yes)	0.788	0.758				
Cirrhosis (no)	0.765					
Tumor no. > 3	0.804	< 0.001	0.317	1.37	0.99–1.90	0.055
Tumor no. ≤ 3	0.778					
Tumor size > 5cm	0.822	< 0.001	0.268	1.31	1.08–1.58	0.006
Tumor size ≤ 5cm	0.731					
Capsule (incomplete)	0.805	< 0.001	0.174	1.19	0.97–1.46	0.095
Capsule (complete)	0.746					
HBsAg (positive)	0.793	0.161				
HBsAg (negative)	0.716					
ALB ≤ 35 g/L	0.791	0.999				
ALB > 35 g/L	0.723					
ALT > 40 U/L	0.804	0.016	0.091	1.10	0.91–1.32	0.340
ALT ≤ 40 U/L	0.759					
AFP > 400 ng/mL	0.851	< 0.001	0.340	1.40	1.16–1.71	0.001
AFP ≤ 400 ng/mL	0.741					
Macrovascular invasion (present)	0.914	< 0.001	0.660	1.94	1.46–2.56	< 0.001
Macrovascular invasion (absent)	0.763					

AFP = alpha fetal protein, ALB = serum albumin, ALT = alanine transaminase, CI = confidence interval, CIF = cumulative incidence function, HBsAg = hepatitis B surface antigen, NLR = neutrophil-to-lymphocyte ratio.

(46.1% vs 31.4%) ($P < 0.001$; Figure 1). Median survival time was 56 months among patients with low NLR, significantly longer than the median of 31 months among patients with high NLR. Moreover, patients with low NLR were with significantly lower rate of recurrence than those with high NLR ($P < 0.001$; Figure 2).

Comparison of Prognosis Between Patients With Low or High NLR, Depending on BCLC Stage

Pearson χ^2 test analysis of subgroups of patients with HCC in BCLC stage 0/A, B, or C showed different relationships between low and high preoperative NLR (Table 4). Kaplan–Meier survival analysis among patients in BCLC stage 0/A, OS was significantly higher among patients with low NLR than among those with high NLR at 1 year (95.3% vs 87.8%), 3 years (75.7% vs 56.3%), and 5 years (54.0% vs 39.2%) ($P < 0.001$; Figure 3A). Similar results were observed among patients in BCLC stage B: 85.8% vs 71.4% at 1 year, 55.3% vs 44.3% at 3 years, and 37.8% vs 32.9% at 5 years ($P = 0.027$; Figure 3B). In contrast, no significant relationship was observed between NLR and OS among patients in BCLC stage C ($P = 0.775$; Figure 3C).

Tumor recurrence was significantly higher among patients with high NLR than among those with low NLR group for the subgroups in BCLC stage 0/A ($P = 0.004$; Figure 4A). Moreover, those with high NLR were also with slightly higher tumor

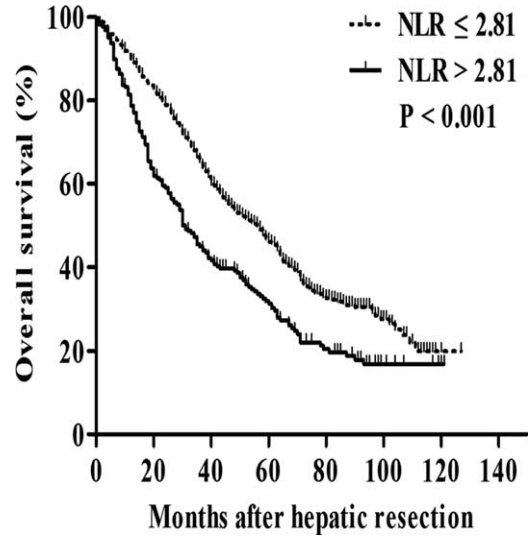

FIGURE 1. Kaplan–Meier survival curves comparing overall survival after potentially curative resection in hepatocellular carcinoma patients with a low or high preoperative neutrophil-to-lymphocyte ratio (NLR). NLR = neutrophil-to-lymphocyte ratio.

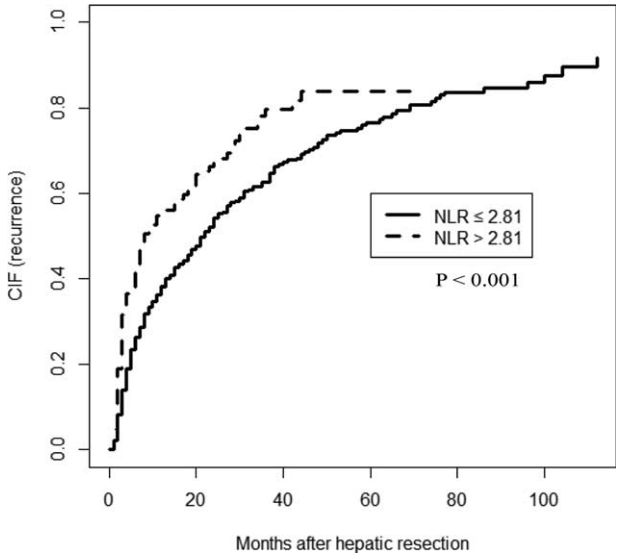

FIGURE 2. Competing risk (Gray Test) model comparing tumor recurrence after potentially curative resection in hepatocellular carcinoma patients with a low or high preoperative neutrophil-to-lymphocyte ratio (NLR). NLR = neutrophil-to-lymphocyte ratio.

recurrence than those with low NLR for the subgroups in BCLC stage B ($P = 0.058$; Figure 4B). However, for the subgroups in BCLC stage C, the 2 groups were with similar tumor recurrence ($P = 0.228$; Figure 4C).

DISCUSSION

HR is thought to be the most effective treatment for resectable HCC,[33,34] and it can benefit even patients in intermediate or advanced stages of disease.[35–37] However, a substantial proportion of patients treated by HR show poor prognosis and high risk of recurrence. In fact, 1 study found that 27.9% of HCC patients in BCLC stage A suffered from recurrence within 1 year after HR.[38] The present study analyzed preoperative NLR as a candidate marker of poor prognosis in patients after HR and found high NLR to be a significant independent predictor of low OS in patients in BCLC stage 0/A or B, and high tumor recurrence only in patients in BCLC STAGE 0/A. Our data provide no evidence that high NLR is associated with risk of OS or tumor recurrence in patients with stage C disease.

Our results support previous studies associating NLR with poor prognosis after HR.[19–21] Those studies analyzed mixed populations in various BCLC stages, whereas the present work provides the first assessment of NLR as a prognostic indicator according to BCLC stage. Our results conflict with 1 study reporting no association of NLR with OS or RFS among patients with BCLC stage 0/A HCC.[23] The discrepancy may be due to the fact that we used a much larger sample size than they did (963 vs 324), or the fact that we used a different cut-off point for defining low and high NLR (2.81 vs 5). The value in our study was derived from time-dependent receiver-operating characteristic curve analysis of 958 patients,[19] whereas their value was derived from receiver-operating characteristic curve analysis of 96 patients.[21] We failed to find any evidence of association of NLR with OS or tumor recurrence in patients with stage C disease. This highlights the stage-specific nature of NLR as a disease indicator and prognostic marker. It also raises the question of whether other prognostic indicators reported in the HCC literature are clinically effective only for certain BCLC stages.

Why elevated preoperative NLR may be linked to poor prognosis after HR is unclear. Available evidence suggests that elevated NLR arises in part due to infiltration of macrophages into tumors,[19] and it is associated with increased tumor-associated macrophage activity,[39] leading to neutrophilia and/or lymphocytopenia.[40] Neutrophils secrete several vascular endothelial growth factors that contribute to tumor angiogenesis,[41] and neutrophil count correlates with tumor cell adhesion to hepatic sinusoids and tumor cell motility, which may be linked to tumor metastasis.[42,43] Lymphocytopenia may lead to a decrease in the numbers of tumor-specific T cells, weakening antitumor immunity.[44] Thus, elevated NLR appears to indicate relatively strong tumor-related inflammation and weak antitumor immune response.

Our findings suggest the potential usefulness of reducing elevated NLR before HR, at least in HCC patients in stages 0/A or B. One approach to reduce NLR may be antiviral treatment. As chronic infection with HBV or hepatitis C virus, which is strongly associated with HCC, can cause persistent inflammation that promotes tumor growth and metastasis,[40] antiviral treatment may improve the systemic inflammation. Another approach may be immunopotentiation therapy, which may enhance antitumor immunity. Future studies should examine the potential clinical benefits of reducing NLR before HR.

The insights provided in the present work are limited by its retrospective design and by its failure to evaluate other systemic inflammation markers, such as levels of C-reactive protein or the ratio of platelets to lymphocytes. In addition, we applied an NLR cut-off value obtained in another study, instead of conducting our own receiver-operating characteristic curve analysis. Future studies should avoid these limitations in order to provide the most rigorous evidence possible.

TABLE 4. Association Between Preoperative Neutrophil-to-Lymphocyte Ratio and Barcelona Clinic Liver Cancer stage

		No. Patients (%) With NLR		
BCLC Stage	**No. Patients**	**≤ 2.81**	**> 2.81**	***P***
0/A	611	488 (80)	123 (20)	< 0.001
B	211	162 (77)	49 (23)	
C	141	86 (61)	55 (39)	

BCLC = Barcelona Clinic Liver Cancer, NLR = neutrophil-to-lymphocyte ratio.

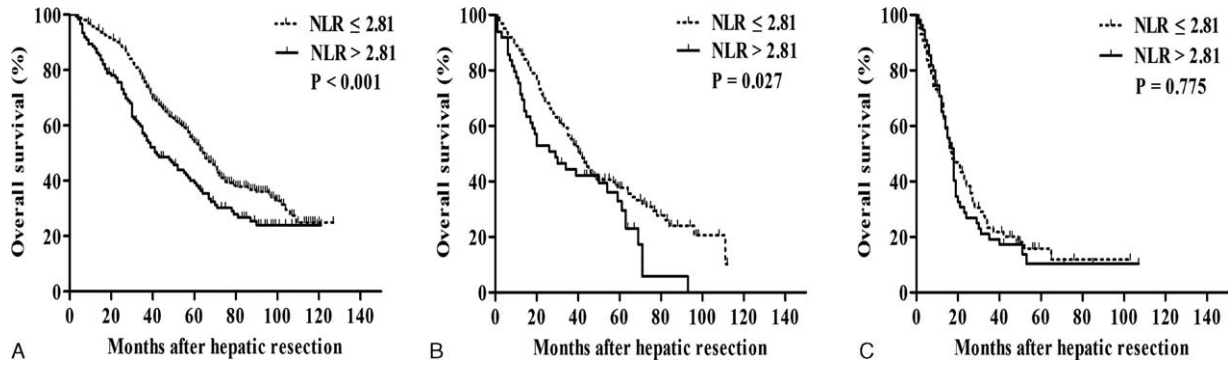

FIGURE 3. Kaplan–Meier survival curves comparing overall survival after potentially curative resection in hepatocellular carcinoma patients with a low or high preoperative neutrophil-to-lymphocyte ratio (NLR), stratified by the BCLC stage. Patients were in (A) stage 0/A, (B) stage B, or (C) stage C. BCLC = Barcelona Clinic Liver Cancer, NLR = neutrophil-to-lymphocyte ratio.

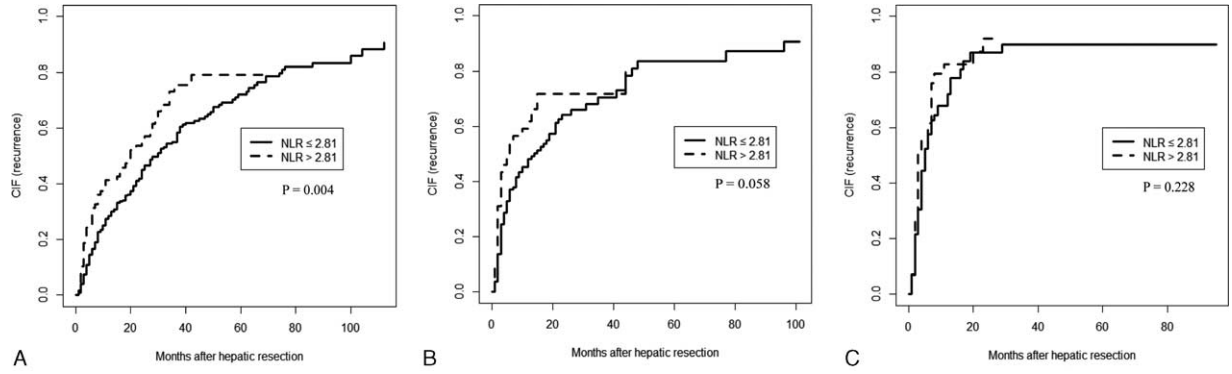

FIGURE 4. Competing risk (Gray Test) model comparing tumor recurrence after potentially curative resection in hepatocellular carcinoma patients with a low or high preoperative neutrophil-to-lymphocyte ratio (NLR), stratified by the BCLC stage. Patients were in (A) stage 0/A, (B) stage B, or (C) stage C.

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