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ORIGINAL RESEARCH

Development and Validation of a Risk Prediction Model Based on Inflammatory and Nutritional Composite Indicators for Posthepatectomy Liver Failure Following Radical Resection of Hepatocellular Carcinoma

Jingfei Li[1], Miao Chen[2], Wei Cai[2], Dalong Yin[1,2]

[1]Department of General Surgery, Anhui Provincial Hospital, Anhui Medical University, Hefei, Anhui, 230001, People's Republic of China; [2]Department of Hepatobiliary Surgery, Centre for Leading Medicine and Advanced Technologies of IHM, The First Affiliated Hospital, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China

Correspondence: Dalong Yin; Wei Cai, Department of Hepatobiliary Surgery, Centre for Leading Medicine and Advanced Technologies of IHM, The First Affiliated Hospital, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China, Tel +86- 18110984879; +86- 15625067917, Email doctoryin@ustc.edu.cn; dr_caiwei@yeah.net

Purpose: A plethora of studies have demonstrated an association between preoperative inflammatory immunonutritional status and the prognosis of patients with hepatocellular carcinoma. Nonetheless, there is a paucity of research examining the predictive value of inflammatory immunonutritional indicators for postoperative liver failure in this patient population. This study seeks to identify independent predictors of post hepatectomy liver failure (PHLF) in patients with hepatocellular carcinoma and to develop a nomogram model.

Patients and Methods: Clinical data were collected from 760 patients diagnosed with hepatocellular carcinoma who underwent surgical treatment at a hospital in China between January 2020 and January 2024. The dataset was randomly divided into a training set (n=570, 75%) and a validation set (n=190, 25%). To identify independent predictors of PHLF in these patients, univariate analysis and least absolute shrinkage and selection operator (LASSO) regression were employed. Subsequently, a multivariate logistic regression model was developed to construct a predictive model. The predictive performance of the nomogram was evaluated using receiver operating characteristic (ROC) curve analysis, calibration curve assessment, and decision curve analysis (DCA).

Results: AAPR, ALBI, GAR, LMR, PNI, INR, APTT, and TT are independent factors associated with PHLF in patients with hepatocellular carcinoma. The C indices for the training and validation datasets were 0.691 (95% CI: 0.634–0.747) and 0.680 (95% CI: 0.556–0.804), respectively. The area under the curve (AUC) and calibration curve analyses demonstrated the nomogram's accuracy in predicting PHLF in this patient population. Furthermore, DCA indicated that the model provides a significant clinical net benefit. A comparison was made of the predictive efficacy of the nomogram prediction model and the associated composite liver function score. ROC curves were plotted for the nomogram prediction model, Child-Pugh score and ALBI score, and AUC values were calculated, which were 0.686 (95% CI 0.635–0.737) for the prediction model, 0.558(95% CI 0.512–0.603) for the Child-Pugh score. The AUC for ALBI score was 0.577 (95% CI 0.530–0.624), indicating that this nomogram prediction model was more effective than other scoring systems in predicting the study population in our center. In this study population, the nomogram model demonstrated an AUC of 0.707 (95% CI 0.620–0.794) for Child-Pugh score grade A and 0.572 (95% CI 0.501–0.643) for Child-Pugh score grade B. For tumors with a diameter of less than 5 cm, the AUC was 0.679 (95% CI 0.608–0.749), and for patients with tumors with a diameter of at least 5 cm, the AUC was 0.715 (95% CI 0.643–0.787).

Conclusion: We have developed an innovative nomogram model designed to predict the incidence of PHLF in patients diagnosed with hepatocellular carcinoma. This nomogram has a good predictive value for PHLF in HCC patients and is important for clinicians to manage patients after hepatectomy.

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Introduction

Hepatocellular carcinoma (HCC) represents the most prevalent primary solid neoplasm of the liver, with its incidence continuing to escalate over recent decades. Between 2010 and 2021, the global incidence and mortality rates of HCC increased by 26% and 25%, respectively.[1] Currently, a range of therapeutic modalities are available for the management of HCC, encompassing surgical intervention, chemotherapy, targeted therapy, and immunotherapy. However, surgical resection remains the most widely acknowledged treatment associated with favorable prognostic outcomes.[2] Hepatectomy is frequently linked to various postoperative risks and complications, such as infection, hemorrhage, bile leakage, and PHLF. Despite ongoing advancements in surgical techniques, perioperative management, and surgeon expertise, the incidence of PHLF following hepatectomy has diminished, however, it continues to be a predominant cause of postoperative mortality in patients with HCC.[3] In 2011, the International Liver Surgery Study Group (ISGLS) introduced diagnostic criteria for PHLF, significantly enhancing clinicians' ability to diagnose and manage this condition. Nevertheless, the diagnosis of PHLF often remains uncertain until the fifth postoperative day, at which point the efficacy of therapeutic interventions is significantly diminished due to the disease's progression. Considering the elevated mortality risk associated with PHLF and the paucity of effective treatment modalities, the prevention of PHLF continues to be a primary objective in contemporary therapeutic approaches.[4]

In the mid-19th century, Rudolf Virchow initially hypothesized the intricate interconnections between inflammation and cancer. This hypothesis was based on his observations of cancer arising from sites of chronic inflammation and the prevalence of inflammatory cells in tumor biopsies.[5] The association between chronic inflammation and tumorigenesis is now well-established, with cancer-related inflammation acknowledged as a fundamental characteristic of cancer.[6] Emerging evidence suggests that inflammation is a critical factor in the pathogenesis of cirrhosis and hepatocellular carcinoma, and it is strongly linked to adverse outcomes following hepatectomy.[7,8] Hepatic TIMP3 deficiency has been shown to trigger lymphocyte infiltration and hepatocyte death by enhancing TNF-α converting enzyme activity, leading to sustained activation of the TNF signalling pathway. This persistent inflammatory microenvironment has been demonstrated to inhibit liver regeneration and accelerate functional failure of residual liver tissue.[9] Furthermore, preoperative nutritional status has been identified as a significant prognostic indicator for patients with advanced liver disease.[10] There appears to be a specific correlation between the inflammatory state and nutritional status of patients with hepatocellular carcinoma prior to hepatectomy and the incidence of hepatic failure following surgery. Building upon the aforementioned evidence, certain researchers have initiated investigations into the relationship between inflammatory and nutritional indicators and PHLF.[11] However, the prognostic significance of these indicators in predicting liver failure following hepatectomy remains inadequately elucidated. Consequently, the potential of inflammatory and nutritional indices as predictive tools for PHLF warrants further investigation.

Given that a single blood marker is insufficient to comprehensively represent the inflammatory and nutritional status of patients, there has been an increasing emphasis on complex indicators in clinical practice due to their comprehensive nature, predictive efficiency, and stability. Consequently, this study aims to predict the likelihood of PHLF in patients with hepatocellular carcinoma following partial hepatectomy by utilizing complex indicators of inflammation and nutrition.[12] Furthermore, a nomogram was developed based on these complex indicators to enhance predictive accuracy.

Materials and Methods

Data Source

Clinical data were collected from 760 patients diagnosed with hepatocellular carcinoma who underwent partial liver resection at the First Affiliated Hospital of the University of Science and Technology of China between January 2020 and January 2024. Prior to surgery, all patients received comprehensive communication and provided informed consent. The

collection of clinical data for this study received approval from the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (approval number: 2024-RE-279).

Patient Admission Standard

The inclusion criteria for this study are: (1) individuals aged over 18 years; (2) a confirmed diagnosis of HCC through pathological examination; (3) the surgical intervention was a partial hepatectomy. The exclusion criteria are: (1) a history of concurrent malignant tumors; (2) the presence of extrahepatic metastasis; (3) Serious extrahepatic diseases (eg, severe cardiovascular disease, active autoimmune disease); (4) incomplete clinical data.

Data Collection and Variable Definition

The collected data encompassed three primary categories: (1) demographic characteristics, including age, gender, body mass index (BMI), and underlying conditions such as diabetes, hypertension, and coronary heart disease; liver function-related data, comprising hepatitis B status, anti-hepatitis B virus therapy, presence of ascites, Child-Pugh score, and cirrhosis; and perioperative laboratory results, which included measurements of red blood cells (RBC), white blood cells(WBC), platelets(PLT), absolute neutrophil count(ANC), hemoglobin(HGB), lymphocytes, monocytes, creatinine(Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase(GGT), total bilirubin(TBil), direct bilirubin, indirect bilirubin, total protein(TP), albumin, globulin, and blood glucose(BG), activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin time (PT), fibrinogen (FIB), and thrombin time (TT). (2) Intraoperative variables, such as surgery time, hepatic portal blockade time(HPT), intraoperative blood loss, and the volume of intraoperative blood transfusion. (3) Tumor-related characteristics, including tumor size (TS), microvascular Invasion (MVI), and alpha-fetoprotein (AFP) levels. (4) The study also focused on 11 biomarkers associated with immunity, inflammation, and nutrition: ALT (7–56 U/L), AST (10–40 U/L), albumin-alkaline phosphatase ratio (AAPR)(0.4–0.8), albumin-globulin ratio (A/G)(1.1–2.50), albumin-bilirubin (ALBI) grade, and gamma-glutamyl transferase-albumin ratio (GAR), neutrophil to lymphocyte ratio (NLR)(1–3), platelet to lymphocyte ratio (PLR)(50–150), prognostic nutritional index (PNI)(≥45), systemic immunoinflammatory index (SII) (300–900), lymphomononuclear ratio (LMR)(2.2–3.5). Biomarkers are calculated as follows: AAPR = albumin (g/L)/ALP (IU/L), AG= albumin (g/L)/ globulin (g/L), ALBI= log10 bilirubin (mol/L) × 0.66 – albumin (g/L) ×0.085, GAR= GGT (U/L)/ albumin (g/ l), NLR = ANC ($\times 10^9$/L)/ absolute value of lymphocytes ($\times 10^9$/L), PLR = peripheral blood plate count ($\times 10^9$/L)/ lymphocyte count ($\times 10^9$/L), PNI = 5× (serum albumin (g/dL)/ lymphocyte count ($\times 10^9$/L))+100, SII = peripheral blood plate count (×109/L) ×ANC ($\times 10^9$/L)/lymphocyte absolute value ($\times 10^9$/L), LMR= lymphocyte count ($\times 10^9$/L)/absolute value of monocytes ($\times 10^9$/L). ALBI grades are divided according to cutoff values, as previously mentioned: ≤-2.60 (ALBI Grade 1), >-2.60 to ≤-1.39 (ALBI Grade 2), and ≥-1.39 (ALBI Grade 3).

PHLF Definition

Due to challenges associated with data retrieval and clinical practice, certain patients do not undergo concurrent assessments of TBil and INR on or after the fifth postoperative day. To address potential analytical biases, The incidence of PHLF is characterised on the basis of the ISGLS and in the light of the relevant literature.[13,14]

The specific diagnostic criteria for PHLF are the fifth day after surgery and include the following: TBil value > 24 μmol/L and INR > 1.2, or TBil > 70.1 μmol/L (4.1 mg/dL), or INR > 2.5, or ascites drainage flow > 500 mL/ day. In addition, patients who were discharged within 5 days of surgery were classified as not having liver failure, except for patients who were discharged or died due to bleeding.

Hepatectomy Definition

Hepatic resection is a surgical intervention that involves the partial or total removal of liver tissue. It is primarily utilised in the management of primary liver tumours, such as hepatocellular carcinoma, as well as metastatic liver cancer, including cases of liver metastasis from colorectal cancer. The procedure is also employed in the treatment of benign

liver tumours, liver injury, and other hepatic diseases. Depending on the extent of the procedure, it can be classified into two categories: partial hepatectomy (eg segmental hepatectomy, wedge resection) and extensive hepatectomy (eg hemihepatectomy, extended hemihepatectomy). The core objective is to achieve radical resection of the diseased tissue while ensuring that the remaining liver function is sufficient to maintain metabolic requirements.[15] In this study, the tumours of patients with HCC who underwent hepatectomy were found to meet the Milan criteria (ie a solitary tumour ≤ 5 cm in diameter or a maximum of three nodules, each ≤ 3 cm).[16]

Statistical Analysis

The training group (75% of the sample size) was used to construct the prediction model, and the validation group (25% of the sample size) was used to verify the accuracy of the model. Continuous variables were expressed as median with quartile, while categorical variables are shown as percentage. Continuous variables were compared using Student's t tests or the Mann–Whitney *U*-tests as appropriate, and Pearson's Chi-squared or Fisher's exact tests were used to compare categorical variables. Univariate logistic regression models and LASSO regression models were used to identify independent predictors of PHLF in the training cohort. The AUC of the ROC curve was calculated to assess the discrimination of the nomogram in the training group and the validation group.

Statistical analysis was performed using R version 4.1.3 software equipped with the "glmnet", "rms", and "rmda" packages and SPSS version 26.0. A P-value < 0.05 was statistically significant.

Results

Patient Baseline Data

As illustrated in Figure 1, the study comprised a total of 760 patients diagnosed with hepatocellular carcinoma who underwent hepatectomy, among whom 134 individuals (17.6%) developed PHLF. The cohort was randomly divided into a training set, consisting of 75% of the cases (n=570), and a validation set, comprising 25% of the cases (n=190). The mean age of patients in the training set was 58.91±10.85 years, with a gender distribution of 486 males (85.3%) and 84 females (14.7%). Similarly, the mean age of the validation set was 58.95±10.09 years, with 153 males (80.5%) and 37 females (19.5%). In the training and validation cohorts, the incidence rates of liver failure among patients with hepatocellular carcinoma who underwent partial hepatectomy were 18.9% and 13.7%, respectively. Statistical analysis revealed no significant differences between the training and validation cohorts (p > 0.05), suggesting that the baseline characteristics of the two groups were comparable (Table 1).

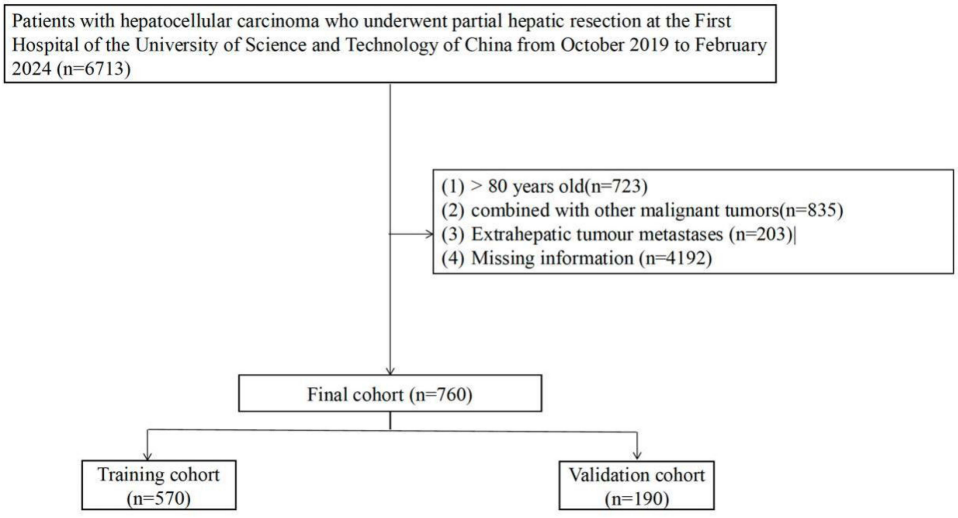

Figure 1 The flowchart of patient selection.

Table 1 Baseline Characteristics of Patients with Hepatocellular Carcinoma Treated Surgically

Variable	Total (n=760)	Training (n=570)	Validation (n=190)	*P* value
Failure, n (%)				0.060
No	626(82.4)	462(81.1)	164(86.3)	
Yes	134(17.6)	108(18.9)	26(13.7)	
Gender, n (%)				0.078
Female	121(15.9)	84(14.7)	37(19.5)	
Male	639(84.1)	486(85.3)	153(80.5)	
Age (years)	58.92±10.66	58.91±10.85	58.95±10.09	0.970
BMI, n (%)				0.510
1	33 (4.3)	25 (4.4)	8(4.2)	
2	390 (51.3)	287 (50.4)	103(54.2)	
3	337 (44.4)	258 (4.3)	79(41.6)	
Hepatitis B				0.801
No	339(44.6)	256(44.9)	83(43.7)	
Yes	421(55.4)	314(55.1)	107(56.3)	
ART*, n (%)				0.669
No	559(73.6)	417(73.2)	142(74.7)	
Yes	201(26.4)	153(26.8)	48(25.3)	
HBP*, n (%)				0.701
No	565(74.3)	426(74.7)	139(73.2)	
Yes	195(25.7)	144(25.3)	51(26.8)	
Diabetes, (n%)				
No	674(88.7)	503(88.2)	171(90.0)	
Yes	86(11.3)	67(11.8)	19(10.0)	
CHD*, n (%)				0.772
No	745(98.0)	558(97.9)	187(98.4)	
Yes	15(2.0)	12(2.1)	3(1.6)	
WBC ($x10^9$/L)	5.37±2.07	5.41±2.09	5.22±2.02	0.268
HGB(g/l)	138.00 (126.00,149.00)	138.00 (126.00,148.00)	138.00 (126.00,149.00)	0.737
PLT ($x10^9$/L)	144.50 (107.00,191.00)	146.00 (107.00,194.00)	136.50 (109.00,183.75)	0.235
RBC ($x10^9$/L)	4.40(4.02,4.77)	4.39(4.03,4.77)	4.42(4.01,4.80)	0.895
Cr (umol/L)	65.70±15.90	66.22±16.51	64.15±13.85	0.121
ALT (IU/L)	28.00 (19.50, 44.73)	28.85 (19.02, 46.00)	26.10 (20.00, 36.00)	0.210
AST (IU/L)	32.00 (24.00, 46.00)	32.00 (23.45,47.22)	31.00 (24.40,41.92)	0.475
TP*(g/dl)	68.86±6.84	69.00±6.58	68.41±7.54	0.298
A/G	1.41(1.26,1.64)	1.46(1.26,1.65)	1.43(1.28,1.61)	0.317
BG(mmol/L)	5.48±1.65	5.51±1.73	5.39±1.35	0.414
ALT/AST	1.11(0.90,1.42)	1.11(0.89,1.440	1.11(0.92,1.38)	0.704
PT(s)	12.76±3.64	12.80±4.09	12.62±1.69	0.538
INR	1.05±0.13	1.05±0.12	1.05±0.13	0.621
APTT(s)	34.31±5.92	34.18±5.95	34.73±5.81	0.269
Fib (g/L)	2.76(2.31,3.37)	2.77(2.33,3.48)	2.73 (2.28,3.23)	0.370
TT(s)	17.20(15.40,18.50)	17.20(15.50,18.40)	17.10(15.00,18.60)	0.641
HYD*, n (%)				0.567
No	739(97.2)	554(97.2)	185(97.4)	
Yes	21(2.8)	16(2.8)	5(2.6%)	
Child-Pugh				0.358
1	323(42.5)	236(41.4)	87(45.8)	
2	434(57.1)	332(58.2)	102(53.7)	
3	3(0.4)	2(0.4)	1(0.5)	

(*Continued*)

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Table 1 (Continued).

Variable	Total (n=760)	Training (n=570)	Validation (n=190)	*P* value
AAPR	0.44(0.33,0.56)	0.44(0.33,0.56)	0.43(0.33, 0.56)	0.851
ALBI				0.967
1	439(57.8)	329(57.7)	110(57.9)	
2	315(41.4)	237(41.6)	78(41.1)	
3	6(0.8)	4(0.7)	2(1.1)	
GAR	1.19(0.65,2.30)	1.23(0.65, 2.41)	1.08(0.65, 2.17)	0.320
NLR	2.10(1.55,2.95)	2.09(1.57,2.95)	2.16(1.48,2.99)	0.792
PLR	103.00 (76.52,140.95)	102.88 (77.46,143.06)	103.50 (71.53,136.14)	0.296
PNI	116.32±7.55	116.29±7.56	116.40±7.53	0.865
SII	295.7 (192.63, 509.93)	298.62 (196.99, 513.56)	292.23 (179.00, 470.88)	0.338
LMR	3.35(2.55,4.29)	3.38(2.55,4.30)	3.23(2.53,4.27)	0.967
Surgery time (/min)	185.00 (139.00,240.00)	185.00 (140.00, 241.75)	178.50 (130.00, 238.75)	0.169
HPT*(/min)	12.00(0.00,30.00)	12.00(0.00,30.00)	9.00(0.00,28.75)	0.400
Cirrhosis, n(%)				0.204
No	233(30.7)	182(31.9)	51(26.8)	
Yes	527(69.3)	388(68.1)	139(73.2)	
IBL*(/mL)	150.00 (100.00,300.00)	150.00 (100.00,300.00)	100.00 (50.00,300.00)	0.122
IBT*(/mL)	0.00(0.00,300.00)	0.00(0.00,300)	0.00(0.00,275.00)	0.842
TS*(/cm)	4.50(3.00,7.50)	4.50(3.00,8.00)	4.00(3.00,7.00)	0.102
AFP				0.241
No	361(47.5%)	278(48.8%)	83(43.7%)	
Yes	399(52.5%)	292(51.2%)	107(56.3%)	
MVI				0.960
0	336(44.2)	259(45.4)	77(40.5)	
1	286(37.6)	205(36.0)	81(42.7)	
2	138(18.2)	106(18.6)	32(16.8)	

Abbreviations: ART, antiretroviral therapy; HBP, high blood pressure; CHD, coronary heart disease; TP, total protein; HYD, hydroperitoneum; HPT, hepatic portal blockade time; IBL, Intraoperative blood loss; IBT, Intraoperative blood transfusion; TS, Tumor size.

Single Factor Logistic Regression Analysis

Using univariate logistic regression analysis, several factors were identified as significant risk factors for PHLF. These factors include AST (P = 0.006, OR = 1.008, 95% CI: 1.002–1.013), INR (P = 0.001, OR = 13.359, 95% CI: 2.718–65.657), APTT (P = 0.001, OR = 1.063, 95% CI: 1.025–1.103), TT (P = 0.028, OR = 1.119, 95% CI: 1.012–1.237), and the Child-Pugh score (P = 0.047, OR = 1.553, 95% CI: 1.007–2.397). Additionally, AAPR (P < 0.001, OR = 0.048, 95% CI: 0.013–0.180), ALBI (P = 0.001, OR = 2.041, 95% CI: 1.358–3.066), GAR (P = 0.005, OR = 1.073, 95% CI: 1.022–1.127), PLR (P = 0.018, OR = 1.003, 95% CI: 1.001–1.006), PNI (P = 0.015, OR = 1.031, 95% CI: 1.006–1.058), and LMR (P < 0.001, OR = 0.717, 95% CI: 0.603–0.852) were also identified as significant risk factors. For detailed results, refer to Table 2. A 10-fold cross-validation of the initial input LASSO regression method was conducted to address collinearity among the relevant indicators, thereby identifying the predictors of postoperative liver failure in patients with hepatocellular carcinoma who underwent partial hepatectomy. Ultimately, eight variables were selected as optimal based on the best lambda value: AABR, ALBI, GAR, LMR, PNI, INR, APTT, and TT (Figure 2).

Development of Nomogram in Training Set

Eight factors, including AABR, ALBI, GAR, PNI, LMR, INR, APTT, and TT, were selected as predictors to develop a forecasting model for PHLF in patients undergoing partial liver resection for HCC. The resulting nomogram, depicted in Figure 3, indicates that AAPR and LMR significantly impact patient outcomes. By summing the points assigned to

Table 2 Univariate Analysis of Patients with Hepatocellular Carcinoma Treated Surgically in the Training Cohort

Variables	OR	Lower	Upper	*P*
Genders (n%)	0.754	0.400	1.418	0.381
Age (years)	1.009	0.990	1.029	0.353
BMI	1.105	0.765	1.595	0.595
Hepatitis B (n%)	0.933	0.613	1.421	0.748
ART* (n%)	0.836	0.514	1.360	0.471
HBP* (n%)	1.044	0.647	1.685	0.860
Diabetes* (n%)	0.725	0.357	1.471	0.373
CHD* (n%)	0.853	0.184	3.950	0.839
WBC ($x10^9$/L)	1.080	0.985	1.185	0.103
HGB (g/l)	1.002	0.999	1.006	0.226
PLT ($x10^9$/L)	1.000	0.997	1.002	0.813
RBC ($x10^9$/L)	0.824	0.635	1.069	0.144
Cr (umol/L)	1.001	0.989	1.014	0.851
ALT (IU/L)	1.004	0.998	1.009	0.195
AST (IU/L)	1.008	1.002	1.013	0.006
TP*(g/dl)	0.993	0.962	1.025	0.655
A/G	0.238	0.111	0.508	0.000
BG*(mmol/L)	1.030	0.918	1.155	0.617
ALT/AST	1.117	0.857	1.455	0.414
PT(s)	1.014	0.972	1.059	0.513
INR	13.359	2.718	65.657	0.001
APTT(s)	1.063	1.025	1.103	0.001
FIB (g/L)	1.083	0.894	1.312	0.416
TT(s)	1.119	1.012	1.237	0.028
HYD*	1.442	0.456	4.562	0.533
Surgery time(min)	1.000	0.998	1.003	0.855
HBT(min)	1.004	0.995	1.013	0.372
Cirrhosis	1.142	0.723	1.803	0.569
IBL(mL)	1.000	1.000	1.001	0.352
IBT(mL)	1.000	1.000	1.000	0.633
Tumor size(cm)	0.968	0.915	1.024	0.256
MVI	1.015	0.792	1.301	0.906
AFP	0.682	0.447	1.041	0.076
Child Pugh	1.553	1.007	2.397	0.047
AAPR	0.048	0.013	0.180	0.000
ALBI	2.041	1.358	3.066	0.001
GAR	1.073	1.022	1.127	0.005
NLR	1.035	0.985	1.088	0.169
PLR	1.003	1.001	1.006	0.018
PNI	1.031	1.006	1.058	0.015
SII	1.000	1.000	1.001	0.069
LMR	0.717	0.603	0.852	0.000

Abbreviations: ART, antiretroviral therapy; HBP, high blood pressure; CHD, coronary heart disease; TP, total protein; HYD, hydroperitoneum; HPT, hepatic portal blockade time; IBL, Intraoperative blood loss; IBT, Intraoperative blood transfusion; TS, Tumor size.

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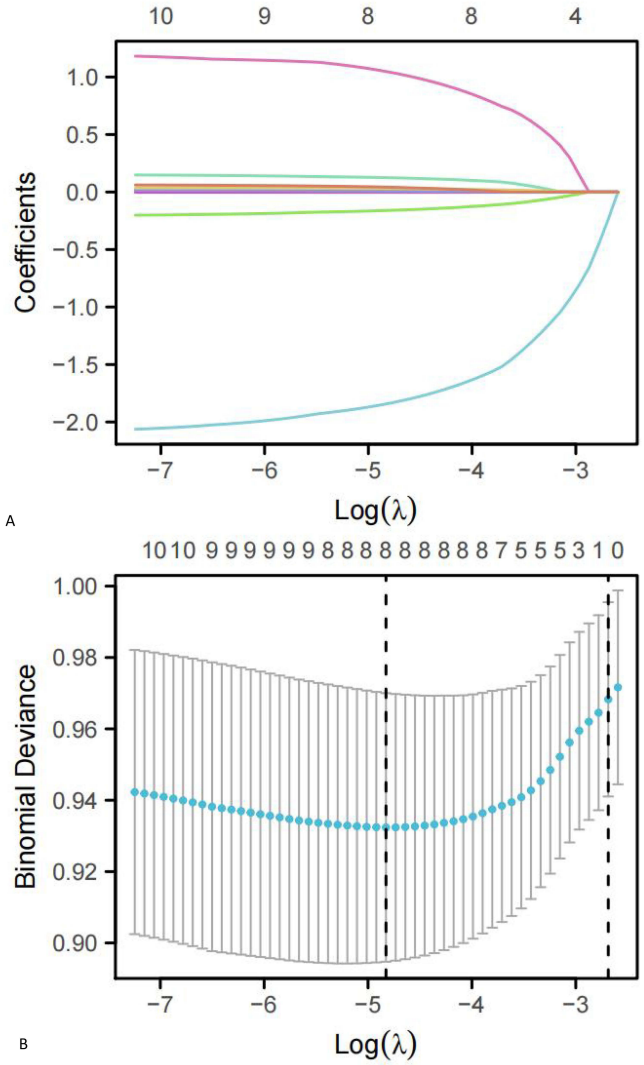


Figure 2 Clinical feature selection by LASSO. (**A**) Plot of LASSO coefficient profiles of the 12 features. The log (lambda) sequence was plotted against a coefficient profile plot. There were 8 features with non-zero coefficients generated by the ideal lambda (λ=2.539628921009624); (**B**) 10-fold cross-validation for LASSO model parameter adjustment. The binomial deviation curve was displayed with log (lambda). The minimum criteria and its one standard error were used to construct dotted vertical lines at the optimal values (the 1-SE criteria).

each variable along the vertical line and referencing the point axis, the likelihood of a patient experiencing PHLF can be estimated.

Model Verification

The concordance index (C-index) for the training and validation datasets was 0.691 (95% CI: 0.634–0.747) and 0.680 (95% CI: 0.556–0.804), respectively, aligning with the results of the ROC curve analysis (Figure 4). These findings indicate that the nomogram model serves as an effective predictor of PHLF) incidence in patients with HCC. Furthermore, calibration curves for both the training and validation cohorts demonstrate that the predicted probabilities closely match the observed outcomes, signifying successful model calibration (Figure 5). As illustrated in Figure 6, DCA demonstrates that the nomogram exhibits an exceptional overall net benefit across a wide and practical range of threshold probabilities, suggesting a significant potential for clinical utility.

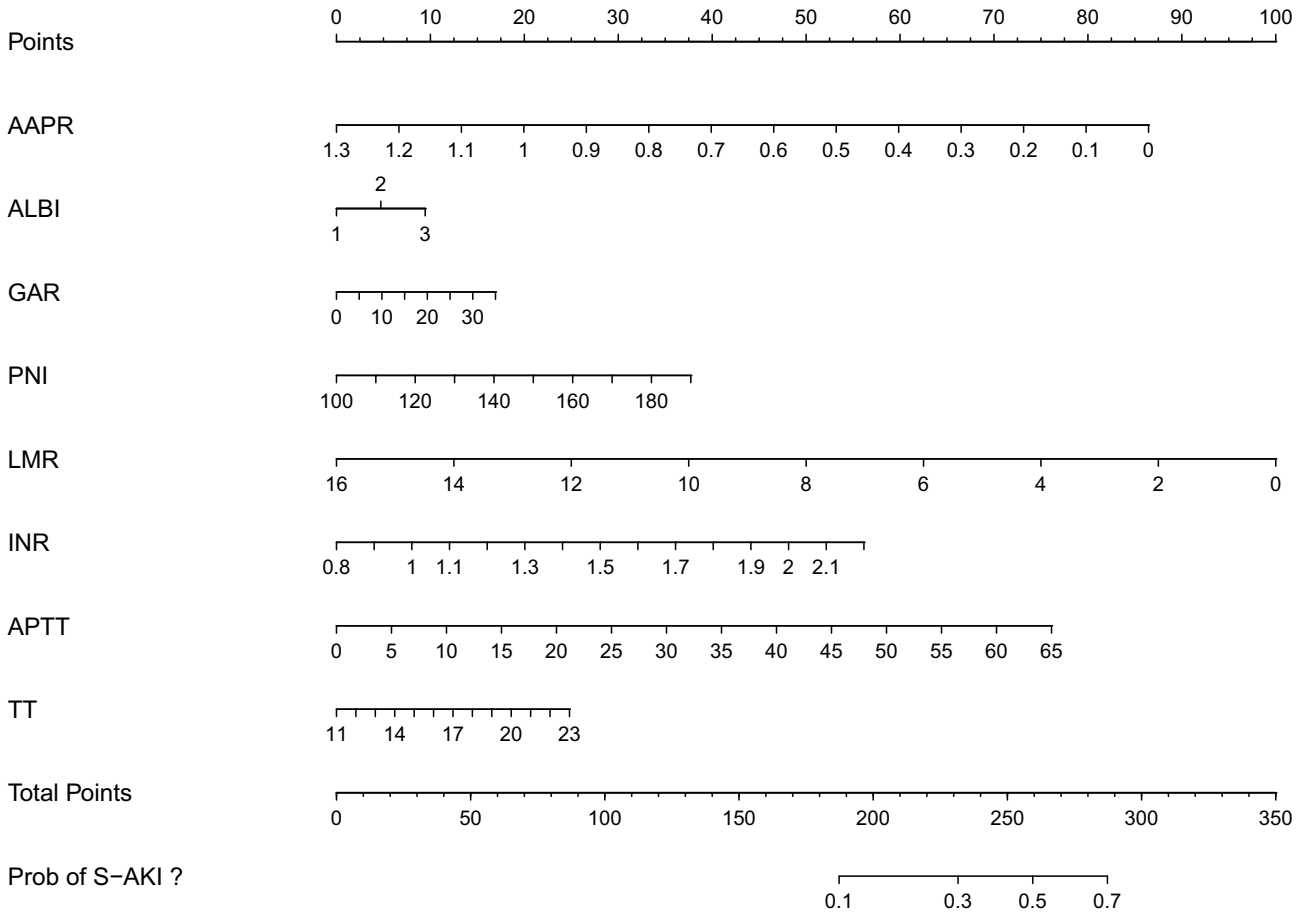


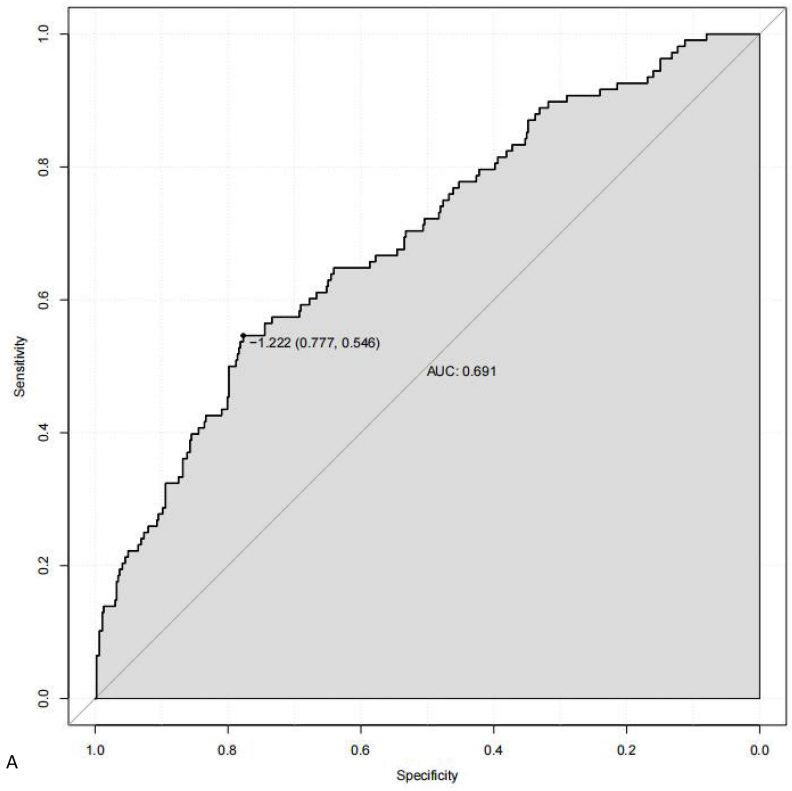
Figure 3 Nomogram model for predicting PHLF in patients with HCC.

Comparison of the Predictive Efficacy of Column-Line Graphical Prediction Models and Associated Liver Function Composite Scores

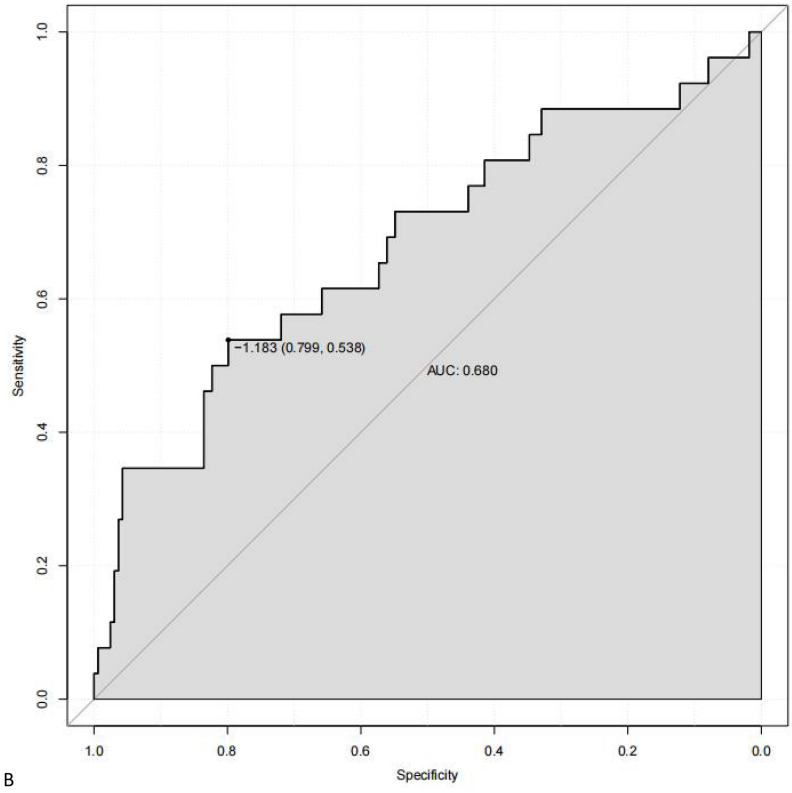
In this study, the predictive efficacy of the nomogram model was compared with that of the associated liver function composite score. The ROC curves for the nomogram prediction model, Child-Pugh score and ALBI score were plotted, and the AUC values were calculated. The AUC of the nomogram model was 0.6863 (95% CI 0.63536–0.73715), the AUC of Child-Pugh grading was 0.5578 (95% CI 0.51249–0.60302), and the AUC of ALBI scoring was 0.5774 (95% CI 0.530 37–0.62449). The results illustrated that both the aforementioned column line drawing prediction model and the results indicated that the above nomogram prediction model and scoring system had predictive value for PHLF, and the AUC value of this nomogram prediction model was larger compared with Child-Pugh score (NRI=0.4474, P<0.001) and ALBI score (NRI=0.5061, P<0.001). The comparison of the ROC curves provides a more intuitive illustration of the differences between the scoring models, thereby suggesting that this nomogram model is more effective than other scoring systems in predicting the study population in our center (see Table 3 and Figure 7).

Comparison of Prediction Performance of Nomogram Prediction Models Under Different Populations

The available data population was divided into Child-Pugh grade A (n=323) and Child-Pugh grade B(n=434) for the prediction of the model, respectively, where the AUC for Child-Pugh grade A was 0.7070 ((95% CI 0.62003–0.79400), and the AUC for Child-Pugh grade B was 0.572 (95% CI 0.50193–0.64345). The population was divided into two groups for the purpose of prediction by the model: those with tumor diameters less than 5cm (n=405) and those with tumor diameters greater than or equal to 5cm (n=355). The AUC for the former group was 0.6785 (95% CI 0.60784–0.74914),



A



B

Figure 4 The area under the ROC curves AUCs of the nomogram for mortality from PHLF in patients with HCC in training set (**A**) and validation set (**B**).

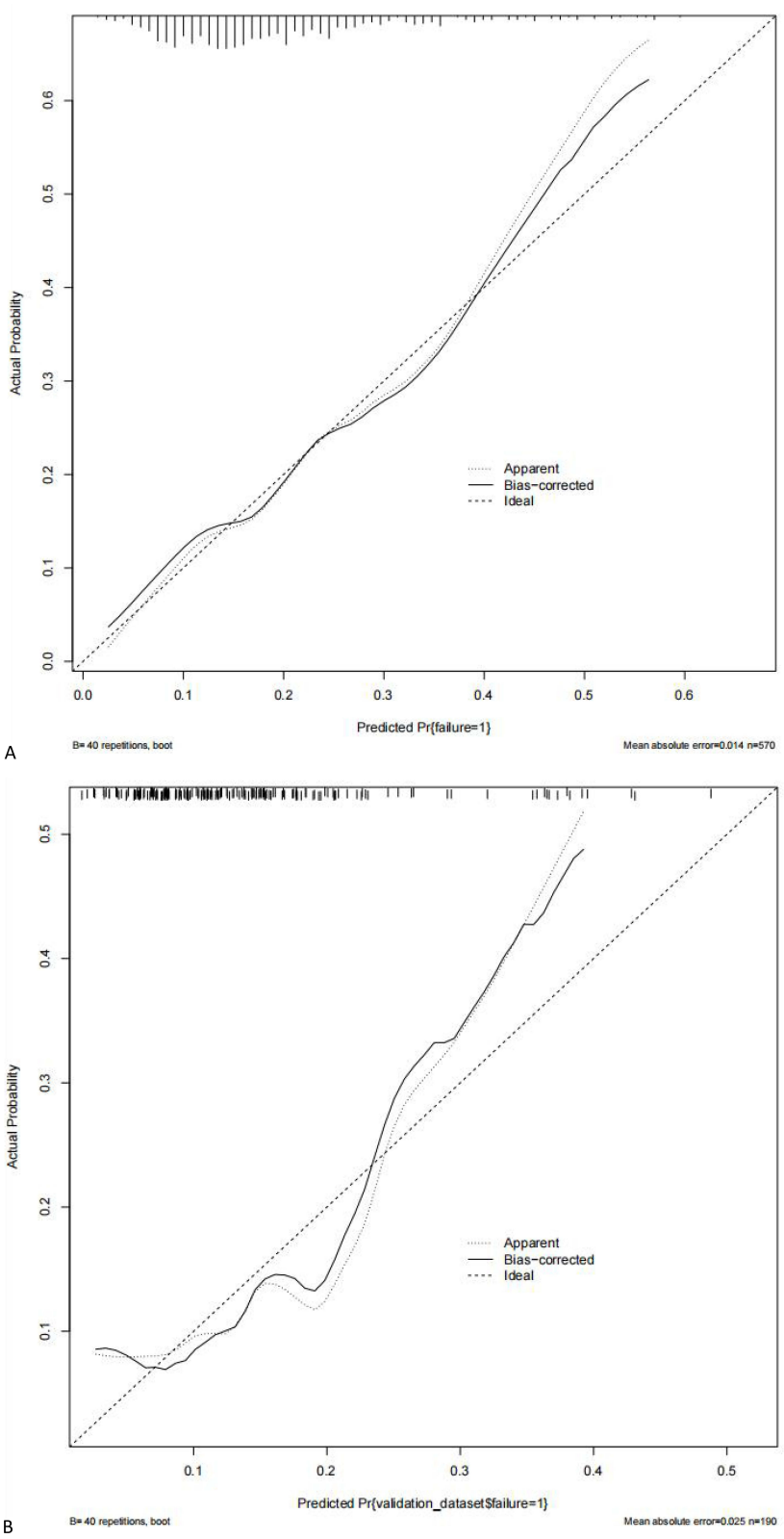


Figure 5 Calibration curves of the predicted nomogram. Evaluation of the predictive performance for mortality from PHLF in patients with HCC of the nomogram in the training set (**A**) and validation set. (**B**).

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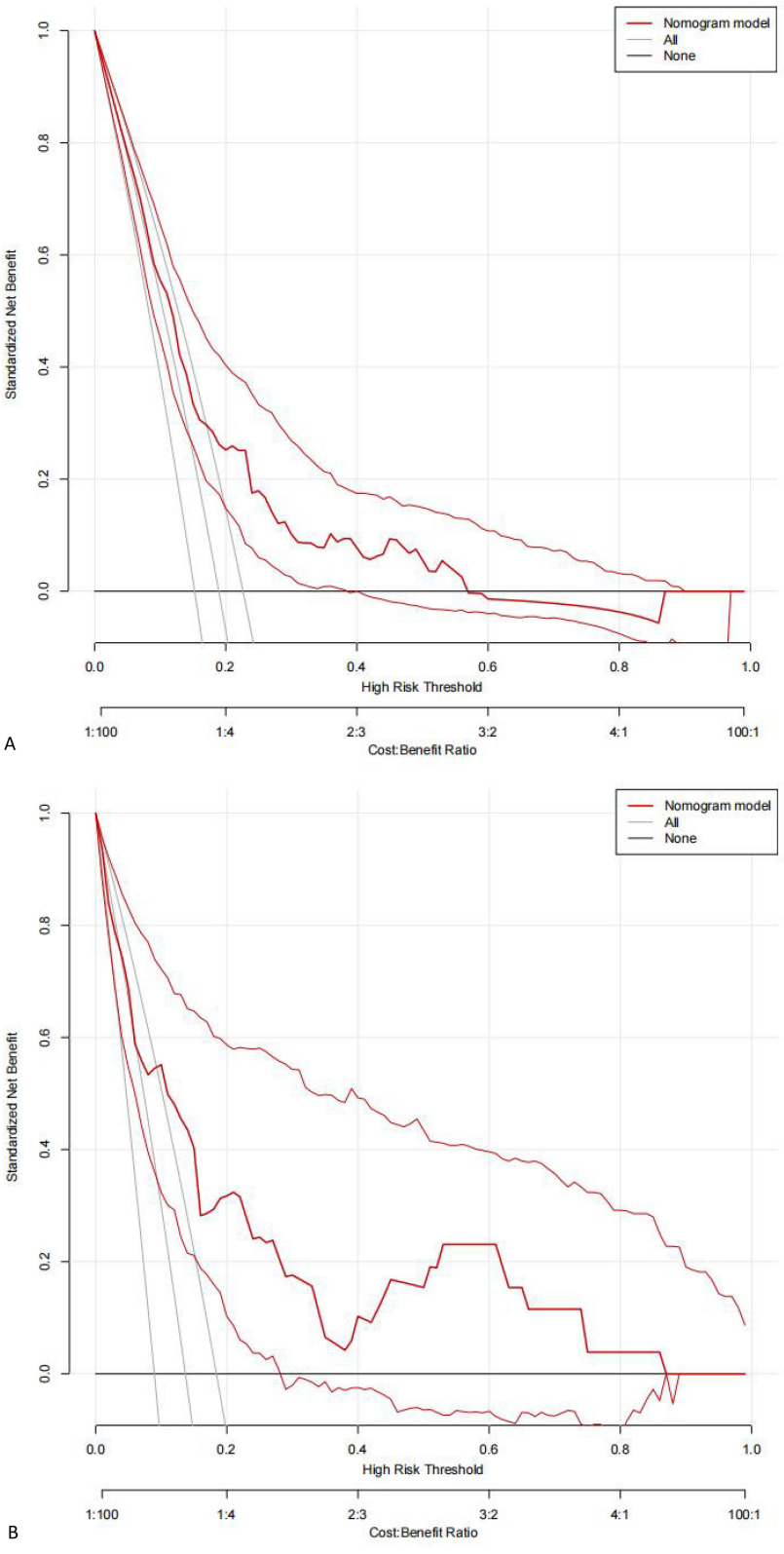

Figure 6 Decision curve analysis of the nomogram. (**A**) Decision curve analysis in the training set; (**B**) Decision curve analysis in validation set.

Table 3 PHLF Prediction Model with Associated Scoring System AUC

	AUC	Standard Error	95% CI	NRI	*P*
New model	0.6863	0.0260	0.63536–0.73715		
Child-Pugh	0.5578	0.0231	0.51249–0.60302	0.4474	<0.001
ALBI	0.5774	0.0240	0.53037–0.62449	0.5061	<0.001

and that for tumor diameters greater than or equal to 5cm was 0.7153 (95% CI 0.64339–0.78730), see Table 4. It is evident that the model demonstrates a certain degree of prediction performance across all populations, however, the prediction performance is more pronounced in the Child-Pugh grade A and tumor diameter greater than or equal to 5cm population. The predictive performance of the nomogram model can be evaluated more intuitively by the ROC curve (Figure 8).

Discussion

In recent years, notwithstanding the ongoing advancements in medical technology, PHLF remains a significant fatal complication following liver cancer surgery. Current reports indicate that the incidence of postoperative hepatocellular carcinoma complicated by liver failure ranges from 3% to 48.5%, with most studies reporting an incidence of approximately 10% to 20%.[17,18] The substantial variability in PHLF incidence may be attributed to differences in study design, patient selection, surgical techniques, and varying interpretations of the definition of liver failure. In this study, the incidence of PHLF was 17.6%, aligning with rates reported in the majority of existing literature. Currently, the diagnostic criteria for PHLF predominantly follow the guidelines established by the ISGLS in 2011. According to these criteria, PHLF is diagnosed when, on or after the fifth postoperative day, a patient's INR and TBIL levels exceed the normal range as defined by the local laboratory.[13] According to the established diagnostic criteria, PHLF is typically diagnosed on or after the fifth postoperative day, by which time the condition has often advanced, rendering therapeutic interventions less effective. Given the limitations of conventional indicators in assessing liver failure following hepatectomy, there is an ongoing pursuit for accessible and reliable predictors associated with PHLF. Recent studies have demonstrated that immune, inflammatory, and nutritional indicators are significant predictors of prognostic risk in solid tumors, such as HCC,[19] nasopharyngeal carcinoma,[20] and pancreatic cancer.[21] This research involved comprehensive collection of biomarkers associated with immunity, inflammation, and nutrition from preoperative peripheral blood tests

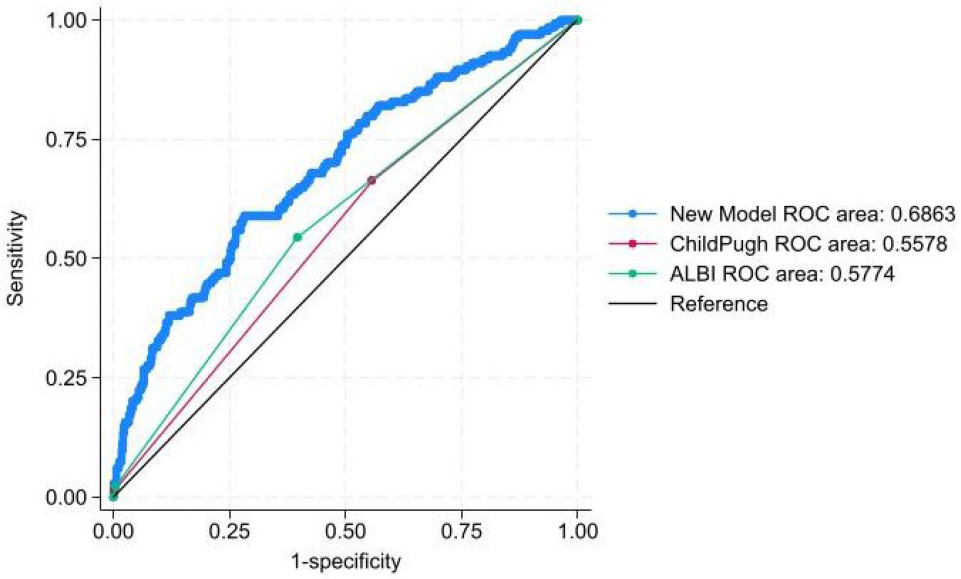

Figure 7 Comparison of PHLF prediction model and related scoring system ROC curves.

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Table 4 Comparison of Predictive Performance of Predictive Models in Different Populations

	n	AUC	Standard Error	95% CI
Child-Pugh A	323	0.7070	0.0444	0.62003–0.79400
Child-Pugh B	434	0.5727	0.0361	0.50193–0.64345
TS<5cm	405	0.6785	0.0360	0.60784–0.74914
TS≥5cm	355	0.7153	0.0367	0.64339–0.78730

of HCC patients, and subsequently calculated composite indicators pertaining to these domains. To the best of our knowledge, this study represents the first comprehensive assessment of the prognostic significance and clinical relevance of a combination of immune, inflammatory, and nutritional markers in predicting PHLF following hepatocellular carcinoma resection. In contrast to conventional predictive indicators, the nomogram employed in this study emphasizes the integration of composite biological markers, thereby providing a more holistic evaluation of the preoperative status of patients with liver cancer. Our results showed that AAPR, ALBI, GAR, PNI, LMR, INR, APTT, TT was associated with a significant PHLF occurred postoperatively in patients with HCC.

Among the various clinical scoring systems, the Child-Pugh scoring system is the most frequently utilized. However, it includes two subjective parameters, hepatic encephalopathy and ascites, which present certain limitations.[22] In response to these limitations, Johnson[23] introduced the ALBI scoring system, which offers a more objective assessment compared to the Child-Pugh system, with easily obtainable indicators. Numerous studies have validated the ALBI score as a significant prognostic tool for hepatocellular carcinoma surgery.[24,25] In this study, the truncation values of the ALBI score were determined to be −0.260 and −0.139, indicating that an elevated ALBI score is associated with an increased risk of postoperative PHLF. Qin[26] similarly identified that an ALBI score of grades 2 or higher serves as an independent risk factor for PHLF. The AAPR was introduced by Anthony[27] in 2015 as a novel inflammatory marker, combining

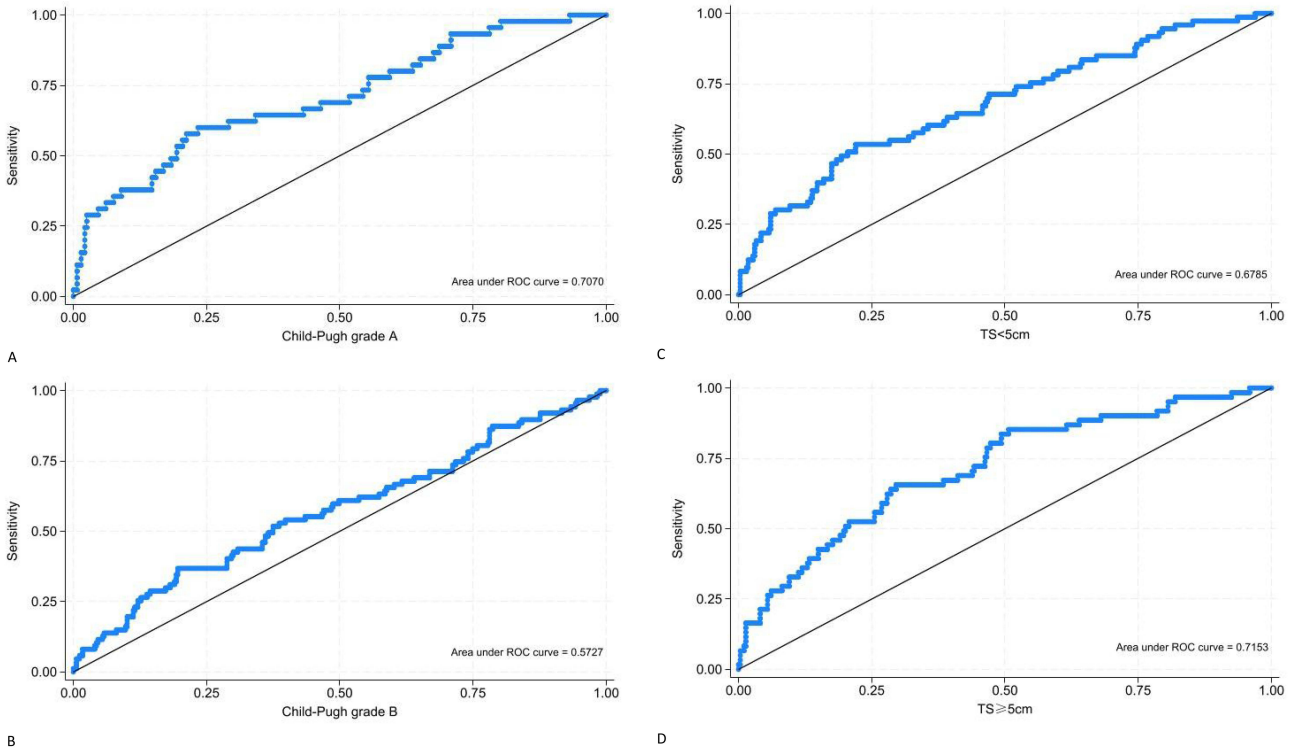

Figure 8 The area under the ROC curves AUCs of the nomogram for mortality from PHLF in patients with HCC in Child-Pugh grade A (**A**), Child-Pugh grade B (**B**), tumor diameters less than 5cm (**C**), tumor diameters greater than or equal to 5cm (**D**).

serum albumin and alkaline phosphatase levels. Their research demonstrated that a lower AAPR value correlates with reduced overall survival in patients with hepatocellular carcinoma.

Numerous studies have corroborated that a low AAPR serves as an independent risk factor for HCC patients undergoing hepatectomy, with diminished preoperative AAPR levels often correlating with reduced overall survival and relapse-free survival rates.[27,28] The present study demonstrated that the incidence of PHLF escalates as AAPR decreases, aligning with findings from existing research. Although the direct association between AAPR and PHLF lacks unequivocal empirical support, the components of AAPR, namely albumin and alkaline phosphatase, are integral to the prognostic evaluation of liver diseases, including possible association with PHLF. The AAPR, serving as a comprehensive marker of both inflammation and nutritional status, may represent a viable preoperative predictor for PHLF. Lymphocytes constitute a fundamental component of the immune system and play a crucial role in the defense mechanisms within the microenvironment where hepatocellular carcinoma develops, particularly in the context of chronic inflammation induced by factors such as hepatitis B or C virus, alcohol consumption, or metabolic syndrome.[29] Furthermore, a correlation between the abundance of tumor-infiltrating lymphocytes and the prognosis of hepatocellular carcinoma has been established.[30] Furthermore, inflammation is crucial in regulating liver regeneration, a process vital for the restoration of liver function following hepatectomy.[31] The LMR, serving as an indicator of the balance between inflammatory response and immune status, may be associated with the incidence of PHLF. This study finds that a low LMR is more likely to contribute to the occurrence of PHLF, aligning with existing research findings.[32] The mechanism by which preoperative patient inflammatory markers contribute to PHLF remains to be elucidated. However, extant research suggests that numerous inflammatory cytokines play a significant role in the anabolism of liver cells. However, extant research has demonstrated that a multitude of inflammatory cytokines exert a pivotal function in the anabolism of liver cells. For instance, transforming growth factor β (TGF-β) has been observed to inhibit albumin production in normal human hepatocytes and hepatocellular carcinoma HepG2 cells, achieving a decrease in albumin mRNA levels of 2-4-fold. Furthermore, lipopolysaccharide (LPS)-induced signalling activation and an increase in NF-κB activity have been shown to significantly reduce albumin expression.[33,34] Moreover, it is evident that the process of hepatic fibrosis may be precipitated by chronic inflammation. This is characterised by the activation of hepatic stellate cells (HSCs) by inflammatory cells, such as macrophages and neutrophils. Consequently, these HSCs undergo a transformation into myofibroblasts, which in turn secrete excess extracellular matrix, ultimately resulting in hepatic fibrosis.[35] The complex interplay of fibrosis, inflammation and progressive cellular damage that is characteristic of chronic disease fundamentally impairs liver regeneration due to the destruction of tissue structure.[36] It is also possible that this is related to the occurrence of PHLF.

Patients with advanced chronic illnesses frequently experience malnutrition and are unable to achieve sufficient nutritional intake solely through oral consumption. Liver disease is no exception, with nutritional status recognized as a prognostic indicator for individuals with advanced liver disease.[10,37] Regrettably, the nutritional challenges faced by patients with chronic liver disease are often underestimated, and comprehensive pre-surgical nutritional assessments are frequently neglected. Nutritional therapeutic interventions for patients with chronic liver disease are frequently under-utilized. Serum albumin accounts for more than 50% of total serum protein in healthy individuals and is a marker of the liver's ability to synthesise it, as well as a major indicator of human nutrition. It is widely acknowledged that low serum albumin levels are a significant predictor of complications, progression, survival and recurrence in a variety of tumours, including those that develop in the liver.[38] Albumin deficiency has been demonstrated to result in an excessive inflammatory response.[39] In murine models of acetaminophen-induced hepatitis, albumin fusion has been demonstrated to ameliorate hepatic redox and inflammatory conditions, thereby suggesting that serum albumin possesses antioxidant and anti-inflammatory properties.[40] Albumin modulates the immune and inflammatory response through binding lipopolysaccharide and bacterial products, reactive oxygen species, nitric oxide, prostaglandins, and endosomal TLR signaling.[41] Consequently, the infusion of serum albumin may represent a novel therapeutic approach to prevent systemic inflammatory response, PHLF and postoperative mortality. Nutritional indicators in this study were also calculated based on albumin. Numerous studies have demonstrated that PNI serves as a potential prognostic indicator in various cancers, including liver, stomach, ovarian, and lung cancers.[42–44] In the present study, PNI exhibits a degree of predictive value for PHLF. This is very important, and early nutritional therapy for patients with hepatocellular carcinoma may help

reduce the occurrence of PHLF, and it is worth further exploring the predictive value of PNI in PHLF. GGT mainly exists on liver cell membrane and microsomes, and is often increased due to liver cell inflammation when liver parenchyma is compressed.[45] The GGT in serum mainly comes from liver. In recent years, GGT has gradually been recognized as an independent prognostic indicator related to tumors, including urinary system tumors and liver cancer.[46,47] Recent studies have also shown that the higher the serum GGT level, the worse the prognosis of HCC patients.[48] Originating in the liver, albumin is the most dominant protein in plasma, accounting for about 50% of total plasma protein, and has been advocated as a marker of the nutritional status of individual patients. The reasons for the low level of albumin before operation may include: less albumin synthesis and secretion due to liver dysfunction; Tumor-related inflammatory responses lead to accelerated protein breakdown.[49] Patients with higher albumin levels tend to have better postoperative recovery speed and prognosis.[50] In this study, GAR was the ratio of GGT to albumin, and as the ratio increased, patients' risk of developing PHLF also increased, that is, high GGT and low albumin levels would have a worse prognosis, which is consistent with the current study.

The liver serves as the primary site for the synthesis of most clotting factors, as well as several proteins involved in fibrinolysis and anticoagulation. Chronic liver disease can substantially impact the synthesis of these factors, consequently affecting the systemic levels of pro-coagulant and anticoagulant factors.[51] Current research has demonstrated that, in addition to the liver's influence on clotting factor synthesis, the activity of these factors also diminishes as liver disease progresses.[52] The APTT serves as a measure of coagulation function, specifically reflecting the intrinsic coagulation pathway and the overall activity of coagulation factors during the initial phase. Prolongation of APTT is observed in patients with impaired hepatic function. The INR is another parameter of coagulation function, primarily utilized to assess the activity of vitamin K-dependent coagulation factors.[53] TT predominantly indicates alterations in the quantity or functionality of fibrinogen. The liver serves as the principal site for the synthesis of vitamin K-dependent clotting factors and fibrinogen. Consequently, impaired liver function leads to a reduction in the synthesis of these components, resulting in prolonged INR and TT. This study found that elevated APTT, INR, and TT were associated with an increased likelihood of developing PHLF. This association may be attributed to diminished liver function prior to surgery in patients exhibiting elevated levels of these indicators. The findings align with the established understanding that poorer preoperative liver function increases the risk of PHLF.

In this study, we constructed and validated a simple nomogram model based on patients' more readily available preoperative laboratory indicators, partially compounded and formed by correlation calculations, for predicting the postoperative development of PHLF in patients with HCC. The designed nomogram was validated and performed well in discrimination, calibration and clinical application. In addition, the nomogram provided valuable information for determining the appropriate treatment regimen for high-risk patients who may develop PHLF. Here we give an example of how to use the nomogram model, assuming a patient with hepatocellular carcinoma who is proposed to undergo hepatectomy, with an AAPR of 0.25 g/IU, ALBI of grade 3, GAR of 20 U/g, PNI of 170, LMR of 2, INR of 1.1, APTT of 35s, TT of 20s, according to Figure 3, obtaining a line graph with the score corresponding to each parameter on the "point" axis was obtained according to Figure 3. The total score was calculated as the sum of the scores for all parameters [70 (AAPR) + 10 (ALBI) + 10 (GAR) + 30 (PNI) + 87.5 (LMR) + 12.5 (INR) + 40 (APTT) + 18 (TT) = 268]. This score corresponds to a 65% risk of developing PHLF. In this study, we sought to ascertain the comparative performance of the nomogram with existing liver function scoring systems. The results demonstrated the nomogram to be superior in terms of predictive performance. Furthermore, a subgroup analysis of the existing population was conducted, which revealed that the nomogram exhibited superior predictive capabilities in Child-Pugh score grade A (AUC=0.707, 95CI 0.620–0.794) and tumor diameter size ≥5cm (AUC=0.715, 95CI 0.643–0.788).

Limitations

The present study is subject to certain limitations. Firstly, although the patient sample size was large, it was not validated using an external dataset. Secondly, a large number of potential factors affecting postoperative complications in hepatic failure in patients with primary hepatocellular carcinoma may have been overlooked, and this Nomogram may have failed to include other important risk variables. Finally, as this was a single-centre study, further validation may be required to ensure the generalisability of the Nomogram.

Conclusion

In conclusion, this study utilized eight preoperative indices—AAPR, ALBI, GAR, PNI, LMR, INR, APTT, TT—related to immunity, inflammation, nutrition, and blood coagulation to develop a nomogram for predicting postoperative PHLF in patients with hepatocellular carcinoma. This nomogram has a good predictive value for PHLF in HCC patients and is important for clinicians to manage patients after hepatectomy.

Data Sharing Statement

The datasets generated and analyzed in this study will be available by the corresponding author upon reasonable request.

Ethics Statement

This study was conducted following the Declaration of Helsinki and was approved by the Ethical Committee of the First Hospital Affiliated to the University of Science and Technology of China. All patient data were analyzed in anonymity. Patient consent was waived by the ethics committee, as no individual data were published, nor was any intervention performed on patients.

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Author Contributions

All authors made significant contributions to the reported work, including conception, study design, execution, data acquisition, analysis, and interpretation. They also participated in drafting, revising, or critically reviewing the article, and gave final approval of the manuscript. Furthermore, they agreed on the journal to which the article would be submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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