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Construction and validation of a novel liver function-tumor burden-inflammation-nutrition (LTIN) score for HCC patients underwent hepatectomy

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Abstract

Objective Liver function, tumor burden, inflammation level, and nutritional status are critical factors influencing tumor onset, progression, and metastasis. This study sought to investigate the prognostic significance and clinical relevance of biomarkers associated with these factors to develop a novel liver function-tumor burden-inflammation-nutrition (LTIN) score for patients with hepatocellular carcinoma (HCC) who received hepatectomy.

Methods A retrospective analysis was conducted on 285 patients with HCC undergoing hepatectomy at two medical centers between July 2019 and July 2023. The patients were divided into a training set ($n=200$) and a validation set ($n=85$). The study evaluated the prognostic significance of eight relevant clinical indicators and developed an LTIN score using Least Absolute Shrinkage and Selection Operator (LASSO) regression. Kaplan-Meier survival curves and multivariate Cox regression analysis were utilized to determine the prognostic value of the LTIN score. Time-dependent receiver operating characteristic (ROC) analyses were used to compare the predictive performance of various prognostic factors.

Results The LTIN score, derived from the albumin-bilirubin (ALBI) grade, tumor burden score (TBS), prognostic nutritional index (PNI), and prognostic inflammatory index (PII), effectively classified patients into high- and low-risk groups based on the optimal cut-off value. Patients with low-risk scores exhibited significantly better overall survival (OS) and recurrence-free survival (RFS) than those with high-risk groups in both the training and validation sets ($P<0.001$). Furthermore, the LTIN score was identified as a significant independent prognostic factor for both OS ($P<0.001$) and RFS ($P<0.001$). The LTIN score also exhibited superior prognostic capabilities compared to the other indicators, Tumor-Node-Metastasis (TNM) staging system, and Barcelona Clinic Liver Cancer (BCLC) staging system.

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Conclusion Our findings indicated that the preoperative LTIN score has significant potential as a reliable predictor of OS and RFS for HCC patients underwent radical surgery. The LTIN score could further effectively guide treatment decisions and optimize follow-up strategies to enhance patients prognosis.

Keywords Hepatocellular carcinoma, Liver function, Tumor burden, Inflammation, Nutrition, Prognosis

Introduction

Hepatocellular carcinoma (HCC) is an aggressive liver malignancy and the third leading cause of cancer-related mortality worldwide [1]. In China, liver cancer ranks fourth in incidence and third in mortality [2]. In the United States, the incidence of liver cancer has been increasing and is associated with a poor prognosis, as evidenced by a 5-year survival rate of just 18% [3]. The global prevalence of liver cancer exceeds 1 million cases annually [4]. For patients with early-stage HCC, surgical resection, liver transplantation, and radiofrequency ablation are the primary curative treatment options [5, 6]. In contrast, for advanced HCC, transarterial chemoembolization (TACE), targeted therapy, and immunotherapy are currently regarded as the most promising therapeutic strategies [7–9]. Despite the implementation of therapeutic interventions, the limited efficacy of radical liver cancer surgery is evident, as indicated by a 5-year survival rate ranging between 50 and 70%, primarily attributed to its high recurrence rate [10]. Therefore, the development of a robust preoperative scoring system is essential to identify patients who are most likely to benefit from surgery and to guide the creation of personalized treatment approaches.

Several commonly used clinicopathological factors, such as tumor size, tumor number, histological grade, multifocality, microvascular invasion (MVI), and individual blood biochemical indicators, are employed for prognosis assessment and risk stratification in HCC patients. However, the prognostic value of these conventional factors for HCC is restricted. Increasing evidence suggests that tumor burden [11, 12], liver function levels [13–16], inflammation levels [17–19], and nutritional status [20–22] are significantly correlated with HCC prognosis. Nonetheless, a single indicator cannot fully represent liver function, tumor characteristics, inflammation, and nutritional status in HCC patients. It remains unclear whether a combination of these factors can address this limitation. Therefore, our research aimed to evaluate various recognized markers and assessments, resulting in the creation of an innovative metric known as the liver function-tumor burden-inflammation-nutrition (LTIN)

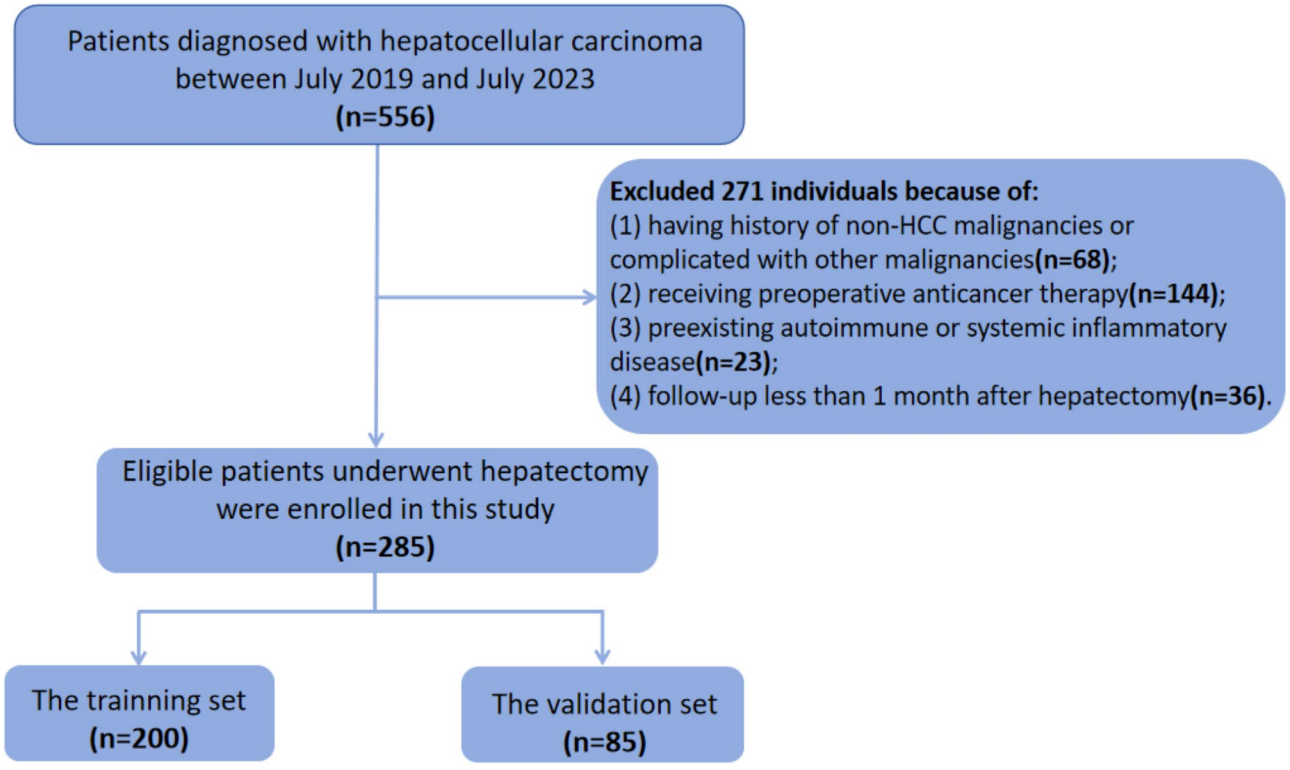

Fig. 1 Patient Selection Flowchart

score. This score combines factors such as liver function, tumor load, inflammation levels, and nutritional status.

Materials and methods

Patients and study design

We conducted a retrospective collection of clinical and pathological data from patients with HCC who underwent radical liver resection at Sichuan Provincial People's Hospital and Sichuan Provincial Cancer Hospital between July 2019 and July 2023. Blood samples and other indicators and imaging evaluation were obtained within one week prior to the surgery. Inclusion criteria for the study were as follows: (1) confirmation of HCC through postoperative histopathological evaluation; (2) age ≥ 18 years; (3) the patient underwent radical surgical resection; (4) no recurrent tumor. Exclusion criteria consisted of: (1) having history of non-HCC malignancies or complicated with other malignancies; (2) preexisting autoimmune or systemic inflammatory disease; (3) receiving preoperative anticancer therapy; (4) follow-up less than 1 month after hepatectomy. Curative hepatectomy was defined as complete removal of all macroscopic tumors with negative surgical margins on microscopy and there is no invasion to adjacent organs or lymphatic and distant metastasis [23]. Ultimately, A total of 285 patients who met the eligibility criteria were included in the study. 200 patients were from Sichuan Provincial People's Hospital, constituting the training set, and 85 patients were from Sichuan Cancer Hospital, constituting the validation set. The study protocol was designed in accordance with the ethical principles outlined in the Helsinki Declaration. Written informed consent was obtained from each participant or their legal guardian.

Follow up

Survival data were gathered through outpatient visits and follow-up calls every three months in the first year after surgery. If no recurrence or metastasis occurred, follow-ups were scheduled every six months thereafter. The primary outcome was overall survival (OS), which was defined as the period from the date of curative surgery to either death, loss to follow-up, or the conclusion of the follow-up period (July 2024), whichever occurred first. The secondary outcome was recurrence-free survival (RFS), defined as the time interval from the date of curative surgery until recurrence, loss to follow-up, or the end of follow-up (July 2024), whichever occurred earlier.

Clinical variables

The clinical and pathological data collected from patients encompassed several variables, including gender, age, body mass index (BMI), hepatitis B virus infection (HBV), Barcelona Clinic Liver Cancer (BCLC) staging, liver function grade, degree of cirrhosis, maximum tumor diameter, tumor quantity, tumor differentiation, MVI, and Portal Vein Tumor Thrombosis (PVTT). In addition, laboratory tests were performed one week before surgery, which included measurements of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), albumin, bilirubin, neutrophil count, monocyte count, lymphocyte count, and platelet count.

From the clinical variables, we derived eight indicators that are associated with tumor morphology, immune function, inflammatory levels, and nutritional status. These indicators encompass albumin-bilirubin (ALBI) grade, tumor burden score (TBS), prognostic nutritional index (PNI), prognostic inflammatory index (PII), systemic immune inflammation index (SII), neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR).

Construction of LTIN score

Kaplan-Meier survival analysis and univariate Cox regression were used to identify biomarkers linked to the prognosis of HCC patients. A *P*-value of less than 0.05 was regarded as statistically significant and justified further investigation. The variables corresponding to the eight indicators were selected using the Least Absolute Shrinkage and Selection Operator (LASSO) regression model. Following this, the LTIN score was calculated using the coefficients derived from the LASSO regression analysis.

Statistical analysis

The clinical and pathological data from 200 cases of HCC patients were utilized as the training set. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For normally distributed variables, Student's t-test was used, with results presented as mean ± standard deviation (SD). For non-normally distributed variables, the Mann-Whitney U test was employed, with results shown as median (interquartile range, IQR). The baseline characteristics of the patient were analyzed using the Pearson chi-square test or Fishers exact test. Survival curves were generated using the Kaplan-Meier method, with differences assessed by the log-rank test. Cox proportional hazards model were used for univariate and multivariate analysis. Additionally, time-dependent receiver operating characteristic (ROC) curves were utilized to assess the prognostic accuracy of the LTIN score for OS. All statistical analyses were conducted using IBM SPSS software (version 26.0), while LASSO regression, predictive model construction and evaluation, and data visualization were carried out using R software (version 4.2.1).

Table 1 Comparison of clinicopathological characteristics in the training and validation sets

Characteristics	All patients (*N* = 285)	Training set (*N* = 200)	Validation set (*N* = 85)	*P* value
Gender				0.650
Male	244 (85.6%)	170 (85%)	74 (87.1%)	
Female	41 (14.4%)	30 (15%)	11 (12.9%)	
Age, years	57 (50,65)	56 (49,66)	59 (54,63)	0.475
BMI, kg/m^2	22.52 (20.82,24.59)	22.36 (20.70,24.03)	23.53 (21.37,25.07)	0.061
Etiology of HCC				0.182
HBV	243(85.3%)	177(88.5%)	66(77.6%)	
Others	42(14.7%)	23(11.5%)	19(22.4%)	
ALB, g/L	38.72 (34.42,40.91)	37.40 (33.08,40.00)	40.10 (37.95,42.45)	0.742
LYM, $10^9/L$	1.33 (0.99,1.74)	1.27 (0.96,1.77)	1.40 (1.03,1.71)	0.421
NEUT, $10^9/L$	3.23 (2.27,4.31)	3.36 (2.24,4.60)	3.02 (2.47,3.96)	0.447
MONO, $10^9/L$	0.42 (0.31,0.56)	0.46 (0.35,0.62)	0.39 (0.27,0.52)	0.323
AFP, ng/mL	18.62 (3.93,343.16)	28.00 (4.07,447.49)	9.25 (3.69,225.93)	0.358
CEA, ng/mL	2.50 (1.68,3.40)	2.51 (1.72,3.42)	2.42 (1.45,3.42)	0.235
NLR	2.34 (1.66,3.42)	2.32 (1.67,3.62)	2.39 (1.54,3.25)	0.764
PLR	100.62 (68.27,145.68)	104.98 (67.96,150.27)	93.48 (69.15,130.25)	0.205
SII	297 (182.14,512.70)	321.85 (178.81,539.63)	277.98 (187.61,448.24)	0.382
PII	0.97 (0.60,1.74)	1.14 (0.63,1.97)	0.95 (0.52,1.74)	0.163
PNI	45.40 (40.50,49.40)	44.29 (39.15,48.23)	47.15 (44.25-,50.03)	0.435
TBS	5.49 (3.64,8.25)	6.08 (4.12,9.06)	4.31 (3.35,6.06)	0.068
ALBI	−2.49 (−2.72,−2.10)	−2.36 (−2.62,−2.00)	−2.71 (−2.84,−2.49)	0.315
Child-Pugh grade				0.064
A	205 (71.9%)	129 (64.5%)	76 (89.4%)	
B	79 (27.7%)	70 (35%)	9 (10.6%)	
C	1 (0.4%)	1 (0.5%)	0 (0%)	
BCLC stage				0.057
0/A	166 (58.2%)	103 (51.5%)	63 (74.2%)	
B	50 (17.5%)	39 (19.5%)	11 (12.9%)	
C	69 (24.3%)	58 (29%)	11 (12.9%)	
Microvascular invasion				0.123
No	189 (66.3%)	127 (63.5%)	62 (72.9%)	
Yes	96 (33.7%)	73 (36.5%)	23 (27.1%)	
Histopathological type				0.113
Poorly differentiation	49 (17.2%)	39 (19.5%)	10 (11.8%)	
Medium-high differentiation	236 (82.8%)	161 (80.5%)	75 (88.2%)	
Cirrhosis				0.155
No	87 (30.5%)	56 (28%)	31 (36.5%)	
Yes	198 (69.5%)	144 (72%)	54 (63.5%)	
PVTT				0.612
No	247 (86.7%)	172 (86%)	75 (88.2%)	
Yes	38 (13.3%)	28 (14%)	10 (11.8%)	
Tumor number				0.071
Single	207 (68%)	136 (68%)	71 (83.5%)	
Multiple	78 (32%)	64 (32%)	14 (16.5%)	
Tumor size	5.0 (3.45,8.0)	6.0 (3.5,9.0)	4.0 (3.1,5.85)	0.064
Dead				0.076
No	172 (60.4%)	114 (57%)	58 (68.2%)	
Yes	113 (39.6%)	86 (43%)	27 (31.8%)	
Recurrence				0.106

Table 1 (continued)

Characteristics	All patients (*N* = 285)	Training set (*N* = 200)	Validation set (*N* = 85)	*P* value
No	140 (49.1%)	92 (46%)	48 (56.5%)	
Yes	145 (50.9%)	108 (54%)	37 (43.5%)	

Abbreviations: BMI, Body mass index; HCC, Hepatocellular carcinoma; HBV, Hepatitis B Virus; ALB, Albumin; LYM, Lymphocyte; NEUT, Neutrophil; MONO, Monocyte; AFP, Alpha-fetoprotein; CEA, Carcinoembryonic antigen; TBS, Tumor burden score; ALBI, Albumin bilirubin; PNI, Prognostic nutritional index; SII, Systemic immune inflammation index; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; PII, Prognostic inflammatory index; BCLC, Barcelona Clinic Liver Cancer; PVTT, Portal vein tumor thrombus

Table 2 Abbreviations, definitions and cut-off values of biomarkers

Prognostic indicators and abbreviations	Basis of calculation	Cut-off value
Tumor burden score, TBS	$\sqrt{(\text{Maximum diameter of tumor}^2 + \text{Number of tumors}^2)}$	9.8
Albumin bilirubin, ALBI	log10(Tbil(mol/L))*0.66-Alb(g/L)*0.085	−2.14
Prognostic nutritional index, PNI	Alb(g/L)+5*LY(10^9 /L)	44.4
Systemic immune inflammation index, SII	PLT*NE/LY(10^9 /L)	465
Neutrophil to lymphocyte ratio, NLR	NE/LY(10^9 /L)	2.54
Platelet to lymphocyte ratio, PLR	PLT/LY(10^9 /L)	156
Lymphocyte to monocyte ratio, LMR	MO/LY(10^9 /L)	3.3
Prognostic inflammatory index, PII	NE*MO/LY(10^9 /L)	1.74

Abbreviations: Tbil, Total bilirubin; Alb, Albumin; LY, Lymphocyte; PLT, Platelet; NE, Neutrophil; MO, Monocyte

Results

Classification of patient characteristics and prognostic indicators

This study involved HCC patients who underwent radical surgical resection. The process screening flow chart for including patients is shown in Fig. 1. The mean age of the patients was 57 years (50–65 years), with 244 males (85.6%) and 41 females (14.4%). The median follow-up duration was 15 months (range:9–24 months), and at the end of the follow-up, 145 patients experienced tumor recurrence (108 patients in the training set and 37 patients in the validation set) and 113 patients died (86 patients in the training set and 27 patients in the validation set). Correlation analyses of clinical baseline characteristics and pathological features in both the training set ($n = 200$) and validation set ($n = 85$) showed a comparable distribution between the two groups ($P < 0.05$, Table 1). Prognostic indicators included ALBI, NLR, PLR, LMR, PII, PNI, SII, and TBS. Additionally, X-tile software was utilized to calculate the optimal cut-off values for each indicator, with specific classifications and calculation formulas presented in Table 2

Survival analysis of LTIN score

Univariate Cox regression analysis indicated that OS was significantly correlated with eight indicators ($P < 0.05$, Fig. 2A), and Kaplan-Meier survival analysis revealed low TBS, PII, SII, ALBI, NLR, and PLR grades, as well as high PNI and LMR, which were significantly associated with improved OS and RFS ($P < 0.05$, Figs. 3 and 4). Subsequently, LASSO regression analysis of these eight indicators demonstrated that ALBI, TBS, PNI, and PII were significantly correlated with OS (Fig. 2B and C). Using the coefficients obtained from LASSO regression analysis, we developed the LTIN score as: risk score = 0.828 + 0.059 x ALBI + 0.05 x TBS − 0.017 x PNI − 0.029 x PII. We categorized LTIN scores into low-risk group (≤ 0.26) and high-risk group (> 0.26) and further investigated the correlation between LTIN score and clinicopathological features in the training and validation sets. The results showed a significant correlation between LTIN score, Child Pugh grade, BCLC stage, and PVTT (Table 3). The Kaplan-Meier curves demonstrated that the low-risk group based on the LTIN score had significantly improved OS and RFS outcomes compared to the high-risk group ($P < 0.001$, Fig. 5A and D). Comparative analysis of the predictive value for prognosis indicated that the LTIN score had a significantly higher area under the curve (AUC) than any of the individual indicators alone (Fig. 5E and F). We also compared the LTIN score prediction model with commonly used Tumor-Node-Metastasis (TNM) staging system, BCLC staging system, and serum biomarkers such as AFP and CEA. The comparative analysis of prognostic prediction values showed that the AUC of LTIN score is significantly higher than the models and biomarkers mentioned above (Supplementary Fig. 1).

In addition, time-dependent ROC curves of OS over 1 to 3 years were plotted using LTIN scores from both the training and validation sets. The 1-, 2- and 3-year AUC values obtained were 0.914, 0.903, and 0.890 for the training set, and 0.886, 0.863, and 0.773 for the validation set, respectively (Fig. 5G and H). Moreover, in the training set, we conducted univariate and multivariate Cox regression analyses to assess the impact of various clinical and pathological features along with the LTIN

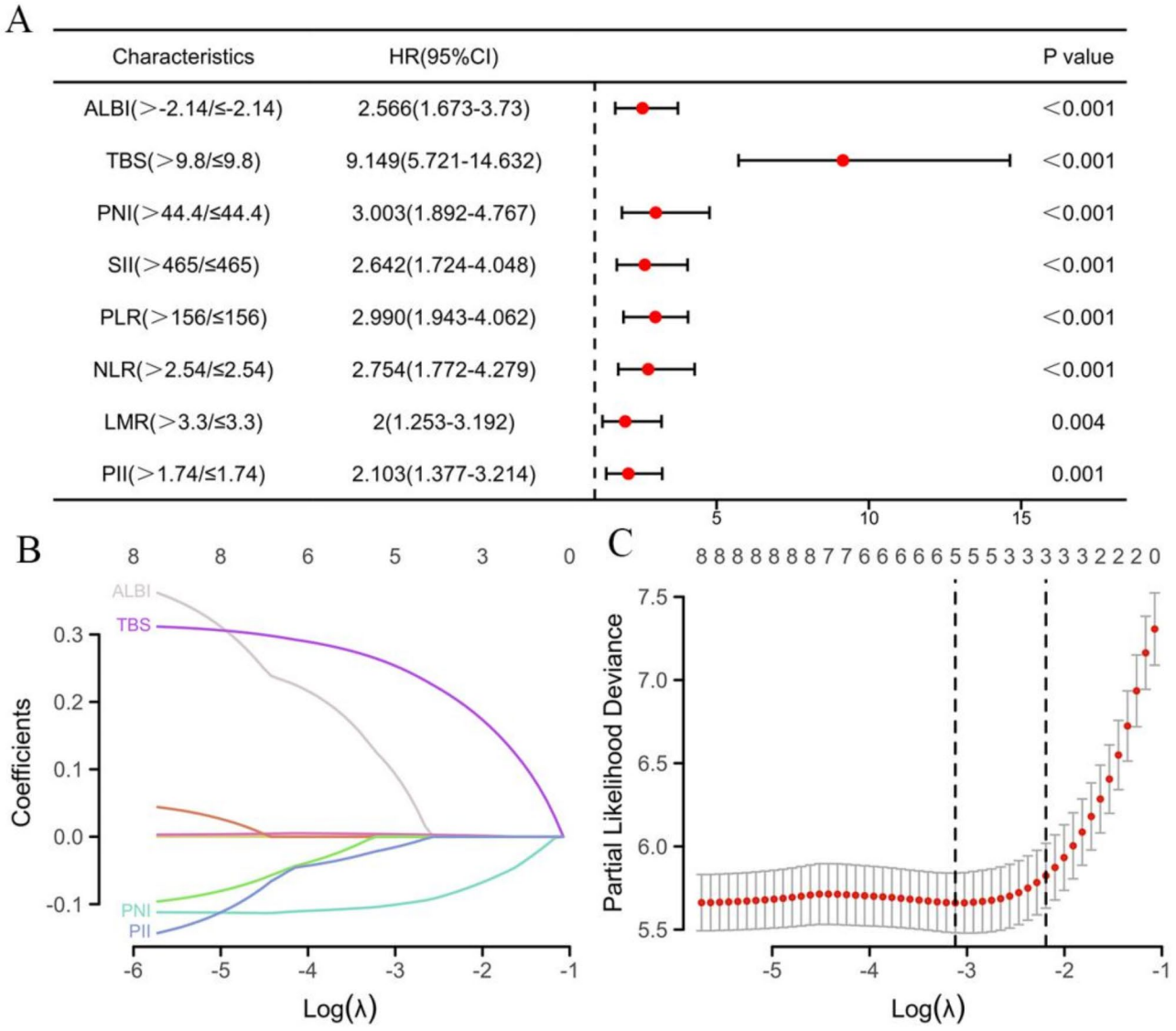

Fig. 2 The LTIN score was constructed using the LASSO Cox regression model. (**A**) Forest plot of the univariate Cox regression analysis for OS of the training set. (**B**) Partial likelihood deviance for LASSO coefficient profiles. (**C**) LASSO coefficient profiles of 8 biomarkers. The red dots indicate the values of partial likelihood, while the grey lines represent the standard error. and the vertical dotted line shows the optimal values by 1-s.e. Abbreviations: LTIN, Liver function-tumor burden-inflammation-nutrition; LASSO, Least absolute shrinkage and selection operator; OS, Overall survival; TBS, Tumor burden score; ALBI, Albumin bilirubin; PNI, Prognostic nutritional index; SII, Systemic immune inflammation index; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; PII, Prognostic inflammatory index; LMR, lymphocyte to monocyte ratio; HR, Hazard ratio

score as an independent risk factor on OS (*HR* = 14.31, 95% *CI* = 7.77–26.39, *P* < 0.001) and RFS (*HR* = 7.93, 95% *CI* = 4.92–12.78, *P* < 0.001) (Table 4). Internal validation involves analyzing the consistency index of the training set to calculate the discrimination between the predicted values of the Cox model in survival analysis and the true values, which is commonly used to evaluate the prediction accuracy of patient prognosis models. In this study, clinical data from 200 patients from Sichuan Provincial People's Hospital formed the training set. The Concordance index (C-index) analysis of the LTIN score prediction model was 0.839 (95% *CI* = 0.820–0.857), indicating that the model has good accuracy. In conclusion, the LTIN score showed displayed remarkable prognostic potential as a composite indicator encompassing liver function level, tumor morphology, inflammation level, and nutritional status.

Discussion

Surgical removal is widely accepted as a primary approach for treating HCC globally. Nevertheless, it is crucial to consider patient-specific factors when assessing potential surgical benefits. Extensive research has demonstrated that liver function level, tumor burden,

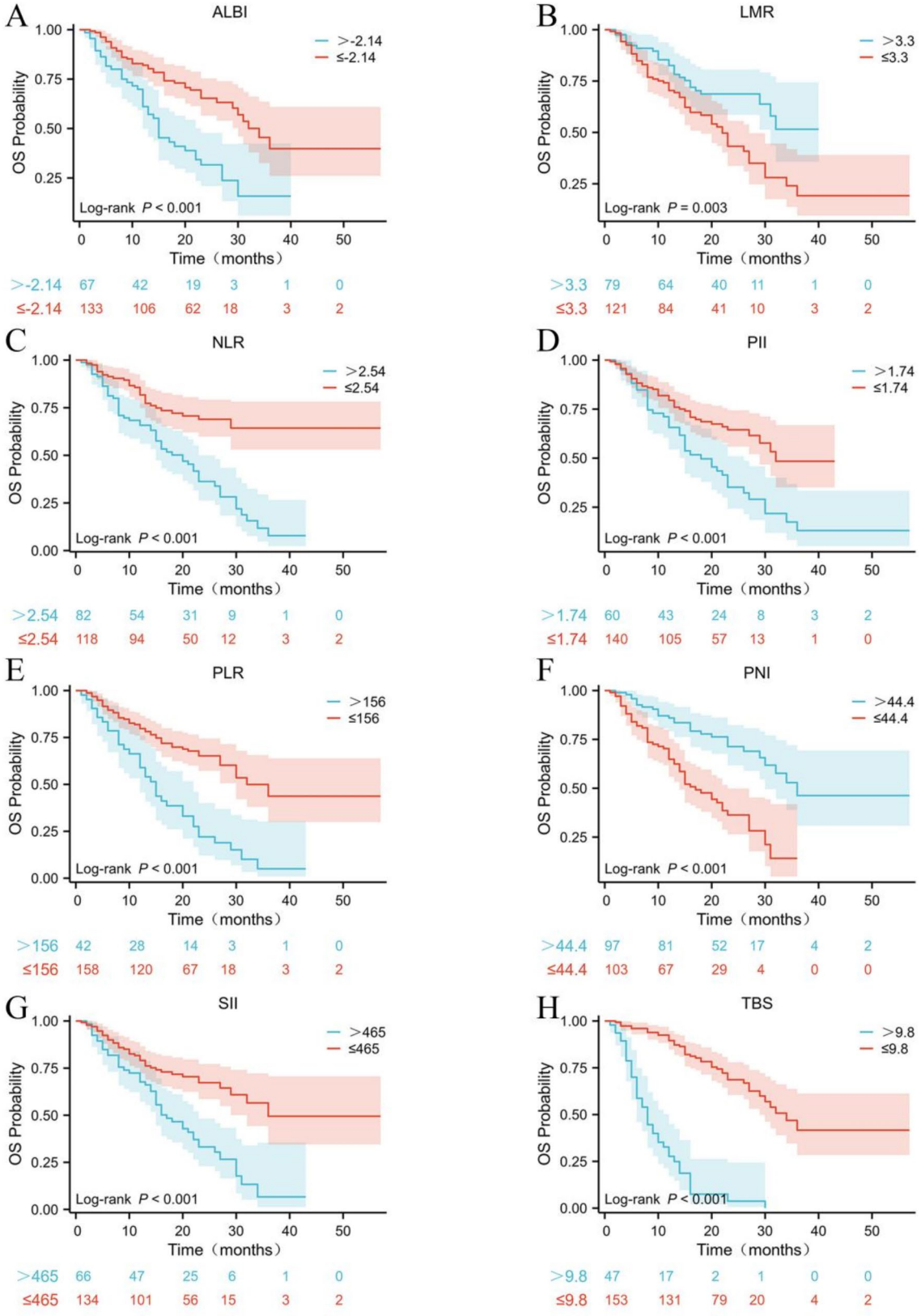

Fig. 3 Kaplan-Meier curves for OS, stratified by (**A**) ALBI, (**B**) LMR, (**C**) NLR, (**D**) PII, (**E**) PLR, (**F**) PNI, (**G**) SII, and (**H**) TBS in patients with HCC. Abbreviations: OS, Overall survival; TBS, Tumor burden score; ALBI, Albumin bilirubin; PNI, Prognostic nutritional index; SII, Systemic immune inflammation index; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; PII, Prognostic inflammatory index; LMR, lymphocyte to monocyte ratio; HCC, Hepatocellular carcinoma

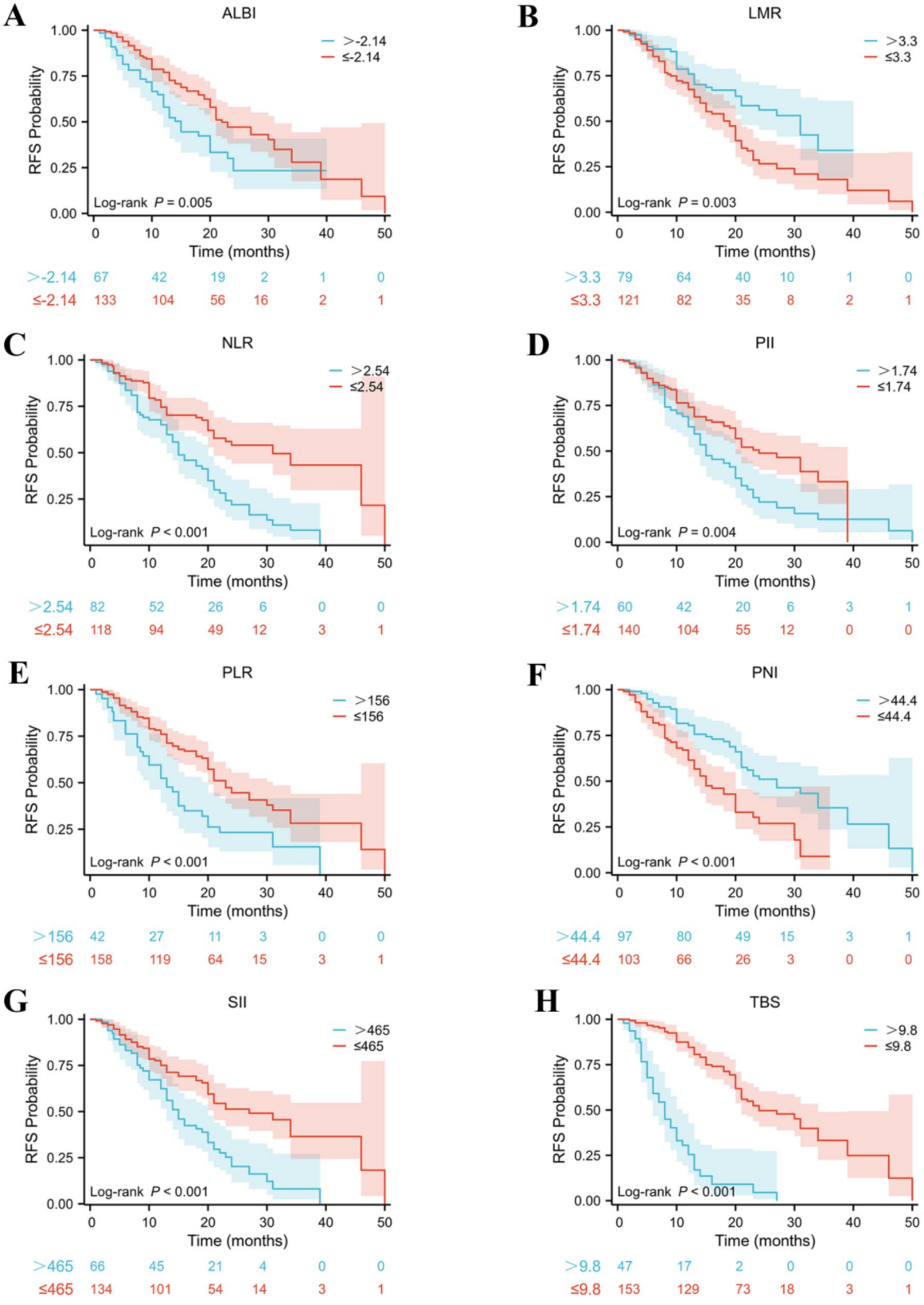

Fig. 4 Kaplan-Meier curves for RFS, stratified by (**A**) ALBI, (**B**) LMR, (**C**) NLR, (**D**) PII, (**E**) PLR, (**F**) PNI, (**G**) SII, and (**H**) TBS in patients with HCC. Abbreviations: RFS, Recurrence-free survival; TBS, Tumor burden score; ALBI, Albumin bilirubin; PNI, Prognostic nutritional index; SII, Systemic immune inflammation index; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; PII, Prognostic inflammatory index; LMR, Lymphocyte to monocyte ratio; HCC, Hepatocellular carcinoma

Table 3 Relationship of the LTIN score with clinicopathological characteristics of HCC after radical resection in the training and validation sets

	Training set			Validation set		
Characteristics	**Low risk($n=119$)**	**High risk($n=81$)**	***P* value**	**Low risk($n=68$)**	**High risk($n=17$)**	***P* value**
Gender			0.250			0.076
Male	104(87.4%)	66(81.5%)		57(83.8%)	17(100%)	
Female	15(12.6%)	15(18.5%)		11(16.2%)	0(0%)	
Age, years			0.685			0.084
< 65	84(70.6%)	55(67.9%)		51(75%)	16(94.1%)	
≥ 65	35(29.4%)	26(32.1%)		17(25%)	1(5.9%)	
HBV infection			0.553			0.241
Yes	104(87.4%)	73(90.1%)		51(75%)	15(88.2%)	
No	15(12.6%)	8(9.9%)		17(25%)	2(11.8%)	
AFP, ng/mL			0.757			**0.028**
< 20	57(47.9%)	37(45.7%)		44(64.7%)	6(35.3%)	
≥ 20	62(52.1%)	44(54.3%)		24(35.3%)	11 (64.7%)	
CEA, ng/mL			0.257			0.860
< 5	110(92.4%)	71(87.7%)		61(89.7%)	15(88.2%)	
≥ 5	9(7.6%)	10(12.3%)		7(10.3%)	2(11.8%)	
Child-Pugh grade			**< 0.001**			**0.043**
A	93 (78.2%)	36 (44.4%)		63(92.6%)	13(76.5%)	
B/C	26 (21.8%)	45 (55.6%)		5(7.4%)	4(23.5%)	
BCLC stage			**0.026**			**< 0.001**
0/A	69 (58%)	34 (42%)		59(86.8)	4(23.5%)	
B/C	50 (42%)	47 (58%)		9(13.2%)	13(76.5%)	
Microvascular invasion			0.185			0.143
No	80 (67.2%)	47 (58%)		52(76.5%)	10(58.8%)	
Yes	39 (32.8%)	34 (42%)		16(23.5%)	7(41.2%)	
Cirrhosis			0.827			0.499
No	34 (28.6%)	22 (27.2%)		26(38.2%)	5(29.4%)	
Yes	85 (71.4%)	59 (72.9%)		42(61.8%)	12(70.6%)	
PVTT			**0.006**			**0.042**
No	109 (91.6%)	63 (77.8%)		62(91.2%)	13(76.5%)	
Yes	10 (8.4%)	18 (22.2%)		6(8.8%)	4(23.5%)	
Tumor number			0.521			**< 0.001**
Single	83 (69.7%)	53 (65.4%)		63(92.6%)	8(47.1%)	
Multiple	36 (30.3%)	28 (34.6%)		5(7.4%)	9(52.9%)	
Histopathological type			0.661			0.092
Poorly differentiation	22 (18.5%)	17 (21%)		6(8.8%)	4(23.5%)	
Medium-high differentiation	97 (81.5%)	64 (79%)		62(91.2%)	13(76.5%)	
Postoperative adjuvant therapy			0.584			0.896
No	87 (73.1%)	62 (76.5%)		53 (77.9%)	13 (76.5%)	
Yes	32 (26.9%)	19 (23.5%)		15 (22.1%)	4 (23.5%)	
Dead			**< 0.001**			**< 0.001**
No	92(77.3%)	22(27.2%)		56(82.4%)	2(11.8%)	
Yes	27(22.7%)	59(72.8%)		12(17.6%)	15(88.2%)	
Recurrence			**< 0.001**			**< 0.001**
No	72(60.5%)	20(24.7%)		48(70.6%)	0(0%)	
Yes	47(39.5%)	61(75.3%)		20(29.4%)	17(100%)	

Abbreviations: LTIN, Liver function-tumor burden-inflammation-nutrition; HCC, Hepatocellular carcinoma; HBV, Hepatitis B Virus; AFP, Alpha-fetoprotein; CEA, Carcinoembryonic antigen; BCLC, Barcelona Clinic Liver Cancer; PVTT, Portal vein tumor thrombus

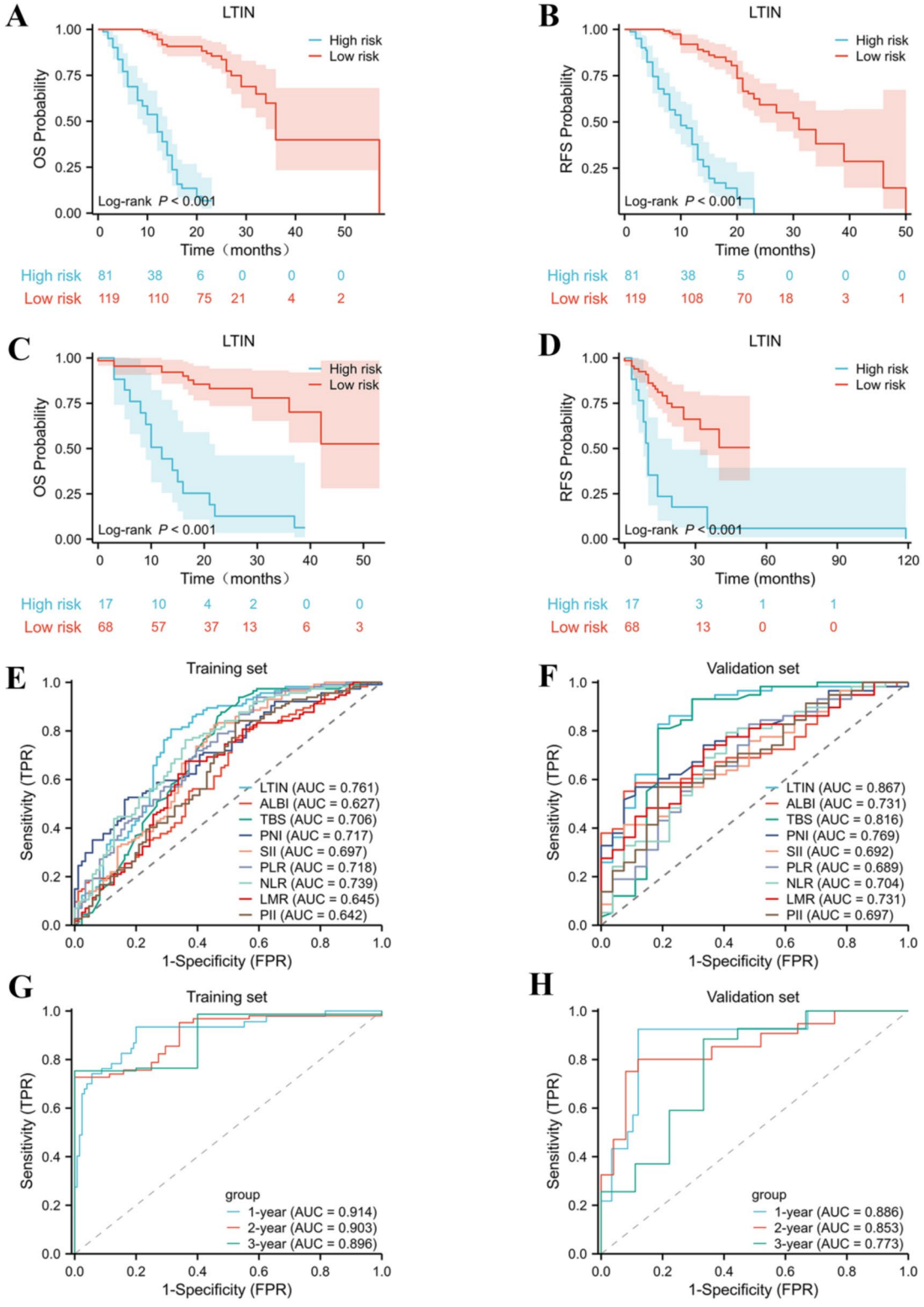

Fig. 5 Prognostic implications of the LTIN score. Kaplan-Meier curves of OS (**A**) and RFS (**B**) for patients in the low-and high-risk groups according to the LTIN score in the training set. Kaplan-Meier curves of OS (**C**) and RFS (**D**) for patients in the low-and high-risk groups according to the LTIN score in the validation set. Comparison of the predictive performance of LTIN score and 8 biomarkers in the training set (**E**) and validation set (**F**). The ROC curves for predicting OS at 1-, 2-, and 3 years in the training set (**G**) and the validation set (**H**). Abbreviations: LTIN, Liver function-tumor burden-inflammation-nutrition; OS, Overall survival; RFS, Recurrence-free survival; ROC, Receiver operating characteristic; TBS, Tumor burden score; ALBI, Albumin bilirubin; PNI, Prognostic nutritional index; SII, Systemic immune inflammation index; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; PII, Prognostic inflammatory index; LMR, Lymphocyte to monocyte ratio; AUC, Area under the curve

Table 4 Univariate and multivariate analyses of the prognosis for HCC after radical resection in the training set

	RFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
Characteristics	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥ 65 vs.<65	1.222 (0.813–1.835)	0.335			1.131(0.716–1.786)	0.597		
Sex (Male vs. Female)	1.174 (0.699–1.974)	0.544			1.077 (0.597–1.945)	0.804		
Child-Pugh grade (A vs. B-C)	2.041 (1.380–3.019)	**< 0.001**	1.267 (0.840–1.911)	0.259	2.686 (1.749–4.125)	**< 0.001**	1.459 (0.932–2.283)	0.098
BCLC Stage (0-A vs. B-C)	1.377 (0.941–2.017)	0.100			1.392 (0.910–2.129)	0.127		
Tumor number (Single vs. Multiple)	1.209 (0.812-1.800)	0.351			1.039 (0.661–1.634)	0.867		
Microvascular invasion (Negative vs. Positive)	1.440 (0.976–2.125)	0.066			1.541 (1.004–2.365)	**0.048**	1.573 (1.016–2.436)	**0.042**
AFP, ng/ml ≥ 20 vs.<20	1.137 (0.775–1.668)	0.511			1.124 (0.733–1.725)	0.591		
CEA, ng/mL ≥ 5 vs.<5	1.039 (0.541–1.998)	0.908			1.211 (0.606–2.422)	0.588		
Histopathological type (Low vs. Medium-high)	0.805 (0.509–1.271)	0.352			0.800 (0.483–1.324)	0.385		
Cirrhosis (No vs. Yes)	0.793 (0.525–1.198)	0.271			0.981 (0.610–1.576)	0.936		
PVTT (No vs. Yes)	1.457 (0.840–2.562)	0.181			1.677 (0.941–2.990)	0.079		
HBV infection (No vs. Yes)	1.035 (0.587–1.826)	0.906			1.019 (0.539–1.925)	0.954		
LTIN (High vs. Low risk)	8.420 (5.303–13.368)	**< 0.001**	7.932 (4.923–12.779)	**< 0.001**	15.470 (8.614–27.282)	**< 0.001**	14.313 (7.771–26.363)	**< 0.001**

Abbreviations: HCC, Hepatocellular carcinoma; RFS, Recurrence-free survival; OS, Overall survival; HR, Hazard ratio; CI, Confidence interval; HBV, Hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; AFP, Alpha-fetoprotein; CEA, Carcinoembryonic antigen; PVTT, Portal vein tumor thrombus; LTIN, Liver function-tumor burden-inflammation-nutrition

inflammation level, and nutritional status all contribute to determining prognosis in individuals diagnosed with HCC via various mechanisms. This investigation aimed to develop a reliable prognostic indicator called LTIN score specifically tailored for post-hepatectomy HCC patients. Our findings indicated that individuals with lower LTIN scores experienced significantly improved OS and RFS compared to those with higher LTIN scores. Moreover, high LTIN scores were identified as an independent risk factor influencing clinical outcomes among HCC patients treated surgically. After conducting a thorough comparison, it was found that LTIN exhibited superior prognostic capabilities compared to the other indicators, TNM staging system, and BCLC staging system. To the best of our knowledge, this retrospective study stands out as the pioneering effort in identifying the predictive significance of LTIN score among HCC patients who underwent radical hepatectomy.

Based on LASSO regression analysis, LTIN scores were developed by considering four indicators: ALBI, TBS, PNI, and PII. This scoring system offers a comprehensive assessment of liver function, tumor burden, inflammation, and nutritional status. Previous research consistently demonstrated a significant correlation between these four markers and the prognosis of HCC following surgery. High LTIN scores are typically linked to lymphopenia, hypoproteinemia, increased bilirubin levels, a higher number of tumors, and greater maximum tumor diameter, indicating high tumor burden and inflammatory response, as well as impaired liver function and poor nutritional status. Bilirubin and albumin are commonly utilized to assess liver function in HCC patients. HCC often impairs liver function, disrupting the normal metabolism and excretion of bilirubin, which in turn raises total bilirubin levels. Hypoalbuminemia can weaken the systemic immune system, thereby promoting tumor cell proliferation [6]. The ALBI grade is a new tool for evaluating liver function that has been linked to malnutrition and poor prognosis in HCC patients [24–26]. Tumor size and quantity are important staging criteria that strongly influence survival outcomes for individuals with malignant tumors. The TBS integrates tumor size and number, and research suggests it has good predictive value for the prognosis of HCC

patients who undergo hepatic artery chemoembolization, radical resection, or liver transplantation [27–29]. Compared to tumor size and number alone, TBS has demonstrated greater efficacy in predicting postoperative outcomes for HCC patients [30]. Systemic inflammation is closely associated with the growth, invasion, and spread of malignant tumors [31–33]. The PII, which includes neutrophil count, monocyte count, and lymphocyte count, provides a more comprehensive reflection of tumor inflammation levels compared to NLR and LMR. Furthermore, most liver cancers develop in chronically inflamed cirrhotic livers which create an environment conducive to inflammation that supports tumor development and progression [34–36]. Lymphocytes play a crucial role in cell-mediated anti-tumor immune responses, which can inhibit tumor cell proliferation and metastasis. A low lymphocyte count weakens immune surveillance and is linked to unfavorable prognoses across various malignancies [37–39]. The PNI serves as an assessment tool for surgical patients' nutritional status and immune function while also predicting surgical risks and evaluating prognosis. Numerous studies have demonstrated that the PNI can effectively reflect a patient's nutritional status and has significant prognostic value for HCC patients [40–42].

Previous studies have focused on the prediction of early postoperative recurrence (within 1 year) [43–45], while our model is designed to predict long-term outcomes, offering broader clinical applicability and addressing a critical gap in the literature. This study insightfully integrated four representative and clinically accessible indices (ALBI grade, TBS, PNI, and PII) to develop a novel prognostic model. These indices provided valuable information regarding systemic inflammation, nutritional status, and liver function, all of which play pivotal roles in tumor progression and patient prognosis. Moreover, these metrics are cost-effective and readily available from routine preoperative examinations, significantly reducing the economic burden on patients compared to models that rely on postoperative pathological or genetic testing. Our study highlights the role of inflammation and immune-related indicators, which are increasingly recognized as key determinants of cancer prognosis. With the rapid development of tumor immunology, immune-based and cell-based therapies are gaining prominence in the treatment of solid tumors [46, 47], and our findings underscore the potential significance of integrating such factors into prognostic models.

Our research is subject to certain limitations that should be acknowledged. Firstly, the sample size was limited, and all participants were from China. To validate our findings, it is necessary to conduct large-scale prospective studies involving multiple centers. Secondly, being a retrospective study, there is a possibility of selective bias. Lastly, despite efforts made to minimize confounding factors, it may not be possible to completely eliminate the influence of individual differences on the test indicators.

Conclusion

Our findings indicated that the preoperative LTIN score has significant potential as a reliable predictor of OS and RFS for HCC patients underwent radical surgery. The LTIN score could further effectively guide treatment decisions and optimize follow-up strategies to enhance patients prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13867-w.

Supplementary Material 1

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Not applicable.

Author contributions
Yuhao Su and Yuxin Liang was responsible for study conception and design, data acquisition, data analysis and drafting and revision of the manuscript. Xiaolun Huang and Jin Shang were responsible for study conception and design, data analysis and drafting and revision of the manuscript. Deyuan Zhong and Yahui Chen were responsible for data acquisition. Hongtao Yan and Qinyan Yang were responsible for data analysis and drafting and revision of the manuscript. Yuhao Su and Yuxin Liang contribute equally to this manuscript. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in compliance with the ethical principles outlined in the Helsinki Declaration and received approval from the Human Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital and Sichuan Cancer Hospital. All participants provided written consent after being fully informed.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Ganesan P, Kulik LM. Hepatocellular carcinoma: new developments. Clin Liver Dis. 2023;27(1):85–102. https://doi.org/10.1016/j.cld.2022.08.004. Epub 20221018.
2. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and united States, 2022: profiles, trends, and determinants. Chin Med J (Engl). 2022;135(5):584–90. https://doi.org/10.1097/cm9.0000000000002108. Epub 20220209.
3. Siegel RL, Miller KD, Wagle NS, Jemal A, Cancer statistics. 2023. CA Cancer J Clin. 2023;73(1):17–48. https://doi.org/10.3322/caac.21763. PubMed PMID: 36633525.
4. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018;15(10):599–616. https://doi.org/10.1038/s41571-018-0073-4. PubMed PMID: 30061739.
5. Cadier B, Bulsei J, Nahon P, Seror O, Laurent A, Rosa I, et al. Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the united States. Hepatology. 2017;65(4):1237–48. Epub 20170208. https://doi.org/10.1002/hep.28961. PubMed PMID: 28176349.
6. Wang D, Hu X, Xiao L, Long G, Yao L, Wang Z, Zhou L. Prognostic nutritional index and systemic Immune-Inflammation index predict the prognosis of patients with HCC. J Gastrointest Surg. 2021;25(2):421–7. https://doi.org/10.1007/s11605-019-04492-7. Epub 20200205.
7. Song JE, Kim DY. Conventional vs drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma. World J Hepatol. 2017;9(18):808–14. https://doi.org/10.4254/wjh.v9.i18.808. PubMed PMID: 28706579; PubMed Central PMCID: PMCPMC5491403.
8. Baur J, Ritter CO, Germer CT, Klein I, Kickuth R, Steger U. Transarterial chemoembolization with drug-eluting beads versus conventional transarterial chemoembolization in locally advanced hepatocellular carcinoma. Hepat Med. 2016;8:69–74. https://doi.org/10.2147/hmer.S105395. Epub 20160620.
9. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492–502. https://doi.org/10.1016/s0140-6736(17)31046-2. Epub 20170420.
10. Villanueva A, Hoshida Y, Battiston C, Tovar V, Sia D, Alsinet C et al. Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma. Gastroenterology. 2011;140(5):1501-12.e2. Epub 20110212. https://doi.org/10.1053/j.gastro.2011.02.006. PubMed PMID: 21320499; PubMed Central PMCID: PMCPMC3081971.
11. Ho SY, Liu PH, Hsu CY, Huang YH, Liao JI, Su CW et al. A New Tumor Burden Score and Albumin-Bilirubin Grade-Based Prognostic Model for Hepatocellular Carcinoma. Cancers (Basel). 2022;14(3). Epub 20220127. https://doi.org/10.3390/cancers14030649. PubMed PMID: 35158917; PubMed Central PMCID: PMCPMC8833827.
12. Lima HA, Endo Y, Alaimo L, Moazzam Z, Munir MM, Shaikh C, et al. Tumor burden score and serum Alpha-fetoprotein subclassify Intermediate-Stage hepatocellular carcinoma. J Gastrointest Surg. 2022;26(12):2512–21. https://doi.org/10.1007/s11605-022-05469-9. Epub 20220928.
13. Toyoda H, Johnson PJ. The ALBI score: from liver function in patients with HCC to a general measure of liver function. JHEP Rep. 2022;4(10):100557. https://doi.org/10.1016/j.jhepr.2022.100557. Epub 20220818.
14. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550–8. https://doi.org/10.1200/jco.2014.57.9151. Epub 20141215.
15. Demirtas CO, D'Alessio A, Rimassa L, Sharma R, Pinato DJ. ALBI grade: evidence for an improved model for liver functional Estimation in patients with hepatocellular carcinoma. JHEP Rep. 2021;3(5):100347. https://doi.org/10.1016/j.jhepr.2021.100347. Epub 20210805.
16. Chan LL, Chan SL. The combination of ALBI and AFP response: A small step forward in HCC. Liver Int. 2023;43(2):271–3. https://doi.org/10.1111/liv.15494. PubMed PMID: 36680318.
17. Montironi C, Castet F, Haber PK, Pinyol R, Torres-Martin M, Torrens L, et al. Inflamed and non-inflamed classes of HCC: a revised Immunogenomic classification. Gut. 2023;72(1):129–40. https://doi.org/10.1136/gutjnl-2021-325918. Epub 20220223.
18. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212–22. https://doi.org/10.1158/1078-0432.Ccr-14-0442. Epub 20140930.
19. Wenpei G, Yuan L, Liangbo L, Jingjun M, Bo W, Zhiqiang N, et al. Predictive value of preoperative inflammatory indexes for postoperative early recurrence of hepatitis B-related hepatocellular carcinoma. Front Oncol. 2023;13:1142168. https://doi.org/10.3389/fonc.2023.1142168. Epub 20230713.
20. Feng H, Xu F, Zhao Y, Jin T, Liu J, Li R, et al. Prognostic value of combined inflammatory and nutritional biomarkers in HCC within the Milan criteria after hepatectomy. Front Oncol. 2022;12:947302. https://doi.org/10.3389/fonc.2022.947302. Epub 20220905.
21. Ho CT, Chia-Hui Tan E, Lee PC, Chu CJ, Huang YH, Huo TI, et al. Prognostic nutritional index as a prognostic factor for very Early-Stage hepatocellular carcinoma. Clin Transl Gastroenterol. 2024;15(4):e00678. https://doi.org/10.14309/ctg.0000000000000678. Epub 20240401.
22. Hu Y, Cai Y, Ma W, Hu H, Gu H, Jin Y, Li F. The prognostic nutritional index and tumor pathological characteristics predict the prognosis of elderly patients with early-stage hepatocellular carcinoma after surgery. Biosci Trends. 2023;17(5):369–80. https://doi.org/10.5582/bst.2023.01212. Epub 20231010.
23. Wen T, Jin C, Facciorusso A, Donadon M, Han HS, Mao Y, et al. Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus. Hepatobiliary Surg Nutr. 2018;7(5):353–71. PubMed PMID: 30498711; PubMed Central PMCID: PMCPMC6230838.
24. Chen RC, Cai YJ, Wu JM, Wang XD, Song M, Wang YQ, et al. Usefulness of albumin-bilirubin grade for evaluation of long-term prognosis for hepatitis B-related cirrhosis. J Viral Hepat. 2017;24(3):238–45. https://doi.org/10.1111/jvh.12638. Epub 20161114.
25. Cho WR, Hung CH, Chen CH, Lin CC, Wang CC, Liu YW, et al. Ability of the post-operative ALBI grade to predict the outcomes of hepatocellular carcinoma after curative surgery. Sci Rep. 2020;10(1):7290. https://doi.org/10.1038/s41598-020-64354-0. Epub 20200429.
26. Kaneko S, Kurosaki M, Tsuchiya K, Yasui Y, Inada K, Kirino S, et al. Prognosis of intrahepatic cholangiocarcinoma stratified by albumin-bilirubin grade. Hepatol Res. 2021;51(8):902–8. https://doi.org/10.1111/hepr.13673. Epub 20210618.
27. Ho SY, Liu PH, Hsu CY, Ko CC, Huang YH, Su CW, et al. Tumor burden score as a new prognostic marker for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. J Gastroenterol Hepatol. 2021;36(11):3196–203. https://doi.org/10.1111/jgh.15593. Epub 20210705.
28. Elfadaly AN, Tsilimigras DI, Hyer JM, Paro A, Bagante F, Ratti F, et al. Impact of tumor burden score on conditional survival after Curative-Intent resection for hepatocellular carcinoma: A Multi-Institutional analysis. World J Surg. 2021;45(11):3438–48. https://doi.org/10.1007/s00268-021-06265-3. Epub 20210802.
29. Moris D, Shaw BI, McElroy L, Barbas AS. Using Hepatocellular Carcinoma Tumor Burden Score to Stratify Prognosis after Liver Transplantation. Cancers (Basel). 2020;12(11). Epub 20201114. https://doi.org/10.3390/cancers12113372. PubMed PMID: 33202588; PubMed Central PMCID: PMCPMC7697953.
30. Wang J, Chen Z, Wang L, Feng S, Qiu Q, Chen D, et al. A new model based inflammatory index and tumor burden score (TBS) to predict the recurrence of hepatocellular carcinoma (HCC) after liver resection. Sci Rep. 2022;12(1):8670. https://doi.org/10.1038/s41598-022-12518-5. Epub 20220523.
31. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer. 2013;13(11):759–71. https://doi.org/10.1038/nrc3611. PubMed PMID: 24154716.
32. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol. 2013;33(Suppl 1):S79–84. Epub 20121209. doi: 10.1007/s10875-012-9847-0. PubMed PMID: 23225204.
33. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019;18(3):121–6. https://doi.org/10.4103/aam.aam_56_18. PubMed PMID: 31417011; PubMed Central PMCID: PMCPMC6704802.
34. Roth GS, Decaens T. Liver immunotolerance and hepatocellular carcinoma: Patho-physiological mechanisms and therapeutic perspectives. Eur J Cancer. 2017;87:101–12. https://doi.org/10.1016/j.ejca.2017.10.010. Epub 20171113.
35. Buonaguro L, Tagliamonte M, Petrizzo A, Damiano E, Tornesello ML, Buonaguro FM. Cellular prognostic markers in hepatocellular carcinoma. Future Oncol. 2015;11(11):1591–8. https://doi.org/10.2217/fon.15.39. PubMed PMID: 26043213.
36. O'Rourke JM, Sagar VM, Shah T, Shetty S. Carcinogenesis on the background of liver fibrosis: implications for the management of hepatocellular

cancer. World J Gastroenterol. 2018;24(39):4436–47. https://doi.org/10.3748/wjg.v24.i39.4436. PubMed PMID: 30357021; PubMed Central PMCID: PMCPMC6196335.
37. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004;21(2):137–48. https://doi.org/10.1016/j.immuni.2004.07.017. PubMed PMID: 15308095.
38. Wu ES, Oduyebo T, Cobb LP, Cholakian D, Kong X, Fader AN, et al. Lymphopenia and its association with survival in patients with locally advanced cervical cancer. Gynecol Oncol. 2016;140(1):76–82. PubMed PMID: 26571200; PubMed Central PMCID: PMCPMC4782779.
39. Cho Y, Park S, Byun HK, Lee CG, Cho J, Hong MH, et al. Impact of Treatment-Related lymphopenia on immunotherapy for advanced Non-Small cell lung Cancer. Int J Radiat Oncol Biol Phys. 2019;105(5):1065–73. https://doi.org/10.1016/j.ijrobp.2019.08.047. Epub 20190830.
40. Nagata S, Maeda S, Nagamatsu S, Kai S, Fukuyama Y, Korematsu S, et al. Prognostic nutritional index considering resection range is useful for predicting postoperative morbidity of hepatectomy. J Gastrointest Surg. 2021;25(11):2788–95. https://doi.org/10.1007/s11605-020-04893-z. Epub 20210108.
41. Chan AW, Chan SL, Wong GL, Wong VW, Chong CC, Lai PB, et al. Prognostic nutritional index (PNI) predicts tumor recurrence of very early/early stage hepatocellular carcinoma after surgical resection. Ann Surg Oncol. 2015;22(13):4138–48. https://doi.org/10.1245/s10434-015-4516-1. Epub 20150324.
42. Okamura Y, Sugiura T, Ito T, Yamamoto Y, Ashida R, Uesaka K. The optimal cut-off value of the preoperative prognostic nutritional index for the survival differs according to the TNM stage in hepatocellular carcinoma. Surg Today. 2017;47(8):986–93. https://doi.org/10.1007/s00595-017-1491-0. Epub 20170317.
43. He Y, Luo L, Shan R, Qian J, Cui L, Wu Z, et al. Development and validation of a nomogram for predicting postoperative early relapse and survival in hepatocellular carcinoma. J Natl Compr Canc Netw. 2023;22(1d):e237069. https://doi.org/10.6004/jnccn.2023.7069. Epub 20231220.
44. Lin Y, Wang J, Chen Y, Zhou X, Tang M, Chen M et al. Predicting One-year recurrence of HCC based on Gadoxetic Acid-enhanced MRI by machine learning models. Curr Med Imaging. 2024;20(12). Epub 20240307. PubMed PMID: 38462826. https://doi.org/10.2174/0115734056293489240226064955
45. Liu L, Qin S, Lin K, Xu Q, Yang Y, Cai J, et al. Development and comprehensive validation of a predictive prognosis model for very early HCC recurrence within one year after curative resection: a multicenter cohort study. Int J Surg. 2024;110(6):3401–11. https://doi.org/10.1097/js9.0000000000001467. Epub 20240601.
46. Lawal G, Xiao Y, Rahnemai-Azar AA, Tsilimigras DI, Kuang M, Bakopoulos A, Pawlik TM. The immunology of hepatocellular carcinoma. Vaccines (Basel). 2021;9(10). Epub 20211015. https://doi.org/10.3390/vaccines9101184. PubMed PMID: 34696292; PubMed Central PMCID: PMCPMC8538643.
47. Giraud J, Chalopin D, Blanc JF, Saleh M. Hepatocellular carcinoma immune landscape and the potential of immunotherapies. Front Immunol. 2021;12:655697. Epub 20210318. https://doi.org/10.3389/fimmu.2021.655697. PubMed PMID: 33815418; PubMed Central PMCID: PMCPMC8012774.

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