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ORIGINAL RESEARCH

Comparative performance of inflammation-based prognostic scores in patients operated for intrahepatic cholangiocarcinoma

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Objective: Prognostic performance of inflammation-based prognostic scores, including the Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), Prognostic Index (PI) and Prognostic Nutritional Index (PNI) has been explored in patients with varied types of cancer, though little data is available in intrahepatic cholangiocarcinoma (ICC). This study sought to evaluate the impact of systemic inflammation on the overall survival (OS) of ICC patients, and to identify more optimal prognostic indices.

Patients and methods: The prognostic power of all the scores mentioned above was compared in 123 patients underwent curative surgery for ICC using Kaplan–Meier curves, COX regression models and the receiver operating characteristics (ROC) curves. The results were validated in a cohort of 95 ICC patients.

Results: Multivariate analysis identified LMR as the only independent inflammation-based predictor for OS in the training cohort (P=0.007, HR 2.082, 95% CI 1.218–3.558). More importantly, the combined score of LMR and pTNM designated the inflammation-based pathological stage (IPS) outperformed other established scores in terms of discriminatory ability, monotonicity and homogeneity in the training and validation cohorts.

Conclusion: This study reveals that preoperative LMR is an independent predictor of OS in ICC patients after hepatectomy, and the IPS can be applied as a novel prognostic indicator in these patients.

Keywords: inflammation-based prognostic score, the lymphocyte to monocyte ratio, intrahepatic cholangiocarcinoma, prognostic marker, staging system

Introduction

In the last three decades, having witnessed a marked increase in incidence[1] as well as mortality rates[2] globally, intrahepatic cholangiocarcinoma (ICC) remains the second most frequent primary liver cancer after hepatocellular carcinoma (HCC). Surgical resection is considered the only choice of potentially curative treatment for patients with operable ICC. Unfortunately, the surgical outcome is grim even after curative-intent resection, as the median survival period after hepatic resection is only 12.2 months.[3] However, reports on the predictors of survival are relatively scarce.

Inflammation associated factors, such as hepatobiliary flukes, primary sclerosing cholangitis (PSC), chronic hepatitis B/C infection and hepatolithiasis are known to be risk factors for ICC. They cause chronic biliary inflammation and increased

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cellular turnover.[4] Moreover, the presence of systemic inflammation negatively correlates with prognosis of cancer patients.[5,6]

Previous studies have elucidated that preoperative inflammation-based prognostic scores are predictive of survival in patients with malignancies[7–10] including ICC.[11–13] These prognostic indices include the Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (mGPS) based on the serum concentrations of CRP and albumin, the Prognostic Index (PI) based on CRP concentration and white blood cell count, the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR), the lymphocyte to monocyte ratio (LMR), and the Prognostic Nutritional Index (PNI) based on albumin concentration and lymphocyte count. To our knowledge, no study has assessed the prognostic value of all these scores for ICC patients. In the present study, we compared the prognostic ability of these scores as well as pathological staging systems among patients who underwent radical resection for ICC to identify more optimal prognostic predictors for these patients.

Materials and methods

Patients

Medical records of ICC patients who underwent potentially curative hepatectomy at the Liver Cancer Institute of Zhongshan Hospital (Fudan University, Shanghai, China) between 2010 and 2014 were retrospectively reviewed. Curative hepatectomy was defined as the complete removal of all macroscopic tumor nodules with clear microscopic margins and no residual tumors as indicated by CT scan at one month after surgery. Only patients pathologically confirmed to have primary intrahepatic cholangiocarcinoma were enrolled in this study. Patients who underwent preoperative therapies like transarterial chemoembolization, radiofrequency ablation, or percutaneous ethanol injection and those who showed clinical evidence of infection or other inflammatory conditions were excluded. Patients with a history of other malignancies were also excluded. Finally a total of 218 patients with ICC were included and then randomly divided into two groups, termed the training cohort and validation cohort (123 and 95 patients, respectively). The pathological stage was classified according to the AJCC 7th edition.[14] Blood samples were obtained 1–3 days before surgery for measurement of white blood cell count, neutrophil, lymphocyte, platelet (Plt), monocyte count, CRP, albumin, alkaline phosphatase (ALP), total bilirubin and other laboratory data relevant to this study.

This study complied with the standards of the Declaration of Helsinki and the current ethical guidelines, and was approved by the Zhongshan Hospital Ethics Committee. All data were analyzed and displayed anonymously, thus the identity of the study participants is concealed. Written informed consent for the use of clinicopathtological data for study purpose was obtained from participants on admission.

Follow-up and postoperative treatment

According to our routine follow-up procedure, patients were followed up monthly during the first postoperative year and every 3 months thereafter. Tumor markers, such as the CA19-9 and liver ultrasonography were assessed at each visit. A computed tomography (CT) scan of the abdomen was performed every 6 months. Bone scan or magnetic resonance imaging (MRI) was used when needed. If recurrence was suspected, additional investigations, such as hepatic angiography and positron emission tomography-computed tomography (PET-CT) were performed. Patients with confirmed ICC recurrence received further treatment, if the recurrent tumor was localized, a second liver resection, radiofrequency ablation (RFA), or percutaneous ethanol injection (PEI) was suggested. If the recurrent tumor was multiple or diffused, patients were suggested to take transcatheter arterial chemoembolization (TACE) or chemotherapy; as for lymph node or bone metastasis, external radiotherapy was recommended. Overall survival (OS) was defined as the interval between the date of resection and the date of death or the last follow-up.

Statistical analysis

Continuous variables are presented as medians and ranges. Categorical variables are presented as numbers and percentages. Comparisons between groups were performed using the Student's unpaired *t*-test or Mann–Whitney *U* test for continuous or ordinal variables, while Chi square test or Fisher's exact test was adopted for categorical variables, as appropriate. The overall survival rates were calculated using the Kaplan–Meier method, and differences in the survival rates between two groups were compared by the log-rank test. Backward stepwise multivariate Cox proportion analysis was performed to determine the influence of factors on OS which were significant in the univariate analysis.

A binary logistic regression model was fitted, and the regression coefficients derived from the model were used to create a new staging system as a composite score for LMR and pTNM, termed the inflammation-based pathological stage (IPS). To evaluate the discriminatory ability of each

score, receiver operating characteristics (ROC) curves were generated, and the areas under the curve (AUC) were measured. The optimal cutoff was determined by ROC analysis. The monotonicity of each score was evaluated with the linear trend chi-square test, whereas the homogeneity of prognostic prediction across categories was measured using the likelihood ratio test as described in a previous study.[15] The construction of the inflammation-based prognostic scores and their optimal cutoff values are shown in Table 1. Statistical analyses were performed using the SPSS statistical software package, version 17.0 (IBM SPSS Inc.,Chicago, IL, USA), at a significance level of *P* less than 0.05.

Results

Clinicopathologic profile of patients

The detailed baseline characteristics of patients in the training and validation cohorts are summarized in Table 2. Overall, there were no significant differences between the two cohorts with respect to all clinicopathological and demographic data as well as inflammation-based prognostic scores. Among the 218 patients enrolled in the study, 124 (56.9%) were male. A total of 57 (46.3%) patients in the training set and 45 (47.4%) patients in the validation set died at the end of observation (March 2016). The median OS of the training cohort was 11.6 months (range 2.0–62.2 months) while that of the validation cohort was 16.8 months (range 1.3–62.7 months). No significant difference in OS between the two groups was noted.

Table 1 Definition of inflammation-based prognostic scores

Scoring systems	Score
Glasgow Prognostic Score (GPS)	
C-reactive protein ≤10 mg/l and albumin ≥35 g/l	0
C-reactive protein ≤10 mg/l and albumin <35 g/l	1
C-reactive protein >10 mg/l and albumin ≥35 g/l	1
C-reactive protein >10 mg/l and albumin <35 g/l	2
Modified Glasgow Prognostic Score (mGPS)	
C-reactive protein ≤10 mg/l and albumin ≥35 g/l	0
C-reactive protein ≤10 mg/l and albumin <35 g/l	0
C-reactive protein >10 mg/l	1
C-reactive protein >10 mg/l and albumin <35 g/l	2
Prognostic Index (PI)	
C-reactive protein ≤10 mg/l and white cell count ≤11×10^9/l	0
C-reactive protein ≤10 mg/l and white cell count >11×10^9/l	1
C-reactive protein >10mg/l and white cell count ≤11×10^9/l	1
C-reactive protein >10mg/l and white cell count >11×10^9/l	2
Neutrophil to lymphocyte ratio (NLR)	
Neutrophil count: lymphocyte count <2.94	0
Neutrophil count: lymphocyte count ≥2.94	1
Platelet to lymphocyte ratio (PLR)	
Platelet count: lymphocyte count <130.59	0
Platelet count: lymphocyte count ≥130.59	1
Lymphocyte to monocyte ratio (LMR)	
Lymphocyte count: monocyte count <3.62	1
Lymphocyte count: monocyte count ≥3.62	0
Prognostic Nutritional Index (PNI)	
Albumin (g/L) +5× total lymphocyte count ×10^9/l <48.25	1
Albumin (g/L) +5× total lymphocyte count ×10^9/l ≥48.25	0

Univariate and multivariate analyses of prognostic factors for OS

In the training set, univariate analysis revealed that ALP (*P*=0.039), CA19-9 (*P*=0.031), CEA (*P*=0.013), multiple nodules (*P*<0.001), maximal tumor diameter (*P*=0.040), vascular invasion (*P*=0.016), lymph node invasion (*P*=0.006), pTNM stage (*P*=0.001), the GPS (*P*=0.027), mGPS (*P*=0.025), PI (*P*=0.020), NLR (*P*=0.004), PLR (*P*=0.009), LMR (*P*=0.005) and the PNI (*P*=0.023) were risk factors for inferior overall survival. Multivariate analysis identified pTNM (*P*=0.001, HR 1.557, 95% CI 1.200–2.022) and the LMR (*P*=0.007, HR 2.082, 95% CI 1.218–3.558) as independent risk factors for poorer OS as shown in Table 3.

Comparative prognostic performance of scoring systems

The relationship between the prognostic scores and overall survival in the training set is shown in Figure 1. Higher levels of GPS, mGPS, NLR, PLR, LMR, PNI and pTNM were associated with reduced OS, although PI displayed marginal significance for predicting survival (*P*=0.055). A combination score of LMR and pTNM, designated inflammation-based pathological stages (IPS) was constructed as shown in Table 4. Patients were grouped into three categories according to their IPS stages, which resulted in significant differences in OS between all adjacent strata. Compared with patients staged IPS Ⅰ, those with IPS Ⅱ in the training set were 2.641 times more likely to end up with inferior OS. For patients with IPS Ⅲ, the relative hazard ratio was 4.955 (Table 4). In the validation set, only the PI, LMR, pTNM and the IPS were significantly related to overall survival rates (see Figure S1). Stepwise increase in IPS was accompanied with rise in hazard ratio in validation cohort.

To assess the discriminatory capacity of each scoring system, receiver operating characteristic curves were

Table 2 Clinicopathtological characteristics of the patients in two cohorts

Variable	Training cohort (n=123)	Validation cohort (n=95)	*P*-value
Age (years)	60 (31–85)	61 (37–79)	0.476
Gender (Male/Female)	65/58	59/36	0.171
ALP (IU/L)	95(24–946)	95(34–1280)	0.507
Total serum bilirubin (mg/dL)	11 (3.6–355.7)	11.4 (3.3–286.3)	0.996
CA19–9 (U/ml)	49.4 (0.6–10,000)	46.8 (0.6–10,000)	0.807
CEA (ng/ml)	2.8 (0.5–945.2)	3.3 (0.5–133.3)	0.440
HBsAg or HCV (positive/negative)	46/77	32/63	0.571
Tumor number (solitary/multiple)	80/43	69/26	0.232
Maximal tumour diameter (cm)	5.3 (1–13.5)	6 (1–14)	0.695
Liver cirrhosis (%)	18 (14.6)	21 (22.1)	0.154
Vascular invasion (absent/present)	109/14	83/12	0.778
Microscopic vascular invasion (absent/present)	95/28	80/15	0.199
Lymph node invasion (absent/present)	109/14	75/20	0.051
Local extrahepatic invasion (absent/present)*	111/12	84/11	0.664
pTNM (I/II/III/IV)	49/50/10/14	37/29/8/21	0.272
Differentiation (well/moderate/poor)	2/102/19	1/77/17	0.582
GPS (0/1/2)	94/26/3	70/23/2	0.662
Modified GPS (0/1/2)	98/22/3	75/18/2	0.908
PI (0/1/2)	87/33/3	70/24/1	0.594
NLR (0/1)	69/54	59/36	0.372
PLR (0/1)	60/63	56/39	0.136
LMR (0/1)	64/59	49/46	0.947
PNI (0/1)	63/60	56/39	0.256

Note: *Local extrahepatic invasion, tumor perforated the visceral peritoneum or involved the local extrahepatic structures by direct invasion.
Abbreviations: ALP, alkaline phosphatase; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; pTNM, pathological tumor-node-metastasis; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic Nutritional Index.

constructed for survival status at 12-month, 18-month and 24-month follow-up. The area under the ROC curve (AUC) was calculated and compared, as shown in Table 5. The IPS had the highest AUC value at 12-months (0.699), 18-months (0.676) and 24-months (0.669) follow-up in comparison with other inflammation-based prognostic indices and the pTNM in the training set. This conclusion was furthere verified in the validation cohort. The IPS had an AUC value of 0.737, 0.713, 0.717 at 12-month, 18-month and 24-month follow-up, respectively, as shown in Table S1. The IPS with the highest χ^2 according to the linear trend test and the LR test was considered to have the best monotonicity and homogeneity, although pTNM stage appeared to have higher homogeneity in the training group as shown in Table 6 and Table S2.

Relationship between clinicopathological factors and the IPS

Several clinicopathological features were compared among the three groups with different level of IPS in the training cohort (Table 7). Those with the same elements that constituted pTNM or LMR including tumor number, maximal tumor diameter, lymph node invasion, vascular invasion, local extrahepatic invasion, PI, NLR, PLR and PNI were not compared. It turned out that patients with higher ALP, CEA, microscopic vascular invasion, elevated GPS and modified GPS were more likely to have advanced stages of IPS.

Similar conclusions were drawn in the validation cohort; in which the aforementioned factors were significantly associated with advanced IPS level in this set (Table S3).

Discussion

In the present study, we have demonstrated that inflammation-based prognostic scores such as GPS, mGPS, PI, NLR, PLR, LMR and PNI are associated with dismal prognosis in ICC patients underwent radical surgery. Besides, we report for the first time that LMR is an independent prognostic predictor of OS in these patients.

Table 3 Univariate and multivariate analyses of prognostic factors

Variables	n=123	Univariate *P*	Multivariate analysis	
			HR (95% CI)	*P*
Age (yr) (<65/≥65)	90/33	0.841		
Gender (male/female)	65/58	0.593		
ALP (IU/L, <135/≥135)	96/27	0.039		
Total serum bilirubin (mg/dL, ≤20/>20)	106/17	0.860		
CA19-9 (U/ml, ≤37/>37)	56/67	0.031		
CEA (ng/ml, ≤5/>5)	90/33	0.013		
HBsAg or HCV (positive/negative)	46/77	0.204		
Tumor number (solitary/multiple)	80/43	<0.001		
Maximal tumor diameter (cm) (<5/≥5)	49/74	0.040		
Liver cirrhosis (absent/present)	105/18	0.509		
Vascular invasion (absent/present)	109/14	0.016		
Microscopic vascular invasion (absent/present)	95/28	0.099		
Lymph node invasion (absent/present)	109/14	0.006		
Local extrahepatic invasion (absent/present)*	111/12	0.387		
pTNM (I/II+III+IV)	49/74	0.001	1.557(1.200–2.022)	0.001
Differentiation (well/moderate/poor)	2/102/19	0.308		
GPS (0/1/2)	94/26/3	0.027		
mGPS (0/1/2)	98/22/3	0.025		
PI (0/1/2)	87/33/3	0.020		
NLR (0/1)	69/54	0.004		
PLR (0/1)	60/63	0.009		
LMR (0/1)	64/59	0.005	2.082(1.218–3.558)	0.007
PNI (0/1)	63/60	0.023		

Note: *Local extrahepatic invasion, tumor perforated the visceral peritoneum or involved the local extrahepatic structures by direct invasion.
Abbreviations: ALP, alkaline phosphatase; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; pTNM, pathological tumor-node-metastasis; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic Nutritional Index.

Based on this finding, we generated a novel inflammation-based prognostic score named the IPS, which proved to be more effective in stratifying the prognosis of patients with operable ICC.

Several lines of evidence indicate that inflammation acts much like "fertilizer" for the growth of malignancies. Inflammation is observed after activation of almost all common oncogenes including Myc and Ras[16,17] and "is demonstrably capable of fostering the development of incipient neoplasias into full-blown cancers".[18] Both local and systemic inflammatory responses are evident in the progression of human cancer.[19,20] For intrahepatic cholangiocarcinoma, a previous study from our institution have validated that ICC cells are likely to recruit more neutrophils to the tumor foci through overexpressed CXCL5.[21] Lin et al from Sun Yat-sen University Cancer Center demonstrated a significant association between high levels of serum CRP and adverse cancer-specific survival (P=0.001) and recurrence-free survival (P<0.001)[22] in ICC. To assess the level of systemic inflammation in an effective way, several inflammation-based prognostic scores such as GPS,[23] mGPS,[24] PI,[25] NLR,[26–28] PLR,[29–31] PNI[32-34] and LMR have been proposed in the recent decade. The prognostic power of these indices has been demonstrated in various types of malignancies including liver and bile duct neoplasm.[7,9]

However, few studies have looked into the prognostic ability of inflammation-based scores in patients with intrahepatic cholangiocarcinoma. Gomez et al reported, for the first time, that ICC patients with an elevated preoperative NLR (>5) had significantly shorter overall survival after hepatic resection.[11] Similarly, Chen et al found that high NLR (≥2.49) showed notable correlation with early recurrence and poor overall survival in ICC patients.[12] The same research group confirmed that high level of PLR (≥123) might be a significant prognostic factor in ICC patients; PLR values greater than 123 reflected strong correlation with early recurrence and worse OS.[13] In the present study, the prognostic significance of elevated PLR was only observed in the training set. However, PLR did not exert any significant effect on OS in the validation cohort, possibly due to limited cohort size.

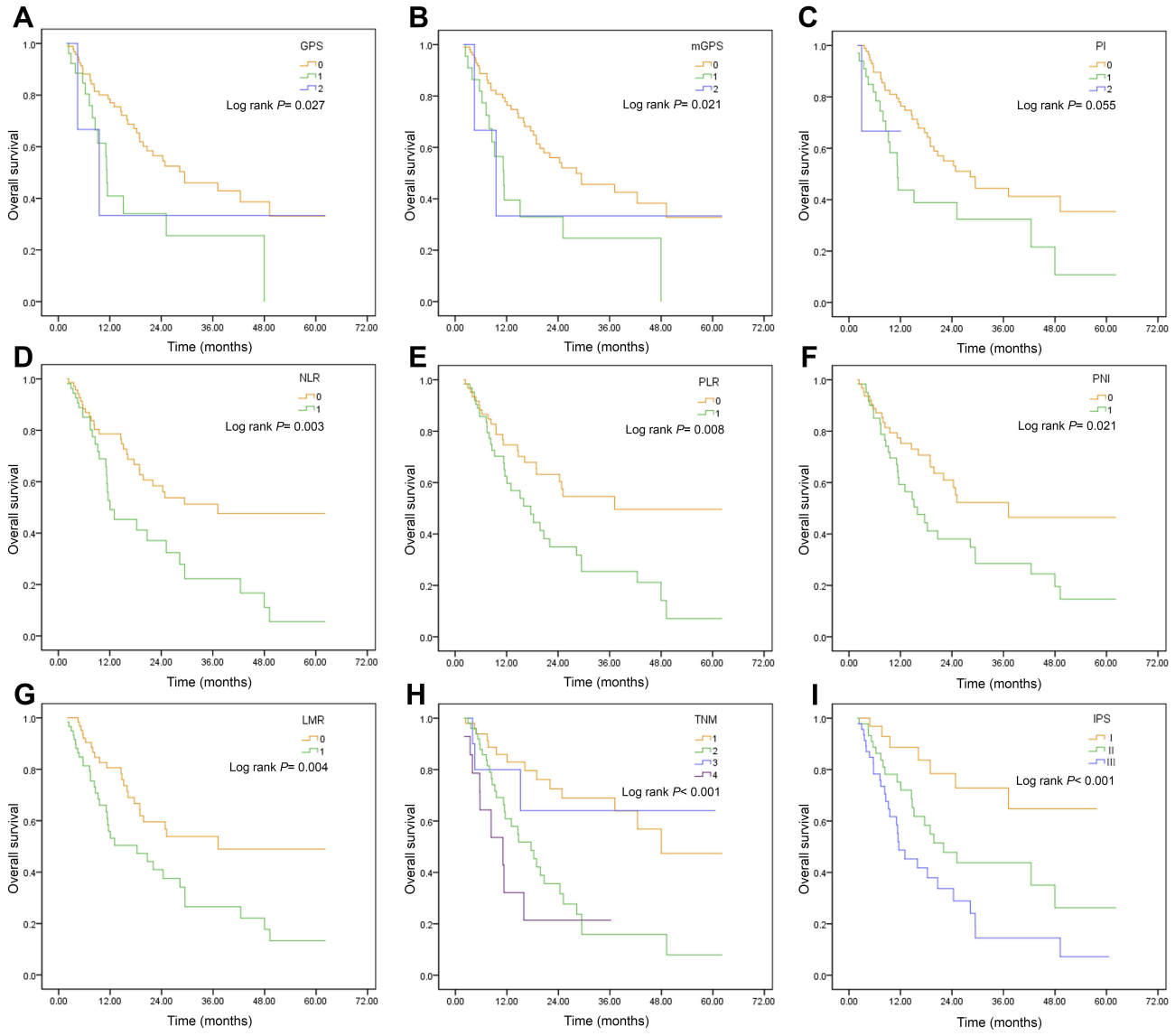

Figure 1 Kaplan–Meier overall survival curves for ICC patients undergoing curative hepatectomy stratified by inflammation-based prognostic scores and staging systems in the training cohort. (**A**) GPS; (**B**) mGPS; (**C**) PI; (**D**) NLR; (**E**) PLR; (**F**) PNI; (**G**) LMR; (**H**) pTNM; (**I**) IPS.

Abbreviations: GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil lymphocyte ratio; PLR, platelet (Plt) lymphocyte ratio; PNI, Prognostic Nutritional Index; LMR, lymphocyte monocyte ratio; pTNM, pathological tumor-node-metastasis; IPS, inflammation-based pathological stage.

Table 4 Construction of the inflammation-based pathological stage (IPS)

IPS = pTNM +2X LMR†	Stage	Hazard ratio (95% CI) *P*	
		Training set	Validation set
IPS =0 or 1	I	1	1
IPS =2 or 3	II	2.641 (1.121–6.222) 0.026	2.591 (1.070–6.275) 0.035
IPS =4 or 5 or 6	III	4.955 (2.154–11.399) <0.001	5.539 (2.375–12.916) <0.001

Note: †LMR was scored 0 or 1 according to Table 1.

Abbreviations: pTNM, pathological tumor-node-metastasis; LMR, lymphocyte to monocyte ratio; CI, confidence interval.

In our comparative analysis of prognostic scores, the prognostic power of LMR, which had been tested by previous investigators, was also validated. Stotz et al demonstrated that elevated preoperative LMR was an independent predictor of increased TTR and OS in patients with stage II and III colon cancer.[35] Lin and colleagues illustrated that the LMR was a significant prognostic factor for OS and DFS in patients receiving curative surgery for

Table 5 Comparison of the AUC between inflammation-based prognostic scores in the training cohort

	Overall survival AUC	Sensitivity	Specificity
12-Month			
GPS	0.644	0.441	0.843
mGPS	0.645	0.412	0.876
PI	0.621	0.471	0.775
NLR	0.583	0.559	0.607
PLR	0.553	0.588	0.517
LMR	0.636	0.676	0.596
PNI	0.569	0.588	0.551
pTNM	0.673	0.824	0.483
IPS	0.699	0.618	0.719
18-Month			
GPS	0.612	0.381	0.840
mGPS	0.618	0.357	0.877
PI	0.583	0.405	0.765
NLR	0.546	0.500	0.593
PLR	0.563	0.595	0.531
LMR	0.588	0.595	0.580
PNI	0.582	0.595	0.568
pTNM	0.675	0.810	0.506
IPS	0.676	0.548	0.716
24-Month			
GPS	0.581	0.333	0.827
mGPS	0.590	0.312	0.867
PI	0.548	0.354	0.747
NLR	0.533	0.479	0.587
PLR	0.575	0.604	0.547
LMR	0.585	0.583	0.587
PNI	0.561	0.562	0.560
pTNM	0.659	0.792	0.520
IPS	0.669	0.521	0.720

Abbreviations: AUC, the area under the receiver operating characteristics curve; CI, confidence interval; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic Nutritional Index; pTNM, pathological tumor-node-metastasis; IPS, inflammation-based pathological stage.

Table 6 Evaluation of monotonicity and homogeneity of scoring systems in the training cohort

Prognostic score	Linear trend test (χ^2)	LR test (χ^2)
GPS	3.594	3.815
mGPS	5.240	5.982
PI	1.047	2.388
NLR	2.081	2.101
PLR	2.997	3.035
LMR	5.761	5.851
PNI	3.503	3.548
pTNM	5.120	14.352
IPS	12.562	13.449

Abbreviations: GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic Nutritional Index; pTNM, pathological tumor-node-metastasis; IPS, inflammation-based pathological stage.

hepatocellular carcinoma.[36] Consistent with their conclusion, Wu et al stated that a high LMR may predict favorable OS and RFS in surgically treated HCC patients.[37] In our study, we demonstrated for the first time that patients with increased pretreatment LMR (≥3.62) exhibited longer overall survival after hepatectomy for ICC. To the best of our knowledge, the prognostic performance of all these established inflammation-based prognostic scores has never been studied in a comparative fashion in intrahepatic cholangiocarcinoma. Our study not only confirmed the prognostic value of the GPS, mGPS, NLR, PLR, PNI, LMR and the PI but also highlighted the prominent prognostic value of LMR for operable ICC patients.

Components of these inflammation-based prognostic scores included in the present study comprise majority of the immune cells. Both innate and acquired immune cells play critical roles in the initiation, invasive growth and metastasis of cancer. Innate immune cells including macrophages, neutrophils, and mast cells are largely responsible for inflammatory reactions.[38] In tumor sites, macrophages (and monocytes) create an inflammatory environment that is mutagenic and growth-promoting during tumor initiation. As tumors progress, they promote angiogenesis, enhance tumor cell migration, invasion and suppression of anti-tumor immunity.[39] Macrophages at the tumor periphery can also foster local invasion by supplying matrix-degrading enzymes such as metalloproteinases and cysteine cathepsin proteases.[18]

The adaptive immune cells (B and T cells), however, can be tumor-suppressing. They carry out cancer immunosurveillance, recognize transformed cells and destroy them, resulting in a return to normal physiological tissue.[40] A major subset of tumors shows evidence of a T cell–infiltrated phenotype. The presence of activated CD8+ T cells both within the tumor and in the peritumor microenvironment has been reported to indicate positive prognosis.[41,42] Therefore, it is conceivable that higher LMR, as a compound outcome of increased peripheral blood lymphocytes and diminished monocytes, indicates favorable prognosis.

Clinicopathological predictors have proved to be suboptimal in identifying high-risk patients. But recent evidence underscored the discriminatory power of combined

Table 7 Clinicopathtological characteristics of the patients grouped according to IPS in the training cohort

Variable	IPS I (n=32)	IPS II (n=45)	IPS III (n=46)	*P*-value
Age (yr), (<65/≥65)	25/7	34/11	31/15	0.268
Gender (Male/Female)	17/15	22/23	26/20	0.692
ALP (IU/L, <135/≥135)	28/4	38/7	30/16	0.012
Total serum bilirubin (mg/dL, ≤20/>20)	28/4	40/5	38/8	0.477
CA19-9 (U/ml, ≤37/>37)	16/16	22/23	18/28	0.307
CEA (ng/ml, ≤5/>5)	26/6	37/8	27/19	0.014
HBsAg or HCV (positive/negative)	19/13	11/34	16/30	0.070
Liver cirrhosis (absent/present)	25/7	42/3	38/8	0.810
Microscopic vascular invasion (absent/present)	32/0	37/8	26/20	<0.001
Differentiation (well+moderate/poor)	29/3	36/9	39/7	0.602
GPS (0/1+2)	30/2	31/14	33/13	0.048
Modified GPS (0/1+2)	31/1	33/12	34/12	0.026

Abbreviations: ALP, alkaline phosphatase; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; GPS, Glasgow rognostic score; mGPS, modified glasgow prognostic score; IPS, inflammation-based pathological stage.

prognostic index of the clinicopathological predictors like staging systems and the inflammation based indices. Pinato et al proposed a new prognostic score based on a combination of mGPS and CLIP scores. They found that the predictive accuracy of the combined score (c score 0.7, 95% CI 0.6–0.8) appeared to be superior to that of the CLIP score alone (c score 0.6, 95% CI 0.5–0.7).[43] Kinoshita and co-workers also elucidated that when GPS was combined with the CLIP system to form a new prognostic system, named inflammation-based CLIP, better prognostic accuracy was achieved compared to GPS or CLIP alone.[44] Unlike hepatocellular carcinoma, there are barely established staging systems for ICC. The most commonly used staging system for ICC is the TNM classification system. In this study, we verified the prognostic power of the inflammation-based pathological stage (IPS). It seems that the IPS is superior to the pTNM staging system and the inflammation-based indices alone in terms of discriminatory power (large differences in prognosis between different stages), homogeneity (small differences in prognosis between patients in the same stage) and monotonicity (mortality of patients increased significantly with the increase of staging). Kaplan–Meier curve revealed that patients with advanced IPS stages, even in the same pTNM stage of ICC when undergoing operation, got inferior overall survival rates. The stratification of prognosis according to the IPS stages was definitive, which totally outperformed the traditional pTNM staging system. In addition, IPS scores were strongly linked to tumor markers including ALP, CEA, and aggressive pathological characteristics like microscopic vascular invasion, all of which reflect poor prognosis. This indicates that more intense follow-up or prophylactic postoperative treatment such as chemotherapy, radiotherapy and transcatheter arterial chemoembolization (TACE) is needed for patients with advanced IPS stages.

In summary, this study reveals that the GPS, mGPS, NLR, PLR, PNI, LMR and the PI possess high prognostic value for OS in operable ICC. LMR was identified as the only independent predictor of OS among those inflammation-based scores. Besides, a novel and powerful inflammation-based prognostic index termed the IPS was established. Given the retrospective, small size and single institution-based nature of this study, certain limitations regarding this prognostic analysis should be acknowledged. Therefore, the findings of this study should be independently validated through prospective multicentric large cohort studies in the future.

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Disclosure

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Supplemantary materials

Table S1 Comparison of the AUC between between inflammation-based prognostic scores in the validation cohort

	Overall survival AUC	Sensitivity	Specificity
12-Month			
GPS	0.584	0.379	0.788
mGPS	0.597	0.345	0.848
PI	0.612	0.414	0.803
NLR	0.575	0.483	0.667
PLR	0.552	0.483	0.621
LMR	0.598	0.621	0.576
PNI	0.602	0.552	0.652
pTNM	0.728	0.862	0.500
IPS	0.737	0.690	0.682
18-Month			
GPS	0.608	0.395	0.825
mGPS	0.630	0.368	0.895
PI	0.655	0.447	0.860
NLR	0.623	0.526	0.719
PLR	0.575	0.500	0.649
LMR	0.645	0.658	0.632
PNI	0.596	0.526	0.667
pTNM	0.657	0.763	0.491
IPS	0.713	0.632	0.702
24-Month			
GPS	0.571	0.341	0.804
mGPS	0.598	0.318	0.882
PI	0.617	0.386	0.843
NLR	0.570	0.455	0.686
PLR	0.541	0.455	0.627
LMR	0.621	0.614	0.627
PNI	0.562	0.477	0.647
pTNM	0.677	0.750	0.510
IPS	0.717	0.614	0.725

Abbreviations: AUC, the area under the receiver operating characteristics curve; CI, confidence interval; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil to lymphocyte ratio; PLR, platelet (Plt)to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic Nutritional Index; pTNM, pathological tumor-node-metastasis; IPS, inflammation-based pathological stage.

Table S2 Evaluation of monotonicity and homogeneity of scoring systems in the validation cohort

Prognostic score	Linear trend test (χ^2)	LR test (χ^2)
GPS	0.326	0.703
mGPS	0.994	1.959
PI	3.028	3.533
NLR	1.810	1.852
PLR	0.59	0.60
LMR	4.931	5.041
PNI	0.357	0.361
pTNM	6.684	8.668
IPS	11.588	12.008

Abbreviations: GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; PI, Prognostic Index; NLR, neutrophil to lymphocyte ratio; PLR, platelet (Plt)to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PNI, Prognostic Nutritional Index; pTNM, pathological tumor-node-metastasis; IPS, inflammation-based pathological stage.

Table S3 Clinicopathtological characteristics of the patients grouped according to the IPS in the validation cohort

Variable	IPS I (n=22)	IPS II (n=32)	IPS III (n=41)	*P*-value
Age (yr), (<65/≥65)	12/10	20/12	24/17	0.871
Gender (Male/Female)	15/7	19/13	25/16	0.663
ALP(IU/L, <135/≥135)	22/0	25/7	28/13	0.005
Total serum bilirubin(mg/dL, ≤20/>20)	21/1	29/3	33/8	0.070
CA199 (U/ml, ≤37/>37)	15/7	12/20	19/22	0.236
CEA (ng/ml, ≤5/>5)	20/2	24/8	27/14	0.035
HBsAg or HCV (positive/negative)	9/13	11/21	12/29	0.357
Liver cirrhosis(absent/present)	17/5	23/9	34/7	0.447
Microscopic vascular invasion (absent/present)	22/0	27/5	31/10	0.015
Differentiation (well+moderate/poor)	19/3	25/7	34/7	0.892
GPS (0/1+2)	20/2	25/7	25/16	0.008
Modified GPS (0/1+2)	21/1	26/6	28/13	0.012

Abbreviations: ALP, alkaline phosphatase; GGT, Gamma Glutamyl Transferase; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; IPS, inflammation-based pathological stage.

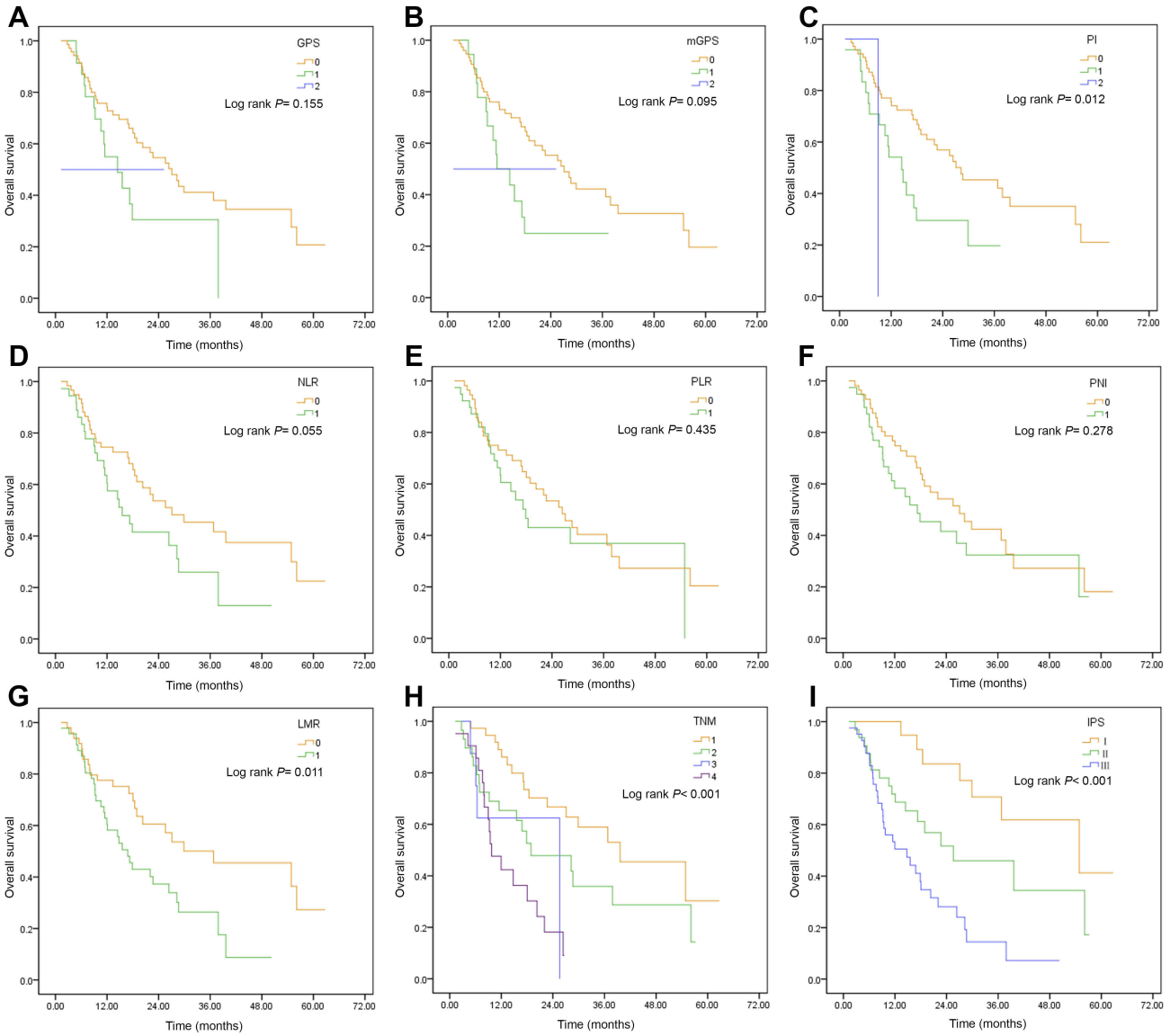

Figure S1 Kaplan–Meier overall survival curves for ICC patients undergoing curative hepatectomy stratified by inflammation-based prognostic scores and staging systems in the validation cohort. (**A**) GPS; (**B**) mGPS; (**C**) PI; (**D**) NLR; (**E**) PLR; (**F**) PNI; (**G**) LMR; (**H**) pTNM; (**I**) IPS.