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The impact of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio among patients with intrahepatic cholangiocarcinoma☆

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ABSTRACT

Background: Neutrophil-to-lymphocyte ratio and platelets-to-lymphocyte ratio may be host factors associated with prognosis. We sought to determine whether neutrophil-to-lymphocyte and platelets-to-lymphocyte ratio were associated with overall survival among patients undergoing surgery for intrahepatic cholangiocarcinoma.

Methods: Patients who underwent resection for intrahepatic cholangiocarcinoma between 1990 and 2015 were identified from 12 major centers. Clinicopathologic factors and overall survival were compared among patients stratified by neutrophil-to-lymphocyte ratio and platelets-to-lymphocyte ratio. Risk factors identified on multivariable analysis were included in a prognostic model and the discrimination was assessed using Harrell's concordance index (C index).

Results: A total of 991 patients were identified. Median neutrophil-to-lymphocyte ratio and platelets-to-lymphocyte ratio were 2.7 (interquartile range [IQR]: 2.0–4.0) and 109.6 (IQR: 72.4–158.8), respectively. Preoperative neutrophil-to-lymphocyte ratio was elevated (≥5) in 100 patients (10.0%) and preoperative platelets-to-lymphocyte ratio (≥190) in 94 patients (15.2%). Patients with low and high neutrophil-to-lymphocyte ratio and platelets-to-lymphocyte ratio generally had similar baseline characteristics with regard to tumor characteristics. Overall survival was 37.7 months (95% confidence interval [CI]: 32.7–42.6); 1-, 3-, and 5-year overall survival was 78.8%, 51.6%, and 39.3%, respectively. Patients with an neutrophil-to-lymphocyte ratio <5 had a median survival of 47.1 months (95% CI: 37.9–53.3) compared with a

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median survival of 21.9 months (95% CI: 4.8–39.1) among patients with an neutrophil-to-lymphocyte ratio ≥5 ($P = .001$). In contrast, patients who had a platelets-to-lymphocyte ratio <190 vs platelets-to-lymphocyte ratio ≥190 had comparable long-term survival ($P > .05$). On multivariable analysis, an elevated neutrophil-to-lymphocyte ratio was independently associated with decreased overall survival (hazard ratio: 1.04, 95% CI: 1.01–1.07; $P = .002$). Patients could be stratified into low- versus high-risk groups based on standard tumor-specific factors such as lymph node status, tumor size, number, and vascular invasion (C index 0.62). When neutrophil-to-lymphocyte ratio was added to the prognostic model, the discriminatory ability of the model improved (C index 0.71).

Conclusion: Elevated neutrophil-to-lymphocyte ratio was independently associated with worse overall survival and improved the prognostic estimation of long-term survival among patients with intrahepatic cholangiocarcinoma undergoing resection.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, with an incidence of approximately 1–2 per 100,000 persons.[1–3] Complete surgical resection remains the only option for cure, yet only a minority of patients (15%) present with resectable disease at the time of diagnosis.[4] Prognosis is generally dismal even after curative-intent surgery, with a median survival ranging from 24 to 36 months.[5–9] As such, better tools to predict long-term prognosis after ICC resection may help to improve preoperative patient selection, as well as to identify which patients might benefit the most from a multidisciplinary approach.[5]

To date, no prognostic staging system or nomogram has had excellent prognostic discrimination among patients with ICC.[10] In addition, most prognostic models are based on pathologic factors only available after surgery, and few models have attempted to estimate long-term prognosis based on factors available before ICC resection.[11–14] To improve the predictive ability of prognostic models for ICC, some authors have proposed to use tumor biomarkers as a surrogate for tumor biology. The most common tumor biomarkers associated with hepatopancreatobiliary diseases are carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9), yet data on the correlation of these markers with clinical outcomes have been discordant.[15,16] Other non–tumor-specific biomarkers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have recently been suggested to be correlated with prognosis.[17–19] Rather than being associated with the primary tumor, NLR and PLR reflect the host response to the underlying malignancy. NLR and PLR are linked to the preoperative host inflammatory response to the tumor and therefore may facilitate estimation of long-term prognosis before surgery. NLR and PLR have been associated with poor survival among patients with several different types of cancers yet have not been examined relative to ICC prognosis.[20–25]

Therefore, the objective of the present study was to define the prognostic impact of NLR and PLR among patients undergoing curative-intent resection for ICC. Furthermore, we sought to examine the relative change in predicting long-term prognosis with the addition of NLR and PLR to other established risk factors for ICC.

Methods

All patients undergoing curative-intent resection for ICC with available follow-up between January 1, 1990, and July 1, 2016 were identified from one of 12 participating major hepatobiliary institutions in the United States, Asia, Australia, and Europe (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia; Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Ottawa General Hospital, Ottawa, Canada; Royal Prince Alfred Hospital, Sydney, Australia; San Raffaele Hospital, Milan, Italy; Erasmus University Medical Centre Rotterdam, the Netherlands). Only patients undergoing surgery for histologically confirmed ICC were included in the study population; patients who did not undergo resection, as well as patients who underwent transplantation or received preoperative chemotherapy, were excluded. The respective Institutional Review Boards of each participating institution approved this study.

Demographic and clinical data were collected, including age, sex, American Society of Anesthesiologists class, serum CEA and CA 19-9, presence of jaundice, history of hepatitis B or C, and presence of cirrhosis. Pathologic data such as tumor number, size, major vascular invasion, presence of extrahepatic disease, morphologic type, histologic grade, presence of nodal metastases, final resection margin, and presence of vascular and/or perineural invasion were also included. Data on treatment-related variables, such as type of surgery and lymphadenectomy, were recorded. A minor hepatectomy was defined as a hepatic resection of less than 3 Couinaud segments. Margin status was categorized as R0 for microscopically negative resection margins and R1 for microscopically positive margins.

Data on short- and long-term outcomes were collected. Short-term outcomes included duration of hospital stay as well as postoperative morbidity and mortality. The date of last follow-up and vital status were also collected on all patients. Mortality was calculated from the date of index operation. Long-term outcome, such as overall survival (OS), was stratified based on NLR and PLR. NLR and PLR were calculated by dividing the absolute number of neutrophils or platelets by the absolute number of lymphocytes. For both the univariable analysis and the predictive model, the previously validated cutoff of 5 was used for NLR and 190 for PLR.[22]

Statistical analysis

Summary statistics were provided as whole numbers and percentages for categorical variables and medians with interquartile range (IQR) for continuous variables. The primary outcome of interest was OS, defined as the time interval between the date of surgery and the date of death or last follow-up, as appropriate. Estimates for OS were calculated using the Kaplan-Meier method. Differences in OS were assessed using the log rank test. Multiple imputations were performed to account for missing values. A multivariable Cox proportional hazards model was used to identify potential risk factors. Backward selection was used to select factors for the multivariable analysis and factors with a significance level <.05 remained in the regression model. Results from the Cox models were reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Linear predictors (log-hazard ratios [logHR]) of the risk factors included into the multivariable analysis

Table I
Baseline characteristics of the validation cohort ($n = 991$).

Variable	n (%)/Median (IQR)
Gender	
Male	536 (54.1)
Female	454 (45.9)
Age, y	59 (50–67)
ASA	
I	99 (11.1)
II	462 (51.9)
III	259 (29.1)
IV/V	69 (7.7)
BMI	25.4 (22.5–28.2)
Hepatitis B	196 (23.6)
Hepatitis C	20 (2.4)
Cirrhosis	107 (13.0)
Preoperative suspicious lymph nodes	167 (19.5)
Period of treatment	
1990–2000	35 (3.5
2001–2005	114 (11.5)
2006–2010	414 (41.8)
2011–2016	428 (43.2)
No. of tumors	1 (1-1)
Bilobar location	191 (19.4)
Tumor size (cm)	6.0 (4.3–9.0)
Major vascular invasion	92 (9.3)
Extrahepatic disease	25 (2.5)
Serum GGT	78.0 (45.8–117.5)
Serum CA 19-9	52.1 (17.8–220.0)
Serum CEA	2.4 (1.4–4.1)
Serum total bilirubin	5.8 (3.3–10.1)
Preoperative jaundice	96 (9.7)
Neutrophil-to-lymphocyte ratio	2.7 (2.0–4.0)
Platelet-to-lymphocyte ratio	109.6 (72.4–158.8)

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, cancer antigen; *CEA*, carcinoembryonic antigen; *GGT*, γ-glutamyltransferase; *IQR*, interquartile ratio.

were used to classify patients into in low- and high-risk groups. The discrimination of the model was assessed using Harrell's concordance index (C index). All analyses were performed using SPSS 22.0 (IBM Corp, Armonk, NY) and the *mice* and *rms* package for R 3.3.3 (https://cran.r-project.org/). All tests were 2-sided.

Results

Patient characteristics

Overall 991 patients were eligible for curative-intent resection in the participating centers and met the inclusion criteria; 536 (54.1%) were male and the median patient age was 59 years (IQR: 50–67) (Table I). Most patients were American Society of Anesthesiologists class II or III ($n = 721$; 81%). One out of ten patients had cirrhosis ($n = 107$; 13%) and one quarter of patients had either hepatitis B or C (hepatitis B, $n = 196$, 23.6%; hepatitis C, $n = 20$, 2.4%). Suspicious lymph nodes were detected on preoperative imaging in 167 (19.5%) patients. Average tumor size was 6.0 cm (IQR: 4.3–9.0), and most patients had a single tumor (IQR: 1–1) that was limited to one hemi-liver ($n = 796$; 80.6%). The most common morphologic type was mass forming ($n = 804$, 86.6%), whereas papillary was the least common ($n = 28$, 3%). A large majority of the operations were conducted within the last decade ($n = 842$; 85%) and involved a major hepatectomy ($n = 583$, 58.5%) (Table II). At the time of surgery, a lymphadenectomy was performed in 44.8% of patients ($n = 443$). Lymph node metastasis occurred in 170 patients (17.2%) and major vascular invasion in 92 patients (9.3%), and 25 patients (2.5%) had extrahepatic disease. On final pathologic examination, the majority of patients had microscopically negative margins (R0, $n = 856$, 87.2%). A postoperative complication occurred in 393 patients (39.8%), and 33 patients (3.7%) died within 90 days of surgery. Median duration of stay was 12 days (IQR: 7–17).

Median NLR and PLR were 2.7 (IQR: 2.0–4.0) and 109.6 (IQR: 72.4–158.8), respectively. The correlation of clinicopathologic characteristics and operative details with NLR and PLR are noted in Table II. Preoperative NLR was elevated ($\geq$5) in 100 patients (10.0%) and preoperative PLR ($\geq$190) in 94 patients (15.2%). Patients with low and high NLR and PLR generally had similar baseline characteristics with regard to performance status and tumor

Table II
Postoperative results by neutrophil-to-lymphocyte ratio.

Variable	Total ($n = 991$)	NLR < 5 ($n = 568$)	NLR ≥5 ($n = 100$)	P
Neutrophil-to-lymphocyte ratio (NLR)	2.7 (2.0-4.0)	2.5 (2.0–3.3)	8.4 (6.2–13.3)	<.001
Platelet-to-lymphocyte ratio (PLR)	109.6 (72.4-158.8)	103.8 (69.1–140.6)	206.7 (143.6–261.9)	<.001
Type of resection				.573
Minor hepatectomy (<3 segments)	408 (41.5)	287 (50.5)	46 (46.5)	
Right hepatectomy	156 (15.9)	74 (13.0)	11 (11.1)	
Left hepatectomy	185 (18.8)	98 (17.3)	17 (17.2)	
Extended right hepatectomy	123 (12.5)	58 (10.2)	10 (10.1)	
Extended left hepatectomy	92 (9.3)	43 (7.6)	13 (13.1)	
Central hepatectomy	20 (2.0)	8 (1.4)	2 (2.0)	
Morphologic type				.035
Mass-forming	804 (86.6)	483 (88.3)	75 (82.4)	
Papillary	28 (3.0)	20 (3.7)	2 (2.2)	
Periductal infiltrating	43 (4.6)	19 (3.5)	3 (3.3)	
Mass-forming and periductal infiltrating	53 (5.7)	25 (4.6)	11 (12.1)	
Microvascular invasion	244 (25.2)	118 (21.0)	19 (20.0)	.825
Perineural invasion	142 (15.9)	70 (13.1)	8 (9.2)	.304
Invasion of adjacent organs	73 (7.4)	39 (6.9)	13 (13.3)	.030
Satellite lesions	764 (77.3)	136 (23.9)	19 (19.0)	.280
Intrahepatic metastases	68 (6.9)	38 (6.7)	5 (5.0)	.523
Lymphadenectomy	443 (44.8)	217 (38.3)	53 (53.0)	.006
Lymph node metastases	170 (17.2)	91 (16.0)	16 (16.0)	.996
Margin status				.559
R0	856 (87.2)	518 (91.7)	89 (89.9)	
R1	125 (12.7)	47 (8.3)	10 (10.1)	
Postoperative complication	393 (39.8)	196 (34.5)	39 (39.4)	.348
Duration of stay, days	12 (7–17)	13 (8–17)	14 (11–21)	.002
Readmission within 30 days	45 (4.5)	16 (3.3)	6 (7.5)	.075
Postoperative mortality	33 (3.7)	16 (3.0)	5 (5.4)	.239

Table III
Postoperative results by platelet-to-lymphocyte ratio.

Variable	Total ($n=991$)	PLR < 190 ($n=562$)	PLR ≥ 190 ($n=94$)	P
Neutrophil-to-lymphocyte ratio (NLR)	2.7 (2.0–4.0)	2.5 (1.9–3.4)	5.2 (3.6–8.4)	<.001
Platelet-to-lymphocyte ratio (PLR)	109.6 (72.4–158.8)	100.0 (63.0–133.0)	250.1 (218.0–292.2)	<.001
Type of resection				.472
Minor hepatectomy (<3 segments)	408 (41.5)	271 (51.5)	39 (41.9)	
Right hepatectomy	156 (15.9)	62 (11.8)	16 (17.2)	
Left hepatectomy	185 (18.8)	91 (17.3)	16 (17.2)	
Extended right hepatectomy	123 (12.5)	51 (9.7)	12 (12.9)	
Extended left hepatectomy	92 (9.3)	42 (8.0)	9 (9.7)	
Central hepatectomy	20 (2.0)	9 (1.7)	1 (1.1)	
Morphologic type				.783
Mass-forming	804 (86.6)	456 (89.4)	73 (91.2)	
Papillary	28 (3.0)	17 (3.3)	2 (2.5)	
Periductal infiltrating	43 (4.6)	14 (2.7)	3 (3.8)	
Mass-forming and periductal infiltrating	53 (5.7)	23 (4.5)	2 (2.5)	
Microvascular invasion	244 (25.2)	110 (21.1)	24 (27.3)	.197
Perineural invasion	142 (15.9)	63 (12.7)	15 (19.7)	.096
Invasion of adjacent organs	73 (7.4)	27 (5.2)	9 (9.7)	.086
Satellite lesions	764 (77.3)	123 (23.4)	17 (18.1)	.258
Intrahepatic metastases	68 (6.9)	36 (6.9)	4 (4.3)	.345
Lymphadenectomy	443 (44.8)	200 (38.1)	46 (48.9)	.048
Lymph node metastases	170 (17.2)	78 (14.8)	12 (12.8)	.601
Margin status				.020
R0	856 (87.2)	483 (92.4)	79 (84.9)	
R1	125 (12.7)	40 (7.6)	14 (15.1)	
Postoperative complication	393 (39.8)	179 (34.1)	40 (42.6)	.114
Duration of stay, days	12 (7–17)	13 (8–17)	12 (9–17)	.733
Readmission within 30 days	45 (4.5)	14 (3.0)	8 (8.7)	.011
Postoperative mortality	33 (3.7)	14 (2.8)	4 (4.7)	.372

characteristics (Tables II and III). In particular, there was no difference in the incidence of liver disease between high- and low-PLR groups; there was also no difference in the NLR groups. No patient in the present study had portal hypertension/hypersplenism or signs of frank cirrhosis. Few differences were noted among patients with NLR <5 and NLR ≥5 (Table II). Patients with NLR ≥5 were more likely to have invasion of adjacent organs (13.3% vs 6.9%; $P=.030$) and a prolonged duration of stay (14, IQR: 11–21 vs 13, IQR: 8-17; $P=.002$). Lymphadenectomy was also more commonly performed among patients with NLR ≥5 (53.0% vs 38.3%; $P=.006$). There were similarly few differences among patients with PLR <190 vs PLR ≥190 (Table III). Patients with PLR ≥190 were, however, more likely to have had a lymphadenectomy (48.9% vs 38.1%, $P=.048$) and were more likely to have had a resection with microscopically positive margins (R1; 15.1% vs 7.6%, $P=.020$).

Long-term outcome

Within a median follow-up of 29 months, OS was 37.7 months (95% CI: 32.7–42.6); 1-, 3-, and 5-year OS was 78.8%, 51.6%, and 39.3%, respectively. Patients with an NLR <5 had a median survival of 47.1 months (95% CI: 37.9–53.3) compared with a median survival of 21.9 months (95% CI: 4.8–39.1) among patients with an NLR ≥5 ($P=.001$; Fig. 1). In contrast, patients who had a PLR <190 vs PLR ≥190 had comparable long-term survival ($P > .05$; Fig. 2). On the univariable analysis, several factors were associated with OS, including preoperative suspicious lymph nodes, tumor size, number of lesions, vascular invasion, preoperative jaundice, extrahepatic disease, and NLR. On the multivariable analysis, after controlling for competing risk factors, lymph node metastases (HR: 1.38, 95% CI: 1.10–1.74; $P=.006$), tumor size (HR: 1.04, 95% CI: 1.02–1.07; $P < .001$), number of lesions (HR: 1.15, 95% CI: 108–1.24; $P < .001$), major vascular invasion (HR: 1.38, 95% CI: 1.03–1.85; $P=.030$), preoperative jaundice (HR: 1.58, 95% CI: 1.20–2.08; $P < .001$), extrahepatic disease (HR: 2.32, 95% CI: 1.01–1.07; $P=.001$), and preoperative serum CEA level (HR: 1.00, 95% CI: 1.00–1.00; $P < .012$) remained as independent predictors of OS (Table IV). In addition, after backward selection of predictors of survival, NLR remained an independent risk factor of OS in the multivariable model (HR: 1.04, 95% CI: 1.01–1.07; $P=.002$). Of note, additional analyses revealed that there was no "dose effect" of NLR on prognosis.

OS was worse among patients who had any one of the risk factors identified on multivariable analysis: suspicious lymph nodes (logHR 3×10^{-1}), CEA > 3 ng/mL (logHR 2×10^{-1}), preoperative jaundice (logHR 5×10^{-1}), tumor size > 6 cm (logHR 4×10^{-1}), 2–3 tumors (logHR 3×10^{-1}), >3 tumors (logHR 7×10^{-1}), major vascular invasion (logHR 3×10^{-1}), and extrahepatic disease (logHR 8×10^{-1}). Using these factors, patients could be stratified into separate risk categories—low risk (logHR 0–4×10^{-1}) versus high risk (logHR > 4×10^{-1})—that had different OS ($P < .001$; Fig. 3). The C index of the prediction model for low- versus high-risk patients was 0.62 (standard error: 0.021). Importantly, when NLR (logHR 4×10^{-1}) was added to the prognostic model, the discriminatory ability of the model improved (C index 0.71, standard error: 0.024). In particular, low-risk patients with NLR ≥5 had a worse OS versus low-risk patients with NRL <5 ($P=.040$) (Fig. 4). In contrast, NLR status did not affect the prognosis of patients who already had a high-risk profile (median survival: NRL <5, 18.7 months, 95% CI: 14.6–22.7 vs NLR ≥5, 20.9 months, 95% CI: 1.8–40.0) ($P=.998$).

Discussion

The incidence of ICC, a rare malignant liver tumor that accounts for 5%–10% of primary liver carcinomas, has been increasing over the last several decades from 3.2 per 1,000,000 in 1975 to 8.5 per 1,000,000 in 2010, particularly in the Western countries.[26–28] ICC is a malignancy associated with high mortality, and even patients undergoing curative intent surgery have a 5-year actuarial survival of only 30%–35%.[8] Some investigators have tried to identify preoperative factors to stratify the long-term outcome of patients with ICC.[11,14] To this end, factors such as tumor number, tumor size, major vascular invasion, and suspicious lymph node metastases have been proposed in staging schemes and

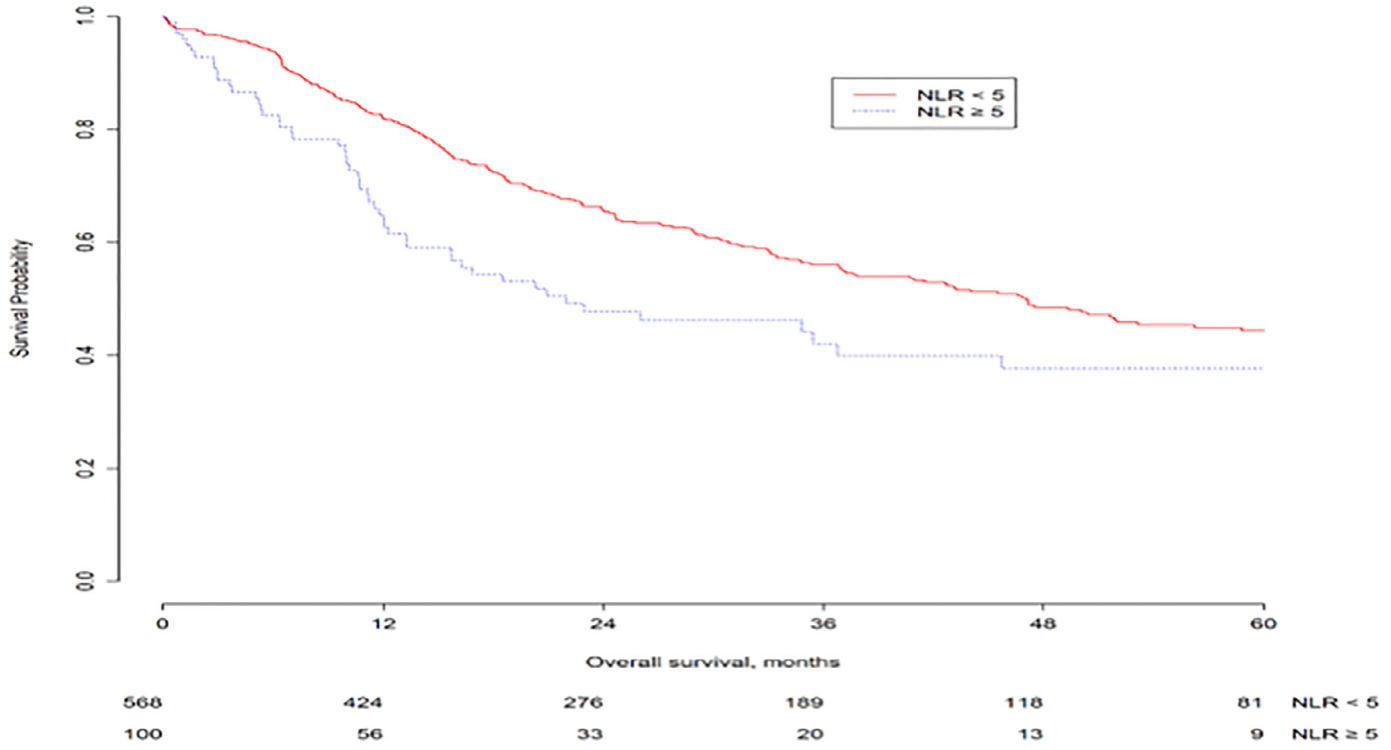

Fig. 1. Overall survival stratified by neutrophil-to-lymphocyte ratio (NLR) ($P = .001$).

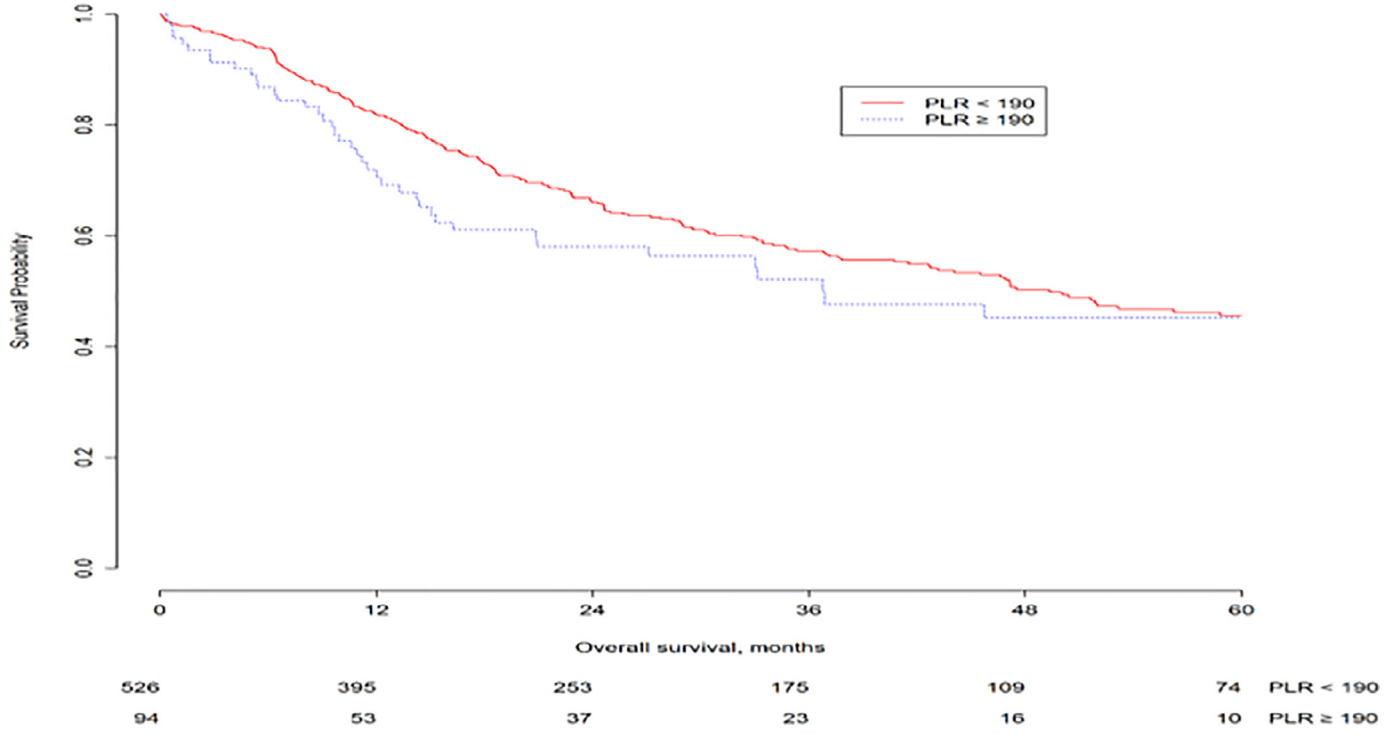

Fig. 2. Overall survival stratified by platelets-to-lymphocyte ratio (PLR) ($P = .109$).

nomograms to stratify patients with regard to OS.[11,14] These previous models have largely included only tumor-specific clinicopathologic factors, many of which can only be definitively determined on postoperative pathologic examination. More recently, other investigators have suggested the inclusion of preoperative tumor-specific biomarkers such as CEA or CA 19-9 to help anticipate postoperative prognosis.[4,29,30] The present study was important because—unlike most previous studies—we focused on non–tumor-specific inflammatory biomarkers. Specifically, we defined the prognostic impact of NLR and PLR among patients undergoing curative-intent resection of ICC. Although PLR was not associated with prognosis, an elevated NLR was independently associated with poor OS among patients with ICC undergoing resection. In addition, when NLR was added to a prognostic model that included traditional

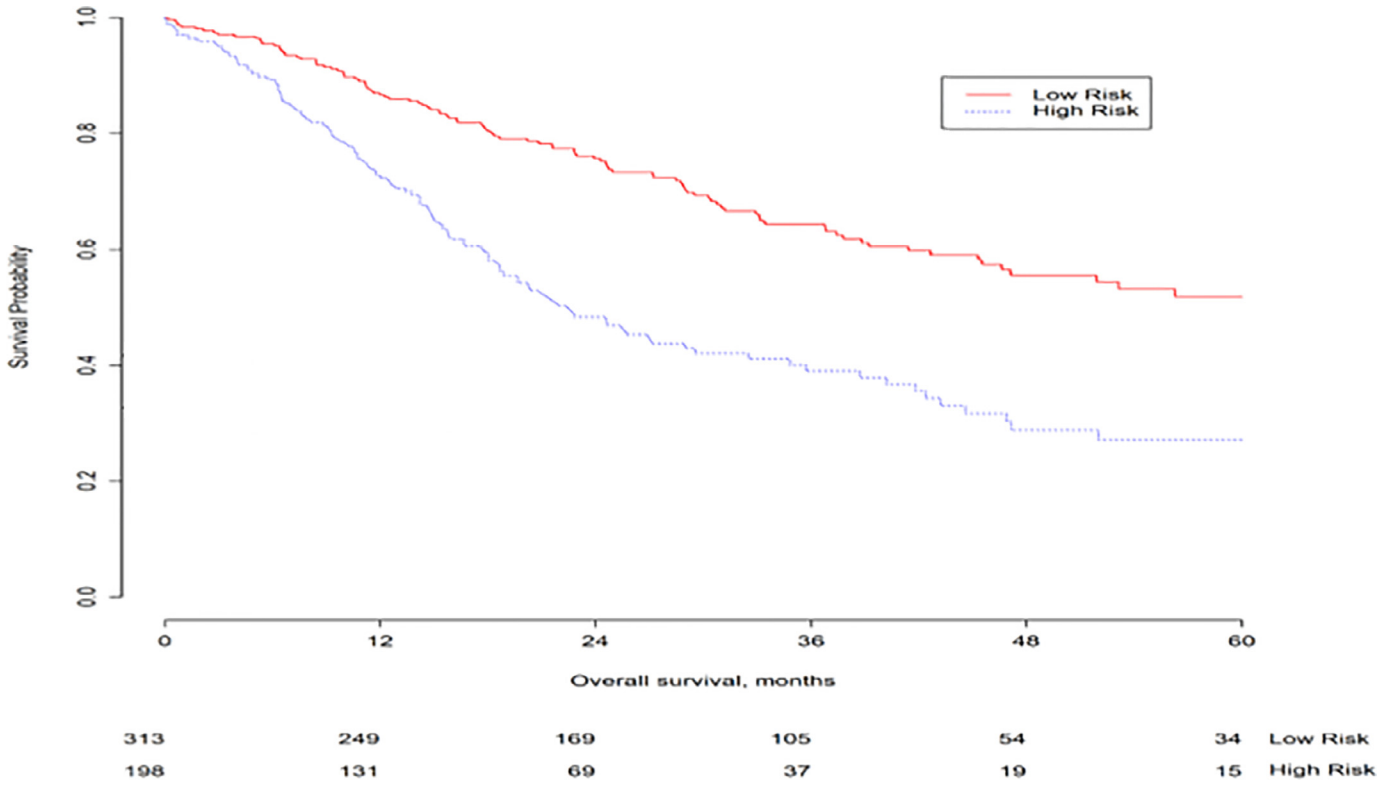

Fig. 3. Overall survival stratified by low-risk (log-hazard ratio [logHR] 0–4) and high-risk factors (logHR > 4) ($P < .001$).

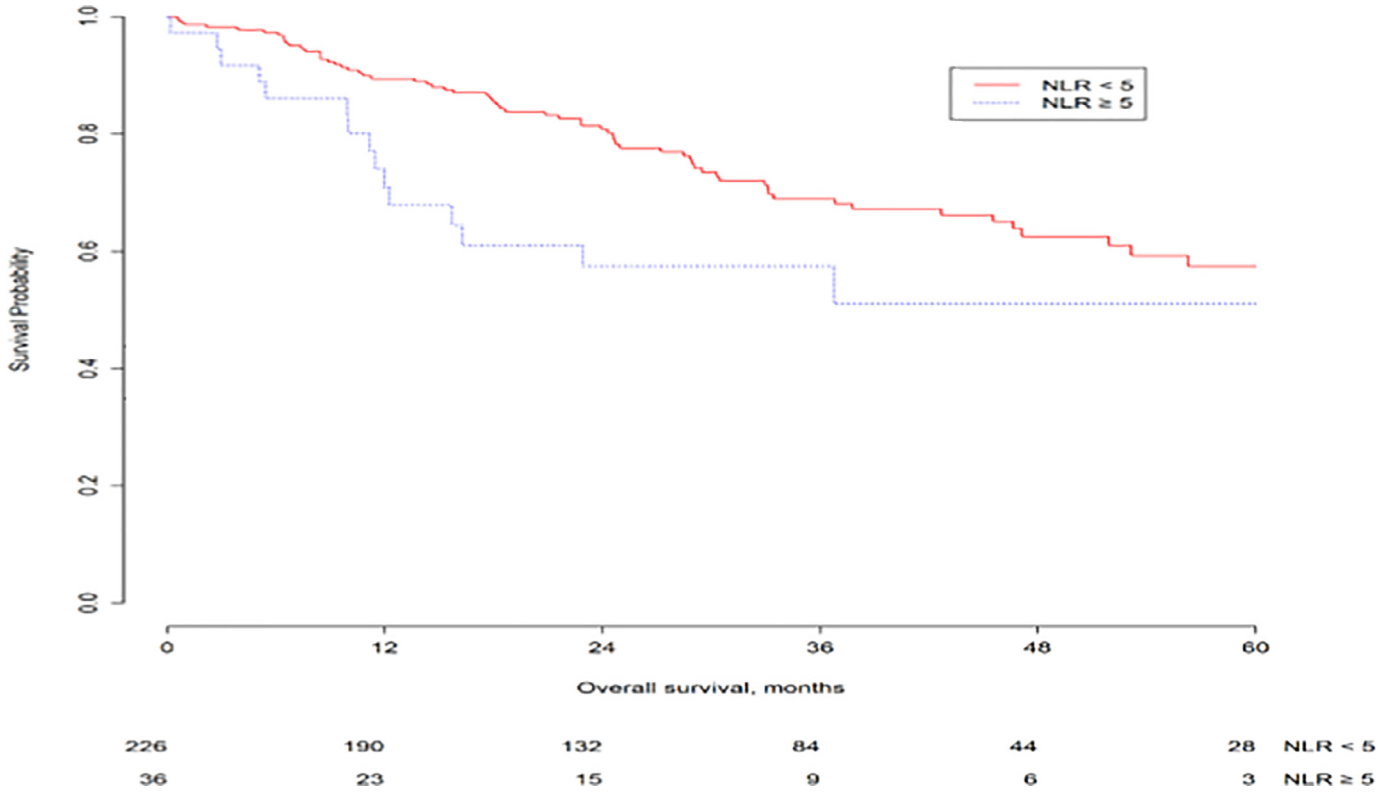

Fig. 4. Low-risk patients stratified by neutrophil-to-lymphocyte ratio (NLR) status ($P = .040$).

Table IV
Univariable and multivariable analysis of overall survival.

Characteristic	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y	1.00	0.99–1.01	.695			
Gender						
Male	Ref	—	—			
Female	0.96	0.80–1.14	.628			
ASA III/IV	1.22	1.01–1.47	.038			
BMI	1.02	1.00–1.03	.095			
Hepatitis B	0.98	0.76–1.26	.889			
Hepatitis C	1.16	0.65–2.08	.607			
Preoperative suspicious lymph nodes	1.64	1.32–2.04	<.001	1.38	1.10–1.74	.006
Bilobar location	1.45	1.17–1.79	<.001			
Tumor size (cm)	1.07	1.04–1.09	<.001	1.04	1.02–1.07	<.001
No. of lesions	1.25	1.17–1.33	<.001	1.15	1.08–1.24	<.001
Major vascular invasion	1.66	1.25–2.19	<.001	1.38	1.03–1.85	.030
Serum GGT	1.00	1.00–1.00	.001			
Serum CA 19-9	1.00	1.00–1.00	.861			
Serum CEA	1.00	1.00–1.00	<.001	1.00	1.00–1.00	.012
Serum total bilirubin	1.00	0.99–1.01	.822			
Preoperative jaundice	1.88	1.45–2.43	<.001	1.58	1.20–2.08	.002
Cirrhosis	1.11	0.85–1.45	.439			
Extrahepatic disease	2.79	1.74–4.48	<.001	2.32	1.38–3.91	.001
NLR	1.04	1.02–1.07	<.001	1.04	1.01–1.07	.002
PLR	1.00	1.00–1.00	.085			

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, cancer antigen; *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *GGT*, γ-glutamyltransferase; *HR*, hazard ratio; *NLR*, neutrophil-to-lymphocyte ratio; *PLR*, platelet-to-lymphocyte ratio.

tumor-specific factors, the discriminatory ability of the model improved.

Several previous studies have evaluated the prognostic role of NLR and PLR in different diseases.[20–25] A recent meta-analysis reported a strong correlation between NLR and poor postoperative outcomes for biliary tract cancers,[31] whereas other studies have suggested that PLR may have a prognostic role among patients with colorectal, hepatocellular, pancreatic, and ovarian cancers.[32,33] In addition, a recent study by our own group found that elevated preoperative NLR and PLR levels were associated with long-term prognosis among patients with pancreatic and secondary metastatic cancers of the liver.[22] The present study expanded on past work because the prognostic impact of NLR and PLR among patients undergoing curative intent surgery for ICC had not been a specific topic of previous inquiry. Of note, elevated NLR was indeed an independent predictor of poor overall survival among patients with ICC who underwent curative intent resection. Specifically, patients with an NLR ≥5 had a median survival that was less than half that of patients who had an NLR <5 (21.9 months vs 47.1 months, respectively; $P = .001$). These findings were consistent with the results from our previous work that investigated patients with pancreas and secondary liver metastasis.[22] In fact, in that series, the proportion of patients with NLR ≥5 who survived to 5 years was roughly half that compared with patients who had an NLR ≥5 (29.2% vs 61.8%, respectively; $P = .01$). However, unlike previous data that suggested PLR also affected prognosis, we failed to find an association of elevated PLR with OS among patients undergoing resection of ICC.

There is a biological rationale for the association of NLR with OS. Neutrophilic granulocytes are the most common type of white blood cells and the most important factor in the innate immune system.[18] The number of neutrophils is upregulated in the presence of malignancy, and neutrophil-mediated inflammation plays an important role in tumorigenesis and tumor progression.[17,18] Although the influence of neutrophils is multifaceted and can either enhance or slow tumor growth, most published clinical studies support the notion that neutrophils promote cancer progression.[17–19] Furthermore, neutrophilia can inhibit the adaptive immune response and may decrease the effect of activated lymphocytes.[34,35] The NLR, as a measure of this effect, can therefore be related to a worse prognosis in several solid tumors.[19–25] The present study confirmed the prognostic role of NLR among patients undergoing curative intent surgery for ICC. In contrast, PLR was not associated with survival. Platelets are also part of the tumor inflammatory response and thrombocytosis can be related to tumor growth, invasion, and angiogenesis.[32,36] In addition, thrombocytosis has been suggested to protect tumor cells from cell-mediated lysis and facilitates tumor spreading.[37] Interestingly, in the present study, PLR elevation was not associated with a more aggressive tumor phenotype because there were few clinicopathologic differences among patients with a PLR <190 vs PLR ≥190. Although patients with a PLR ≥190 were more likely to have had a resection with microscopically positive margins, PLR was not associated with long-term prognosis on multivariable analysis.

Although any single factor may be associated with survival, the combination of clinicopathologic variables into a single "score" or nomogram may allow for better prognostic stratification. Hyder et al[11] created a nomogram based on age at diagnosis (HR: 1.31), tumor size (HR: 1.50), multiple tumors (HR: 1.58), cirrhosis (HR: 1.51), lymph node metastasis (HR: 1.78), and macrovascular invasion (HR: 2.10) (all $P < .001$).[11] On the basis of these factors, a nomogram was created to predict survival of ICC after resection that revealed good predictive abilities. Similarly, in the present study, several preoperative factors (eg, suspicious lymph nodes, CEA, jaundice, tumor size and number, major vascular invasion) that were significant on multivariable analysis were included in a score to predict long-term prognosis. Using these factors, patients could be stratified according to prognosis with a good to moderate C index. Of interest, the predictive model improved markedly when NLR was included as one of the prognostic variables (C index 0.71). These data suggest that the combination of tumor-specific factors (eg, size, number, vascular invasion) with information about host response (eg, NLR) may improve the ability to estimate long-term prognosis of patients with ICC undergoing surgical resection.

The present study should be considered in light of several limitations. As with any retrospective analysis, selection bias may have

affected which patients were offered surgical resection. In turn, patients with more aggressive oncologic features may be disproportionately under-represented because these patients were less likely to be offered surgery. Differences in patient selection and surgical technique, as well as adjuvant treatment among different centers, was also possible; however, the multi-institutional nature of the study did allow for a larger sample size and generalizability. Finally, the lack association of PLR with prognosis may have been due to a type II error, although this seems unlikely because roughly the same number of patients had an elevated PLR as did NLR.

In conclusion, long-term outcomes of patients after curative intent surgery were relatively poor, with a 5-year survival of only about 40%. Prognosis was associated with several preoperative tumor-specific factors, such as tumor size and number and major vascular invasion. After controlling for these tumor-specific factors, host-related factors such as elevation in NLR was independently associated with worse long-term outcomes. In fact, the median survival of patients with an elevated NLR was roughly half that of patients with a normal or low NLR. In addition, the inclusion of NLR into a multivariable preoperative model increased the ability to estimate OS. Future staging schemes for ICC should consider the addition of host-related factors such as NLR to tumor-specific factors to improve the ability to predict long-term outcomes.

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