ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 December 28; 30(48): 5104-5224

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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Weekly Volume 30 Number 48 December 28, 2024

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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PUBLICATION DATE
December 28, 2024

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Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

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World J Gastroenterol 2024 December 28; 30(48): 5130-5151

DOI: 10.3748/wjg.v30.i48.5130

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Prognostic value of preoperative systemic immune-inflammation index/albumin for patients with hepatocellular carcinoma undergoing curative resection

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B, Grade C

Novelty: Grade A, Grade A, Grade B

Creativity or Innovation: Grade A, Grade B, Grade B

Scientific Significance: Grade A, Grade B, Grade C

P-Reviewer: Engida YE; Liu QS; Tan JT

Received: June 20, 2024

Revised: September 20, 2024

Accepted: October 8, 2024

Published online: December 28, 2024

Processing time: 161 Days and 21.5 Hours

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a major factor for cancer-associated mortality globally. Although the systemic immune-inflammation index (SII) and albumin (ALB) show individual prognostic value for various cancers, their combined significance (SII/ALB) in HCC patients undergoing curative hepatectomy is still unknown. It is hypothesized that a higher SII/ALB ratio correlates with poorer outcomes with regard to overall survival (OS) and recurrence-free survival (RFS).

AIM

To investigate the effect of preoperative SII/ALB in predicting the prognosis of HCC patients undergoing hepatectomy.

METHODS

Patients who received curative surgery for HCC at a single institution between 2014 and 2019 were retrospectively analyzed. Cox proportional hazards models and Kaplan-Meier curves were utilized to estimate OS and RFS. A nomogram was created using prognostic factors determined by the least absolute shrinkage and selection operator method and analyzed using multivariate Cox regression. This nomogram was assessed internally through the calibration plots, receiver operating characteristic (ROC) analysis, decision curve analysis (DCA) and the concordance index (C-index).

RESULTS

This study enrolled 1653 HCC patients. Multivariate analyses demonstrated that SII/ALB independently predicted OS [hazard ratio (HR) = 1.22, 95%CI: 1.03-1.46, P = 0.025] and RFS (HR = 1.19, 95%CI: 1.03-1.38, P = 0.022). Age, alpha-fetoprotein, hepatitis B surface antigen, albumin-bilirubin grade, tumor diameter,

portal vein tumor thrombus, tumor number, and SII/ALB were incorporated into the nomogram to predict OS. The nomogram had a C-index of 0.73 (95%CI: 0.71-0.76) and 0.71 (95%CI: 0.67-0.74) for the training and validation cohorts, respectively. The area under the ROC curve, DCA and calibration curves demonstrated high accuracy and clinical benefits.

CONCLUSION
The SII/ALB may independently predict outcomes in HCC patients who receive curative surgical treatment. In addition, the nomogram can be used in HCC treatment decision-making.

Key Words: Hepatocellular carcinoma; Inflammation; Systemic immune-inflammation index/albumin; Liver resection; Prognosis

Core Tip: This study validates the systemic immune-inflammation index/albumin ratio (SII/ALB) as a novel prognostic marker for hepatocellular carcinoma (HCC) patients after hepatectomy. It was shown that SII/ALB independently predicted overall and recurrence-free survival. Incorporating SII/ALB into a predictive nomogram demonstrated superior accuracy and clinical utility, providing a refined tool for personalized treatment strategies in HCC management.

Citation: Chen KL, Qiu YW, Yang M, Wang T, Yang Y, Qiu HZ, Sun T, Wang WT. Prognostic value of preoperative systemic immune-inflammation index/albumin for patients with hepatocellular carcinoma undergoing curative resection. *World J Gastroenterol* 2024; 30(48): 5130-5151
URL: https://www.wjgnet.com/1007-9327/full/v30/i48/5130.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i48.5130

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks 6th among all cancers worldwide, and ranks 4th in terms of cancer mortality[1]. Despite treatment improvements for HCC, the survival outcomes in HCC patients are generally poor. Liver resection remains the principal strategy to cure early-stage HCC[2]. HCC has a high five-year post-surgical recurrence rate of approximately 70%, leading to a poor prognosis[3,4]. Due to intra-tumor heterogeneity, patients at the same HCC stage can have a significantly varied outcome[5]. Therefore, it is important to identify biological markers to select patients who will benefit from surgical treatment.

Host immune status and cancer-associated inflammation have been found to support tumor growth and progression [6]. The systemic immune-inflammation index (SII), formulated from neutrophil, platelet and lymphocyte counts in peripheral blood, serves as an indicator reflecting the balance between host immune function and inflammation[7-9]. The SII is related to the prognostic outcome of liver diseases, including HCC, intrahepatic cholangiocarcinoma, combined hepatocellular-cholangiocarcinoma, nonalcoholic fatty liver disease, and hepatic steatosis[7,10-13]. Albumin (ALB) represents a key nutritional prognostic marker of HCC, which is reported to inhibit human HCC growth and the cell cycle[14-16]. High serum ALB level is related to lower recurrence rates and longer overall survival (OS) in HCC patients [17,18].

The systemic immune-inflammation index/albumin ratio (SII/ALB) is an index reflecting immune, nutritional and inflammatory conditions in cancer patients, and was initially reported by Tian *et al*[19] in 2019. For patients with small cell lung cancer and operable non-small cell lung cancer, a high SII/ALB indicates an adverse outcome[19]. Additionally, SII/ALB independently predicts the outcome of hepatitis B virus (HBV)-related HCC patients following transarterial chemoembolization (TACE) therapy[19]. Nevertheless, the relationship between preoperative SII/ALB and survival outcome after surgical resection of HCC is still unknown.

The present work focused on exploring the impact of preoperative SII/ALB on OS and recurrence-free survival (RFS) among HCC patients who underwent surgical resection. Furthermore, a nomogram was developed to predict the survival of resectable HCC patients.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the West China Hospital of Sichuan University Ethics Committee [No. 2024(189)] and followed the Declaration of Helsinki. Due to the nature of retrospective studies, informed consent was not required. From April 2014 to July 2019, 1653 HCC patients who underwent curative liver resection for the first time at Sichuan University's West China Hospital were consecutively enrolled. Eligibility criteria for the study included patients

with histopathologically confirmed HCC who had received a R0 liver resection. Exclusion criteria were: (1) Presence of additional primary liver cancers (such as cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma) and a history of cancer in another organ at the same time or in the past; (2) HCC with clear bile duct invasion; (3) Positive lymph node metastases; (4) Invasion to adjacent organs; (5) Distant metastasis; (6) Well-preserved liver function; and (7) Lacking sufficient clinicopathological records or follow-up data. Supplementary Figure 1 shows the patient screening procedure.

Preoperative assessment and liver resection

Patients routinely underwent abdominal computed tomography (CT), contrast-enhanced ultrasound, chest CT, or magnetic resonance imaging (MRI). Moreover, clinical examinations were performed, including HBV-related tests, tumor marker measurements, and liver function tests. Preoperative laboratory values were obtained as close as possible to the time of surgery. The remnant liver volume was assessed by enhanced CT or MRI to prevent postoperative liver failure. Liver function assessment was conducted using the albumin-bilirubin (ALBI) and Child-Pugh scoring systems. Liver resection was considered feasible if R0 resection was technically feasible and the remaining healthy liver was sufficient to ensure adequate function. The surgical removal of liver tissue was tailored to the specific location, spread, and size of each tumor. Intraoperative ultrasound was performed when necessary.

Definition

The SII/ALB was obtained using the formula [platelets (PLT) × neutrophils (NE)/lymphocytes (LY)]/ALB. The SII was determined by PLT × NE/LY. We also determined the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) using ratios of NE to LY, and PLT to LY, respectively. All counts are in 10^9/L, whereas ALB is in g/L.

Cirrhosis and portal vein tumor thrombus (PVTT) were diagnosed based on the preoperative imaging findings. Hepatectomy involved removal of at least 3 liver segments[20]. Liver anatomy and liver resection type were classified in accordance with the Brisbane 2000 terminology of liver anatomy and resection[21]. The Edmondson-Steiner grading system was adopted for grading tumor differentiation.

Follow-up

The status of patients discharged alive was systematically monitored as part of this observational retrospective cohort study. Our research team collected follow-up data at 2-month intervals in the initial two years and at 3-month intervals thereafter by a combination of reviewing outpatient visit records and conducting telephone calls. The follow-up data included information on routine clinical care, which was already documented as part of standard healthcare practices. Diagnosis of recurrent HCC was determined by routine clinical assessment involving CT and/or MRI, supplemented by evaluations of alpha-fetoprotein (AFP) tumor marker levels. For patients with recurrent HCC during the follow-up period, we documented treatments administered as part of their routine clinical care. Treatment options varied and were based on individual patient factors and clinical decisions made by their healthcare providers. The primary endpoint of the study was OS (between surgery date and the final follow-up), while RFS (between surgery date and confirmation of recurrence and/or metastasis date) was the secondary endpoint.

Statistical analysis

Continuous data were indicated by median (interquartile range), whereas categorical data by number (%). Fisher's exact test and the χ^2 test were adopted for comparison of categorical data. To assess the predictive capacity of different inflammatory indices for OS and RFS, we employed time-dependent receiver operating characteristic (ROC) curves. Restricted cubic splines were utilized within the Cox proportional hazards model for estimating the non-linear relationship between SII/ALB and OS. A suitable SII/ALB threshold was identified using maximally selected rank statistics. Survival curves for OS and RFS were constructed using the Kaplan-Meier approach and analyzed by the log-rank test.

The patients were randomized into the training group or validation group at the ratio of 7:3. In the training group, multivariate regression and least absolute shrinkage and selection operator (LASSO) Cox regression were conducted to screen factors independently predicting prognosis and create the nomogram that forecast 5-year survival rates. A 10-fold cross-validation was conducted to analyze the LASSO tuning parameter [lambda (λ)]. Performance of the nomogram was subsequently assessed with ROC curves for discrimination and calibration curves for accuracy of predictions. We also utilized the DeLong test for assessing significant differences between two areas under the curve (AUC). The nomogram's clinical net benefits were assessed by decision curve analysis (DCA). To facilitate the clinical application of this nomogram, a web-based tool was developed (https://nomogramfiles.shinyapps.io/dynnomapp/). A P-value < 0.05 indicated a statistically significant difference. Version 4.2.2 of the R software was adopted for statistical analysis.

RESULTS

Patient features

Table 1 shows detailed patient characteristics. All participants were followed until January 31, 2021. The patients were followed up for a median of 46 months, and any medical interventions were part of standard clinical care and not influenced by this research.

Table 1 Patient demographics and baseline characteristics, *n* (%)

Characteristics	Total (*n* = 1653)
Sex	
Female	247 (15)
Male	1406 (85)
Age, years	
≤ 60	1185 (72)
> 60	468 (28)
Hepatitis B surface antigen	
Negative	263 (16)
Positive	1390 (84)
Alpha-fetoprotein, ng/mL	
< 400	1370 (83)
≥ 400	283 (17)
Platelets, 10^9/L	
> 100	1,178 (71)
≤ 100	475 (29)
Neutrophil, 10^9/L	
≤ 6.3	1577 (95)
> 6.3	76 (5)
Lymphocyte, 10^9/L	
> 0.8	1547 (94)
≤ 0.8	106 (6)
Alanine transaminase, U/L	
≤ 40	1199 (73)
> 40	454 (27)
Aspartate transaminase, U/L	
≤ 40	966 (58)
> 40	687 (42)
Prothrombin time, second	
≤ 13	1360 (82)
> 13	293 (18)
Total bilirubin, μmol/L	
≤ 32.4	1630 (99)
> 32.4	23 (1)
Albumin, g/L	
> 35	1572 (95)
≤ 35	81 (5)
Albumin-bilirubin grade	
1	1279 (77)
2	374 (23)
Tumor diameter, cm	
< 5	785 (47)

≥ 5	868 (53)
Number of tumors	
Single	1389 (84)
Multiple	264 (16)
Barcelona Clinic Liver Cancer stage	
0	152 (9)
A	1192 (72)
B	184 (11)
C	125 (8)
Hypertension	
No	1397 (85)
Yes	256 (15)
Diabetes	
No	1518 (92)
Yes	135 (8)
Cardiovascular disease	
No	1624 (98)
Yes	29 (2)
Anatomical resection	
No	1068 (65)
Yes	585 (35)
Major hepatectomy	
No	1415 (86)
Yes	238 (14)
Transfusion	
No	1557 (94)
Yes	96 (6)
Differentiation	
I-II	898 (54)
III-IV	755 (46)
Microvascular invasion	
No	1177 (71)
Yes	476 (29)
Cirrhosis	
No	795 (48)
Yes	858 (52)
Portal vein tumor thrombus	
No	1528 (92)
Yes	125 (8)
Systemic immune-inflammation index/albumin	6 (4, 10)
Systemic immune-inflammation index	271 (170, 447)
Neutrophil-to-lymphocyte ratio	2.10 (1.58, 2.93)
Platelet-to-lymphocyte ratio	88 (63, 125)

Median (interquartile range) for continuous variables.

Comparison of the predictive power of SII/ALB with several inflammatory indices of OS and RFS

As indicated by time-dependent ROC curve analysis, SII/ALB demonstrated superior prediction performance in terms of OS and RFS when compared to additional inflammatory markers, including SII, NLR, and PLR (Figure 1).

Determination of the cutoff value of SII/ALB

The restricted cubic splines analyses revealed the significant nonlinear relationship between SII/ALB and 5-year OS (P nonlinear < 0.0001), as shown in Figure 2A. SII/ALB = 9.25 was determined as the cutoff value based on maximally selected rank statistics (Figure 2B).

Relationship between SII/ALB and HCC clinicopathological factors

SII/ALB was correlated with HBV, platelets (PLT), neutrophils (NE), aspartate transaminase (AST), prothrombin time (PT), ALB, ALBI grade, tumor diameter, Barcelona Clinic Liver Cancer (BCLC) stage, anatomical resection, major hepatectomy, transfusion, differentiation, microvascular invasion (MVI), cirrhosis and PVTT (P < 0.05), but not with sex, age, AFP, lymphocytes (LY), alanine transaminase (ALT), total bilirubin, number of tumors, hypertension, diabetes and cardiovascular disease (P > 0.05) (Table 2).

Relationship between preoperative SII/ALB and both OS and RFS

Patients in the low SII/ALB group showed superior 1-year, 3-year, and 5-year OS rates (88.6%, 71.4%, and 61.5%) compared to the high SII/ALB group (72.8%, 52.4%, and 43.3%; P < 0.0001) (Figure 2C). The low SII/ALB group showed superior 1-year, 3-year, and 5-year RFS rates (69.4%, 51.0%, and 42.4%) compared to the high SII/ALB group (50.5%, 35.3%, and 30.8%; P < 0.0001) (Figure 2D).

Subgroup analysis

Subgroups were categorized based on high or low SII/ALB levels. High SII/ALB was associated with poorer OS across various subgroups [female, male, age ≤ 60 years, hepatitis B surface antigen (HbsAg) negative or positive, AFP < 400 ng/mL or AFP ≥ 400 ng/mL, ALBI grade 1 or grade 2, tumor diameter ≥ 5 cm, single or multiple tumors, BCLC stage A or B, anatomical or non-anatomical resection, major or non-major hepatectomy, with or without transfusion, differentiation grade I-II or grade III-IV, with or without MVI, with or without cirrhosis, and without PVTT (Figure 3)]. Similarly, high SII/ALB was associated with poorer RFS in various subgroups [female, male, age ≤ 60 years, HBsAg negative or positive, AFP < 400 ng/mL, AFP ≥ 400 ng/mL, ALBI grade 1 or grade 2, tumor diameter ≥ 5 cm, single or multiple tumors, BCLC stage A, B, or C, anatomical or non-anatomical resection, major or non-major hepatectomy, with or without transfusion, differentiation grade I-II or grade III-IV, with or without MVI, with or without cirrhosis, and with or without PVTT (Figure 4)].

Univariate and multivariate regression using Cox proportional hazards models of OS and RFS

Univariate analysis revealed that age, HBsAg, AFP, ALT, AST, PT, ALBI grade, tumor diameter, tumor number, hypertension, anatomical resection, major hepatectomy, transfusion, differentiation, MVI, PVTT and SII/ALB were notably correlated with OS. Multivariate Cox regression analysis indicated that age, HBsAg, AFP, AST, ALBI grade, tumor diameter, number of tumors, major hepatectomy, differentiation, MVI, PVTT and SII/ALB, were independent risk factors for OS (Table 3).

Univariate regression indicated that age, HBsAg, AFP, ALT, AST, PT, ALBI grade, tumor diameter, tumor number, hypertension, major hepatectomy, transfusion, differentiation, MVI, PVTT and SII/ALB significantly predicted RFS. Based on multivariate Cox regression, age, HBsAg, AFP, AST, tumor diameter, number of tumors, differentiation, MVI, PVTT and SII/ALB, were independent risk factors for RFS (Table 3).

Construction of the nomogram for predicting 5-year OS

The 1653 patients were randomized at a 7:3 ratio between the training data (n = 1157) and validation data (n = 496). Patients in the training and validation groups exhibited similar characteristics, with no significant differences observed (Supplementary Table 1). The Kaplan-Meier curve for OS and RFS indicated that these cohorts were not significantly different (P value = 0.19, P value = 0.95) (Supplementary Figure 2).

The preoperative candidate predictors such as sex, age, HBsAg, AFP, ALT, AST, PT, ALBI grade, tumor diameter, tumor number, hypertension, diabetes, cardiovascular disease, cirrhosis, PVTT, and SII/ALB, were incorporated into the LASSO analysis. The selected features, determined by the λ value in one standard error from minimum (λ 1se), included age, HBsAg, AFP, AST, ALBI grade, tumor diameter, tumor number, PVTT, and SII/ALB. Regression coefficients were calculated as follows: -0.038, 0.097, 0.127, 0.162, 0.079, 0.618, 0.177, 0.903, and 0.232. Tuning parameter (λ) selection and LASSO coefficient profiles are presented in Figure 5.

After selecting the final variables using LASSO regression, both univariate and multivariate Cox regression was conducted, as shown in Supplementary Table 2. Age, HBsAg, AFP, AST, ALBI grade, tumor diameter, tumor number, PVTT, and SII/ALB were independent risk factors for OS.

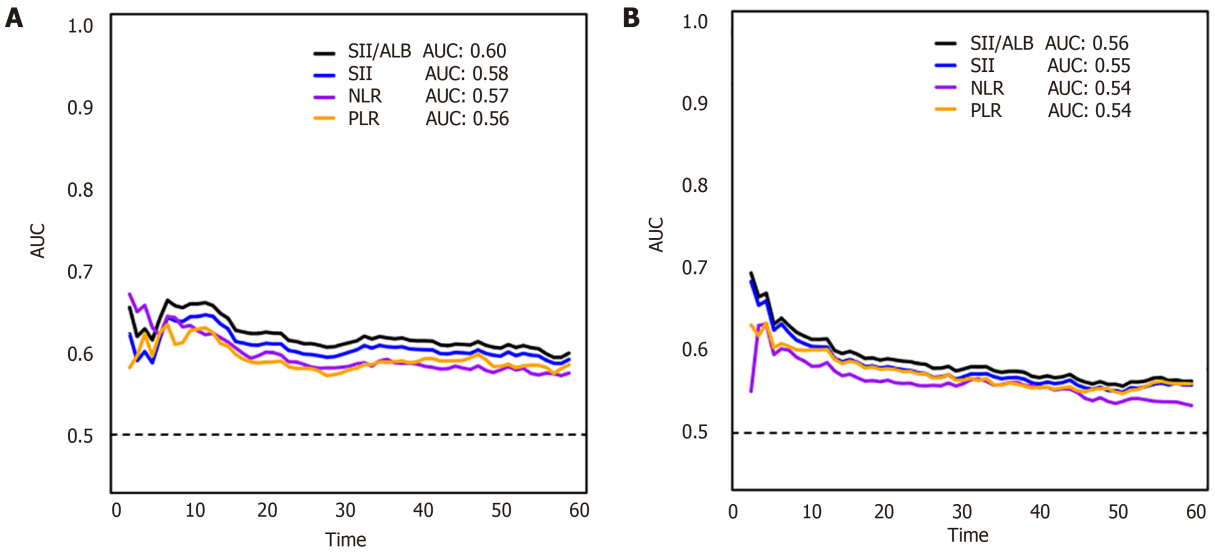


Figure 1 Time-dependent receiver operating characteristic curves for systemic immune-inflammation index/albumin, systemic immune-inflammation index, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predicting. A: Time dependent area under the curve (AUC) for overall survival; B: Time dependent AUC for recurrence-free survival. SII/ALB: Systemic immune-inflammation index/albumin; ALB: Albumin; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; AUC: Area under the curve.

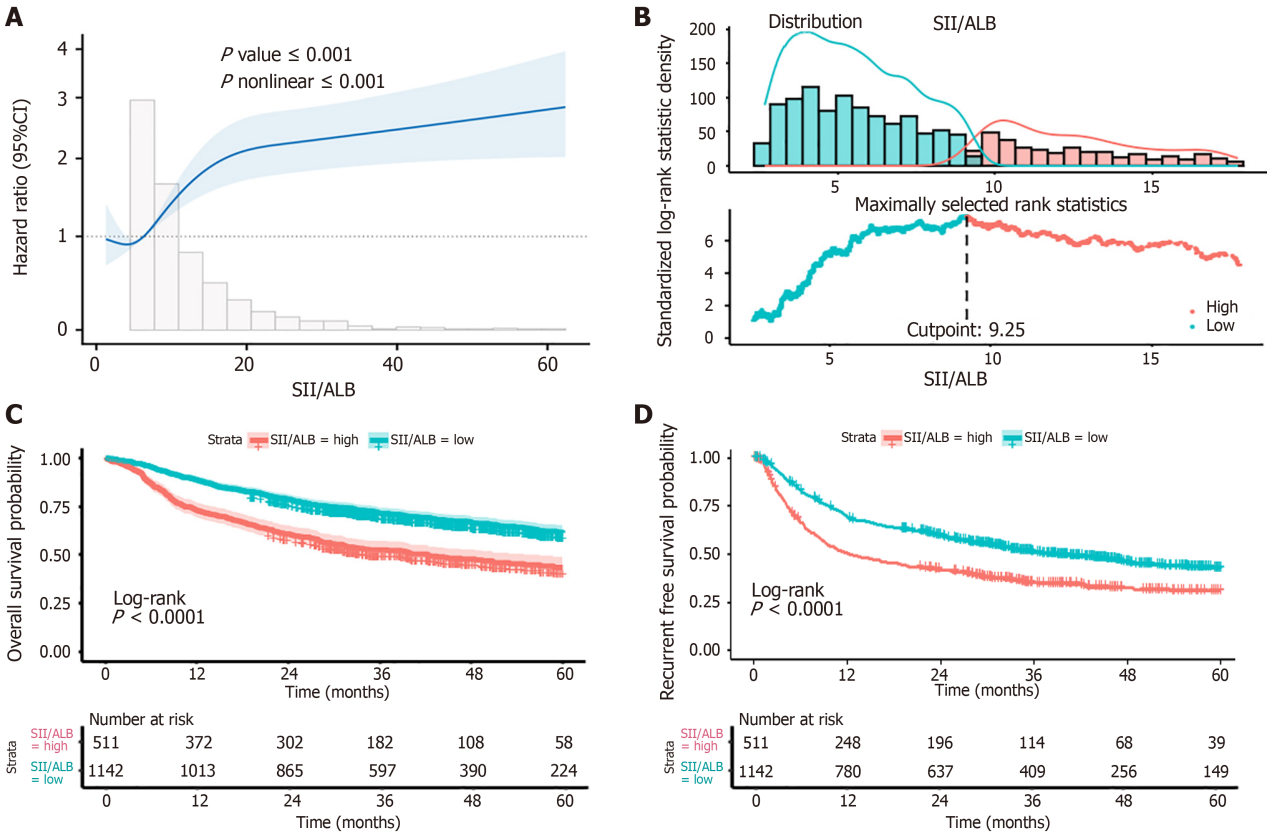


Figure 2 Relationship between systemic immune-inflammation index/albumin and both overall survival and recurrence-free survival. A: Examination of the dose-response relationship between systemic immune-inflammation index/albumin (SII/ALB) and 5-year overall survival (OS) by the restricted cubic splines model; B: Cut-off value of SII/ALB in patients with hepatocellular carcinoma; C: Kaplan-Meier curves depicting the association between SII/ALB and OS; D: Kaplan-Meier curves depicting the association between SII/ALB and recurrence-free survival. SII/ALB: Systemic immune-inflammation index/albumin.

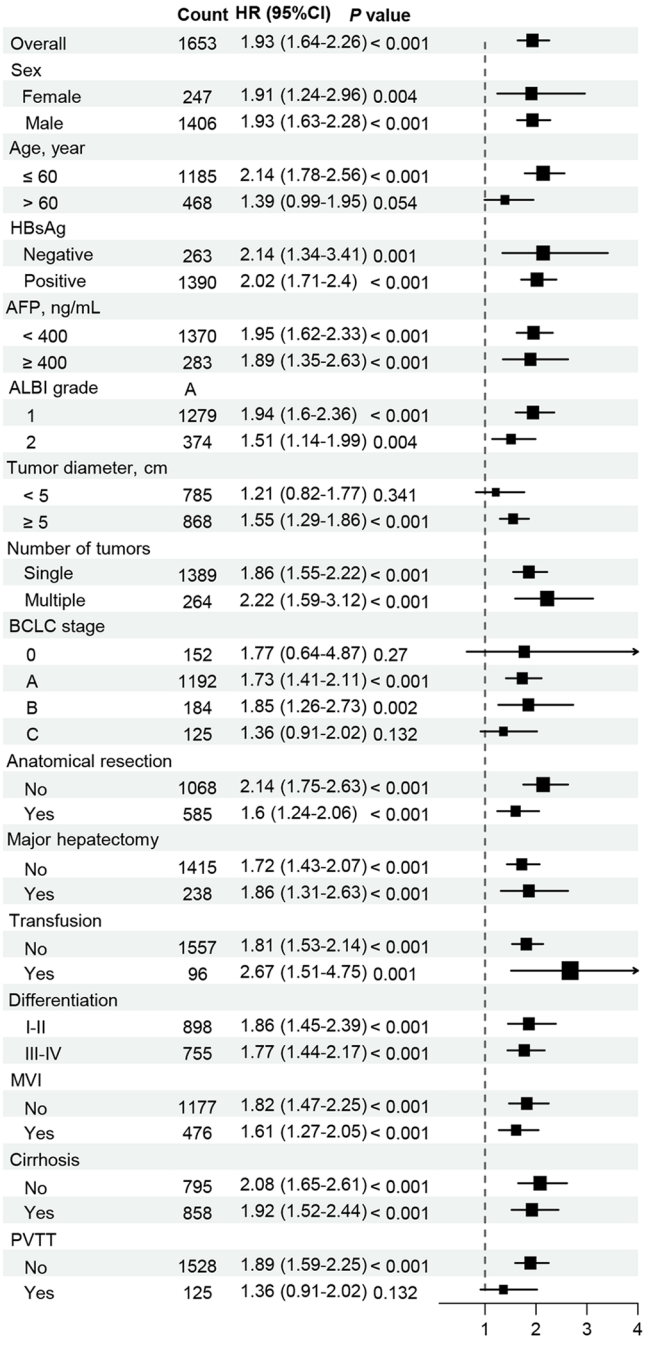


Figure 3 Subgroup analysis of systemic immune-inflammation index/albumin in predicting overall survival. HR: Hazard ratio; HbsAg: Hepatitis B surface antigen; AFP: Alpha-fetoprotein; ALBI: Albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; MVI: Microvascular invasion; PVTT: Portal vein tumor thrombus.

The final Cox model included 9 predictors (age, HBsAg, AFP, AST, ALBI grade, tumor diameter, tumor number, PVTT, and SII/ALB) and was conveniently translated into a user-friendly nomogram, depicted in Figure 5C, which can also be accessed online for practical application.

Assessment of the nomogram performance and applicability

Calibration curve analysis showed the robust correlation between the predicted and actual 1-year, 3-year, and 5-year OS rates across the two groups (Figure 6). The C-indices were calculated using 500 bootstrap resamplings and found to be 0.73 (95%CI: 0.71-0.76) and 0.71 (95%CI: 0.67-0.74) for the training and validation groups, respectively.

In the training cohort, the 1-year, 3-year, and 5-year survival predictions resulted in AUC of 0.81, 0.77, and 0.75, while those in the validation group were 0.73, 0.72, and 0.68, respectively. Our model outperformed four others, showing the highest AUC across these time points for both cohorts (Figure 7).

The 1-year, 3-year, and 5-year DCA curves were used to evaluate our nomogram against the BCLC, China Liver Cancer Staging system, and the Milan Criteria in the training and validation cohorts. The nomogram showed superior predictive accuracy over the other models (Figure 8).

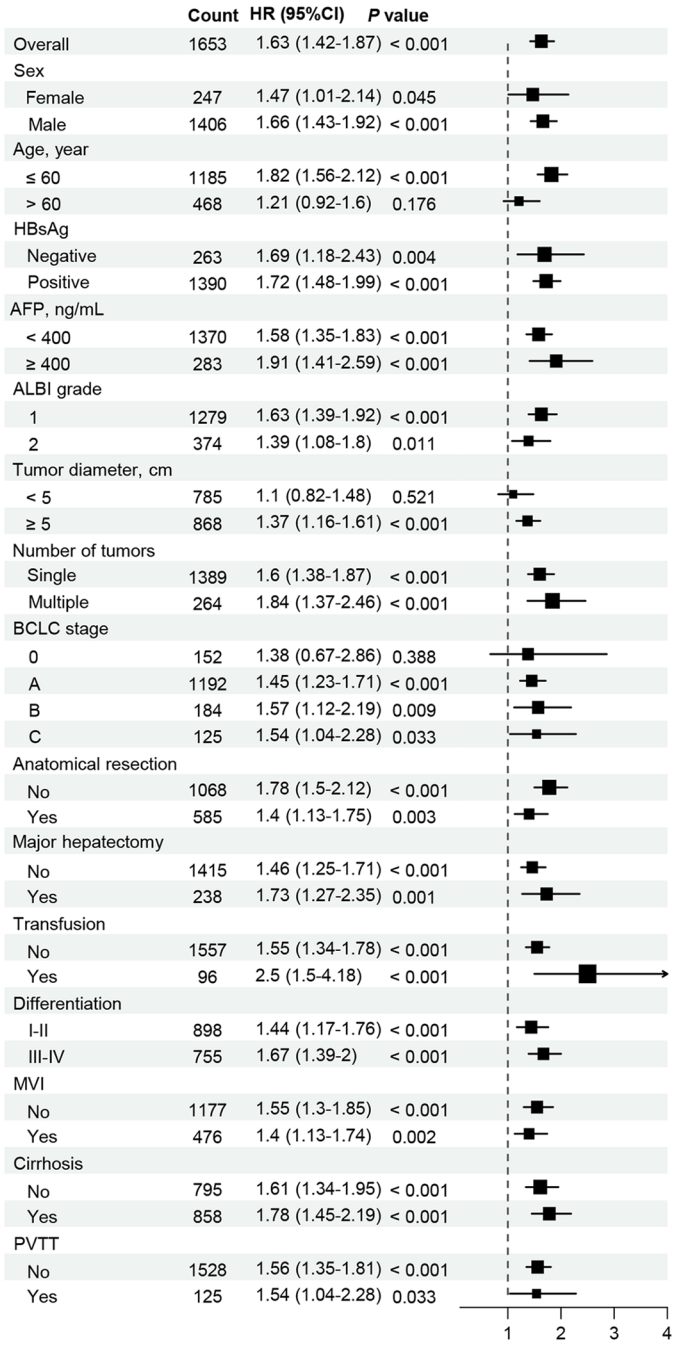


Figure 4 Subgroup analysis of systemic immune-inflammation index/albumin in predicting recurrence-free survival. HR: Hazard ratio; HbsAg: Hepatitis B surface antigen; AFP: Alpha-fetoprotein; ALBI: Albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; MVI: Microvascular invasion; PVTT: Portal vein tumor thrombus.

DISCUSSION

HCC is a solid tumor, which ranks fourth in global cancer mortality rates[22]. The 5-year survival rate of patients with HCC is 18%, and its recurrence rate can reach up to 70% within five years[3,23]. For early recurrence, a consensus exists that critical predictive factors include tumor biologic characteristics[24-26]. However, current guidelines do not recommend biopsy as a routine test for HCC[27,28]. The identification of preoperative factors for OS and HCC recurrence may help manage these patients.

This study is the first to use preoperative SII/ALB to predict OS in HCC patients following surgical resection. SII/ALB was the strongest predictor of OS with the highest AUC among the inflammatory response biomarkers (SII/ALB, SII, NLR, and PLR), which suggests that the SII/ALB can more accurately predict patient outcomes in those with HCC. High SII/ALB is related to worse liver function, a larger tumor diameter, a more advanced BCLC stage, lower differentiation, MVI and PVTT. High SII/ALB ratios were linked to worse OS and RFS across different patient subgroups. The SII/ALB has been shown to independently predict both OS and RFS in HCC patients following curative surgery. AUC, calibration curve and DCA curve were used to assess different models, which showed that our nomogram had good discrimination

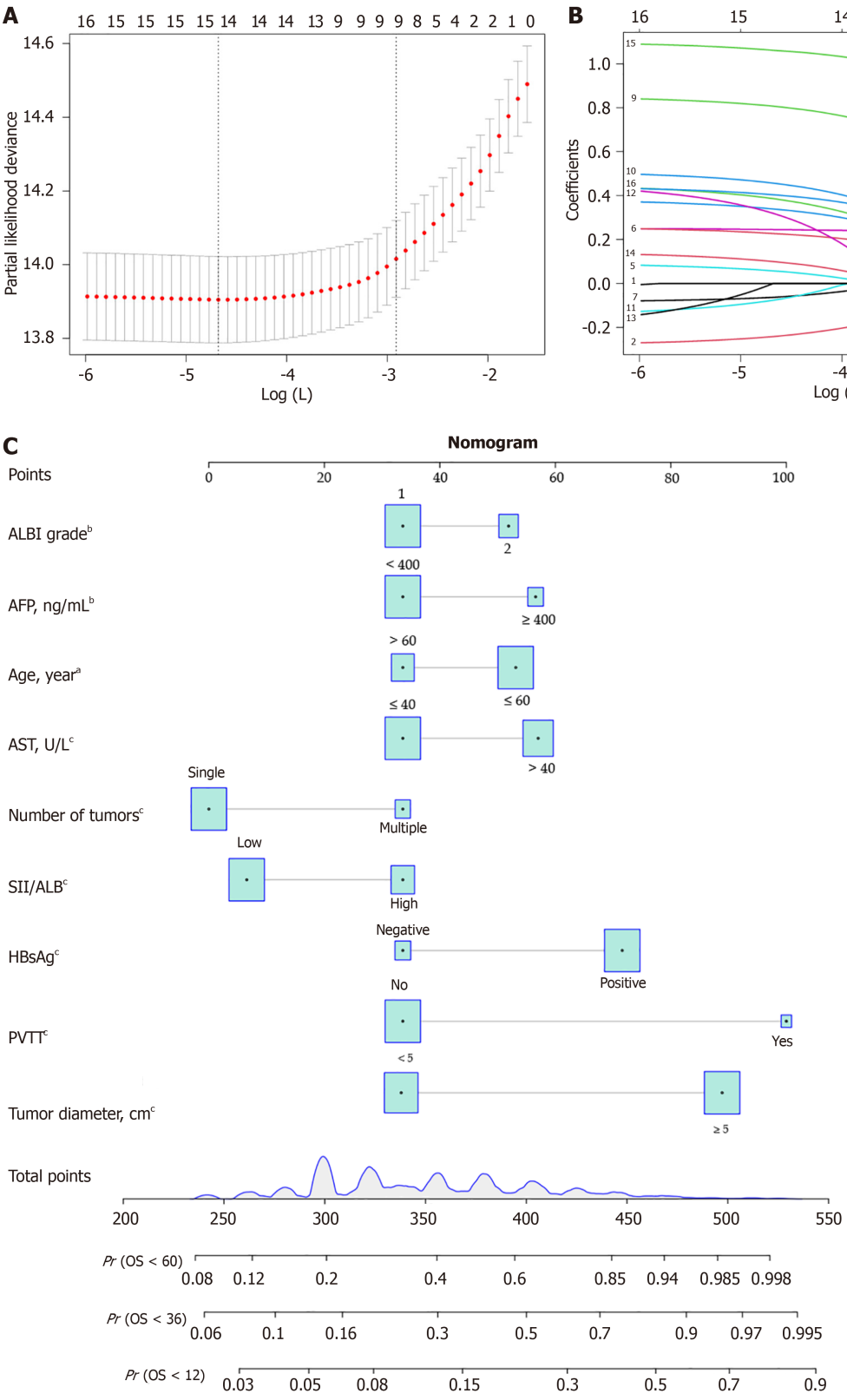


Figure 5 Least absolute shrinkage and selection operator regression analysis for variable selection. A: Cross-validation graph; B: Least absolute shrinkage and selection operator regression analysis coefficients; C: Construction of a nomogram incorporating systemic immune-inflammation index/albumin and clinical parameters. ALBI: Albumin-bilirubin; λ: Lambda; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; HbsAg: Hepatitis B surface antigen; SII/ALB: Systemic immune-inflammation index/albumin; PVTT: Portal vein tumor thrombus; OS: Overall survival.

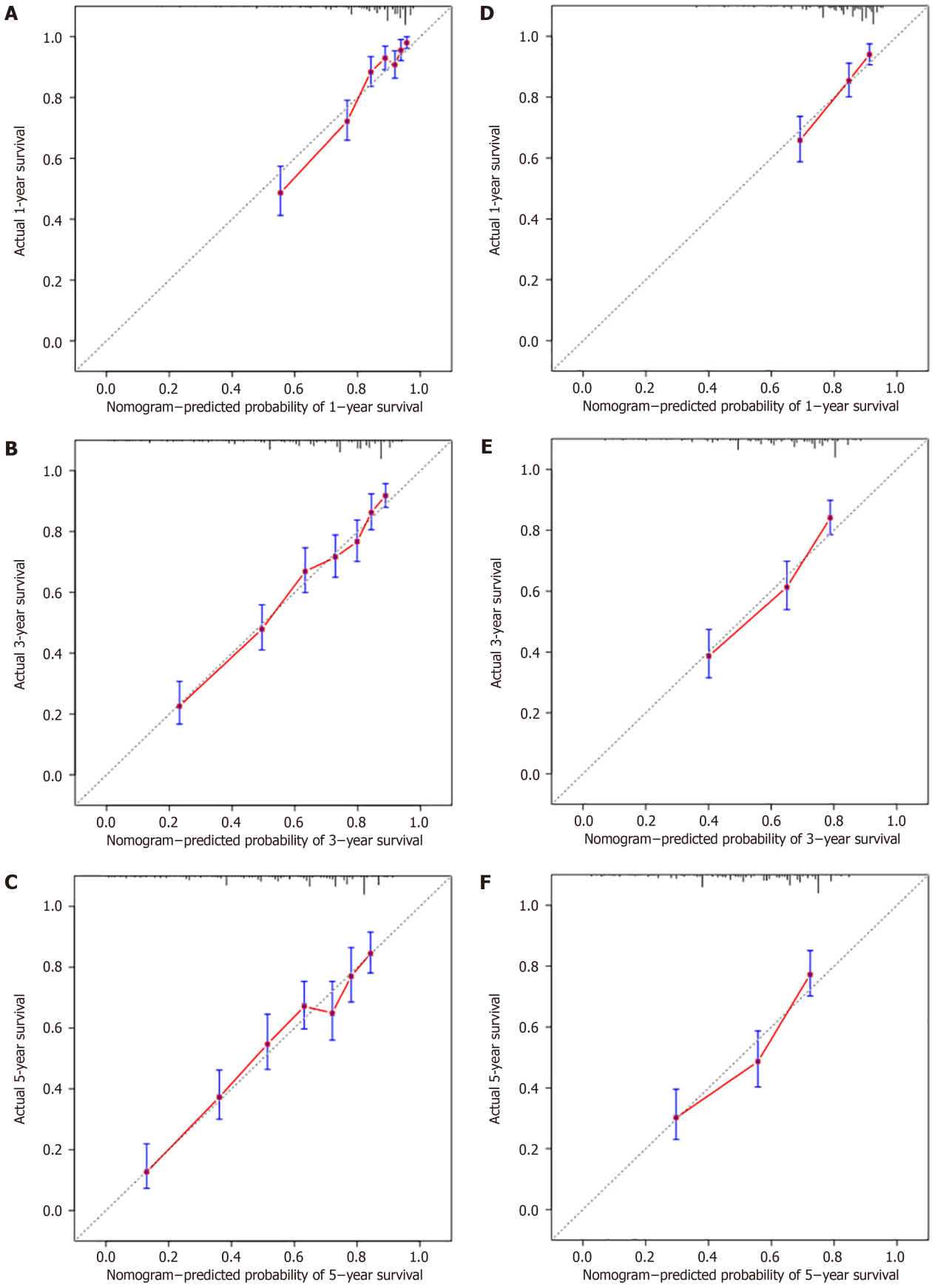
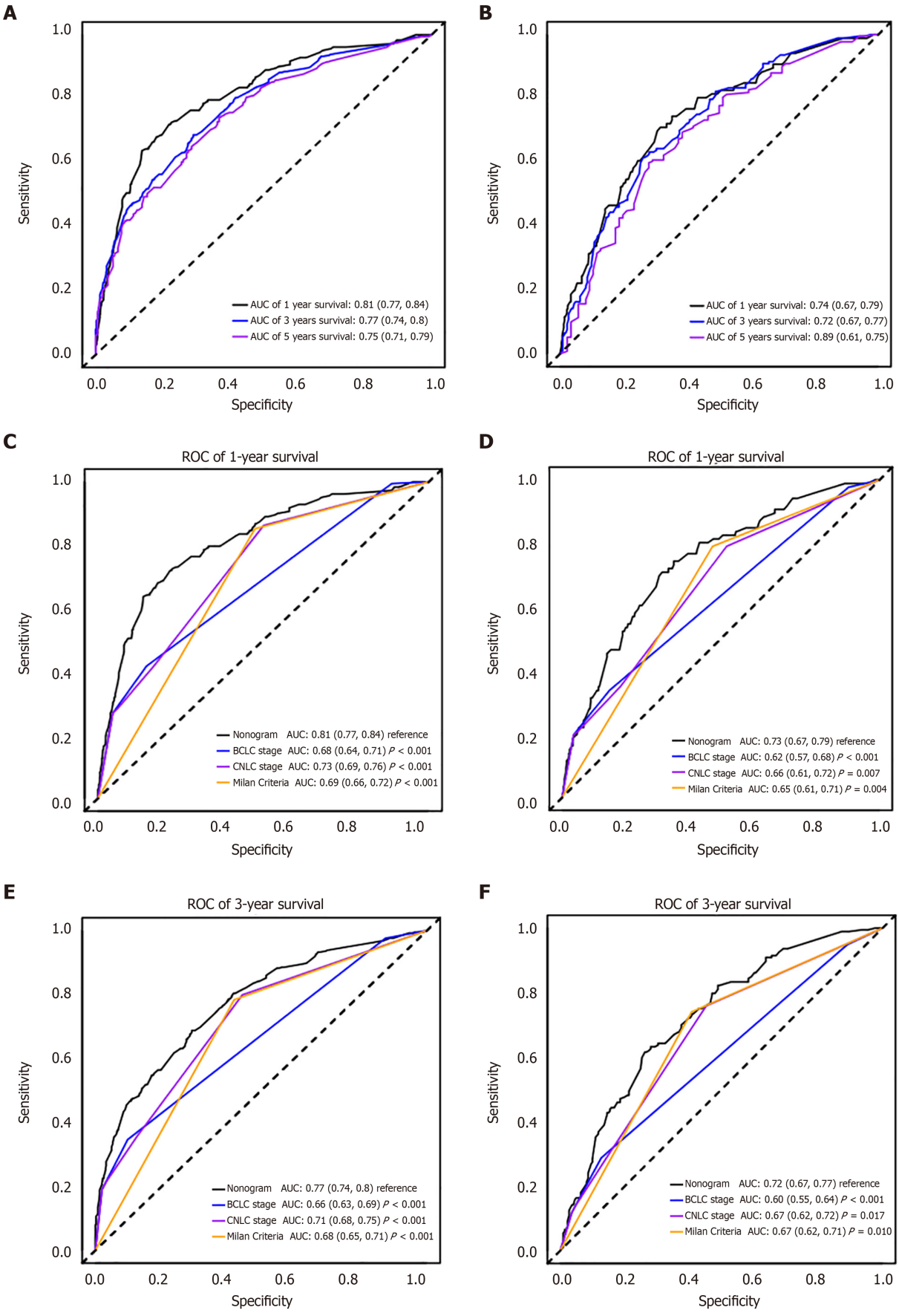


Figure 6 Nomogram calibration curves for different time intervals and cohorts. A: The 1-year, training cohort; B: The 3-year, training cohort; C: The 5-year, training cohort; D: The 1-year, validation cohort; E: The 3-year, validation cohort; F: The 5-year, validation cohort.


A
Sensitivity
Specificity
AUC of 1 year survival: 0.81 (0.77, 0.84)
AUC of 3 years survival: 0.77 (0.74, 0.8)
AUC of 5 years survival: 0.75 (0.71, 0.79)
B
Sensitivity
Specificity
AUC of 1 year survival: 0.74 (0.67, 0.79)
AUC of 3 years survival: 0.72 (0.67, 0.77)
AUC of 5 years survival: 0.89 (0.61, 0.75)
C
ROC of 1-year survival
Sensitivity
Specificity
Nonogram AUC: 0.81 (0.77, 0.84) reference
BCLC stage AUC: 0.68 (0.64, 0.71) P < 0.001
CNLC stage AUC: 0.73 (0.69, 0.76) P < 0.001
Milan Criteria AUC: 0.69 (0.66, 0.72) P < 0.001
D
ROC of 1-year survival
Sensitivity
Specificity
Nonogram AUC: 0.73 (0.67, 0.79) reference
BCLC stage AUC: 0.62 (0.57, 0.68) P < 0.001
CNLC stage AUC: 0.66 (0.61, 0.72) P = 0.007
Milan Criteria AUC: 0.65 (0.61, 0.71) P = 0.004
E
ROC of 3-year survival
Sensitivity
Specificity
Nonogram AUC: 0.77 (0.74, 0.8) reference
BCLC stage AUC: 0.66 (0.63, 0.69) P < 0.001
CNLC stage AUC: 0.71 (0.68, 0.75) P < 0.001
Milan Criteria AUC: 0.68 (0.65, 0.71) P < 0.001
F
ROC of 3-year survival
Sensitivity
Specificity
Nonogram AUC: 0.72 (0.67, 0.77) reference
BCLC stage AUC: 0.60 (0.55, 0.64) P < 0.001
CNLC stage AUC: 0.67 (0.62, 0.72) P = 0.017
Milan Criteria AUC: 0.67 (0.62, 0.71) P = 0.010

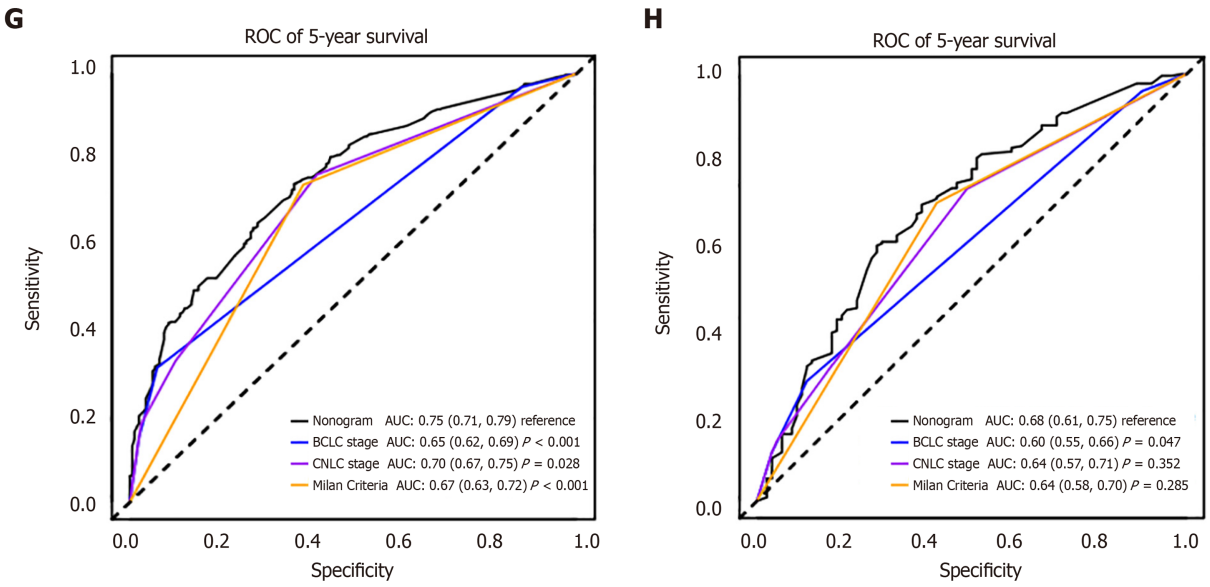


Figure 7 Time-dependent receiver operating characteristic curves and areas under the curve in different models and time intervals. A: 1-year, 3-year, and 5-year in the training set; B: 1-year, 3-year, and 5-year in the validation set; C: The 1-year, different models in the training set; D: The 1-year, different models in the validation set; E: The 3-year, different models in the training set; F: The 3-year, different models in the validation set; G: The 5-year, different models in the training set; H: The 5-year, different models in the validation set. AUC: Area under the curve; ROC: Receiver operating characteristic; BCLC: Barcelona Clinic Liver Cancer; CNLC: China Liver Cancer Staging.

and accuracy, which indicated good clinical utility and favorable efficiency.

Recent theories on cancer-related inflammation have heightened interest in inflammatory indices as potential indicators of prognosis and recurrence risk in HCC[29,30]. This interest is driven by both local and systemic aspects of cancer-associated inflammation[31]. Local inflammation, often linked to tumorigenesis within the tumor microenvironment, and systemic inflammation, characterized by low-grade immune system activation detectable through circulating inflammatory molecules, cells, and cytokines, are pivotal in understanding cancer dynamics[29,32,33]. Systemic inflammatory markers such as the SII, PLR and NLR have proven effective in forecasting HCC prognosis[34,35]. Notably, previous studies have demonstrated that the SII score outperforms other inflammation-based prognostic scores in predicting patient outcomes[36-38]. Serum ALB levels, crucial in evaluating malnutrition, are integrated into various nutritional assessment tools for HCC patients, such as the Child-Pugh score, ALBI score, Controlling Nutritional Status score, Subjective Global Assessment, and Nutrition Risk Screening 2002[39,40]. Our research findings indicate that the SII, particularly when combined with ALB levels to calculate the SII/ALB ratio, offers superior prognostic performance compared to SII alone, NLR, and PLR. According to the retrospective study by Hu *et al*[41], a high SII was markedly related to factors indicative of aggressive disease, such as vascular invasion, larger tumors, and elevated levels of circulating tumor cells. Our study further supports these findings, showing that higher SII/ALB ratios are associated with worse liver function and poor tumor characteristics, including larger tumor diameter, more advanced BCLC stage, lower differentiation, MVI, and PVTT. This growing body of evidence supports the integration of inflammatory markers with tumor-related factors to create more comprehensive prediction models for HCC patients[38,42,43]. For instance, Yang *et al*[44] developed a nomogram incorporating 6 risk factors, including age, AFP, tumor size, satellite nodules, SII, and the Prognostic Nutritional Index, to predict recurrence risk and stratify HCC cases. Our enhanced nomogram, which integrated nine independent risk factors, has shown even greater accuracy, underlining the utility of combining diverse clinical indicators to improve patient management and outcomes in HCC.

SII/ALB independently predicts the prognosis of HBV-related HCC patients after TACE treatment[19]. In the present study, SII/ALB showed excellent discriminative ability in HCC patients undergoing liver resection. Based on this research, we propose that immune inflammation linked to both systemic conditions and the cancer itself, coupled with compromised nutritional health, could explain the poor outcomes observed in HCC patients following hepatic surgery. SII/ALB combines counts of NE, LY, and PLT with serum ALB levels to provide a multifaceted indicator of systemic inflammation and nutritional health. The predictive value of SII/ALB for tumor recurrence and OS may be explained by the roles of the three cell types and serum ALB. Tumor-associated NE facilitate cancer progression by altering immunity for tumor growth[45], secreting enzymes for tissue invasion[46], and activating neutrophil extracellular traps that facilitate inflammatory responses, tumor cell adhesion and metastasis[47,48]. LY secrete cytokines including interferon-γ and tumour necrosis factor-α, which can induce cancer cell death and limit their spread, potentially improving patient outcomes[33,49-51]. PLT contribute to tumor progression and the potential for metastasis by secreting growth factors such as platelet-derived growth factor, platelet-activating factor, and vascular endothelial growth factor, all of which are critical in stimulating blood vessel formation and promoting cancer cell survival[52-54]. Serum ALB is a widely recognized indicator that can reflect nutritional status and is also considered a negative acute phase protein that suppresses proliferation in human HCC and systemic inflammation[55,56].

Table 2 Association between systemic immune-inflammation index/albumin and clinicopathological characteristics, *n* (%)

Characteristics	Systemic immune-inflammation index/albumin		*P* value
	Low (*n* = 1142)	High (*n* = 511)	
Sex			0.424
Female	176 (15.4)	71 (13.9)	
Male	966 (84.6)	440 (86.1)	
Age, years			0.503
≤ 60	813 (71.2)	372 (72.8)	
> 60	329 (28.8)	139 (27.2)	
Hepatitis B surface antigen			< 0.001
Negative	151 (13.2)	112 (21.9)	
Positive	991 (86.8)	399 (78.1)	
Alpha-fetoprotein, ng/mL			0.945
< 400	946 (82.8)	424 (83.0)	
≥ 400	196 (17.2)	87 (17.0)	
Platelets, 10^9/L			< 0.001
> 100	684 (59.9)	494 (96.7)	
≤ 100	458 (40.1)	17 (3.3)	
Neutrophil, 10^9/L			< 0.001
≤ 6.3	1135 (99.4)	442 (86.5)	
> 6.3	7 (0.6)	69 (13.5)	
Lymphocyte, 10^9/L			0.358
> 0.8	69 (6.0)	37 (7.2)	
≤ 0.8	1073 (94.0)	474 (92.8)	
Alanine transaminase, U/L			0.579
≤ 40	833 (72.9)	366 (71.6)	
> 40	309 (27.1)	145 (28.4)	
Aspartate transaminase, U/L			< 0.001
≤ 40	718 (62.9)	248 (48.5)	
> 40	424 (37.1)	263 (51.5)	
Prothrombin time, second			0.022
≤ 13	956 (83.7)	404 (79.1)	
> 13	186 (16.3)	107 (20.9)	
Total bilirubin, μmol/L			0.686
≤ 32.4	1127 (98.7)	503 (98.4)	
> 32.4	15 (1.3)	8 (1.6)	
Albumin, g/L			< 0.001
> 35	1108 (97.0)	464 (90.8)	
≤ 35	34 (3.0)	47 (9.2)	
Albumin-bilirubin grade			< 0.001
1	937 (82.0)	342 (66.9)	
2	205 (18.0)	169 (33.1)	
Tumor diameter, cm			< 0.001

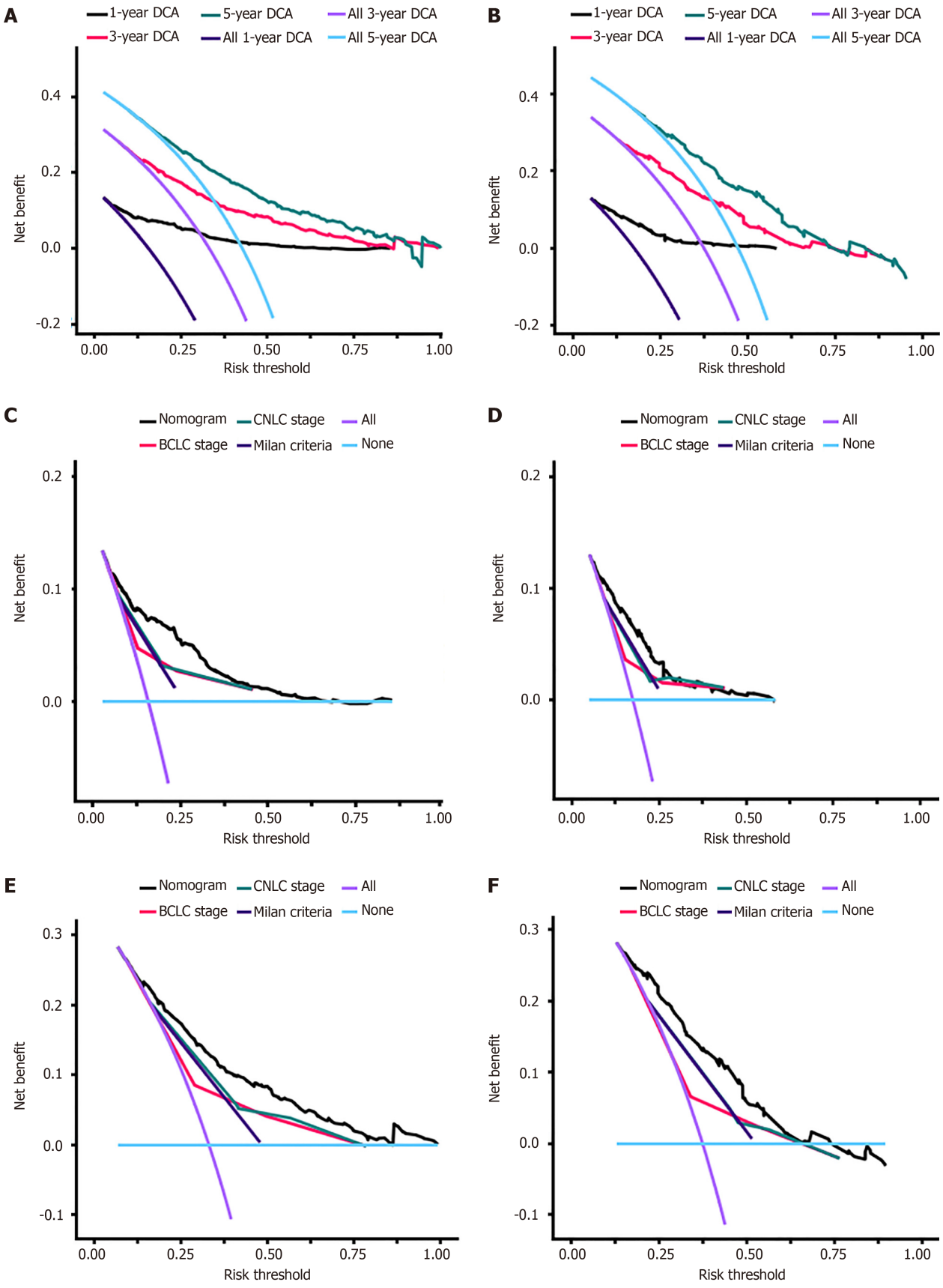
< 5	654 (57.3)	131 (25.6)	
≥ 5	488 (42.7)	380 (74.4)	
Number of tumors			0.353
Single	966 (84.6)	423 (82.8)	
Multiple	176 (15.4)	88 (17.2)	
Barcelona Clinic Liver Cancer stage			< 0.001
0	128 (11.2)	24 (4.7)	
A	837 (73.3)	355 (69.5)	
B	110 (9.6)	74 (14.5)	
C	67 (5.9)	58 (11.4)	
Hypertension			0.784
No	967 (84.7)	430 (84.1)	
Yes	175 (15.3)	81 (15.9)	
Diabetes			0.595
No	1046 (91.6)	472 (92.4)	
Yes	96 (8.4)	39 (7.6)	
Cardiovascular disease			0.409
No	1124 (98.4)	500 (97.8)	
Yes	18 (1.6)	11 (2.2)	
Anatomical resection			< 0.001
No	769 (67.3)	299 (58.5)	
Yes	373 (32.7)	212 (41.5)	
Major hepatectomy			< 0.001
No	1034 (90.5)	381 (74.6)	
Yes	108 (9.5)	130 (25.4)	
Transfusion			< 0.001
No	1099 (96.2)	458 (89.6)	
Yes	43 (3.8)	53 (10.4)	
Differentiation			< 0.001
I-II	664 (58.1)	234 (45.8)	
III-IV	478 (41.9)	277 (54.2)	
Microvascular invasion			< 0.001
No	864 (75.7)	313 (61.3)	
Yes	278 (24.3)	198 (38.7)	
Cirrhosis			< 0.001
No	466 (40.8)	329 (64.4)	
Yes	676 (59.2)	182 (35.6)	
Portal vein tumor thrombus			< 0.001
No	1075 (94.1)	453 (88.6)	
Yes	67 (5.9)	58 (11.4)	

Table 3 Univariate and multivariate Cox proportional hazards regression models for overall survival and recurrence-free survival

Variables	Overall survival				Recurrence-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P* value	AHR (95%CI)	*P* value	HR (95%CI)	*P* value	AHR (95%CI)	*P* value
Sex								
Female	Reference				Reference			
Male	1.19 (0.95-1.50)	0.134			1.18 (0.97-1.42)	0.09		
Age, years								
≤ 60	Reference		Reference		Reference		Reference	
> 60	0.70 (0.58-0.84)	< 0.001	0.79 (0.65-0.96)	0.017	0.73 (0.63-0.85)	< 0.001	0.77 (0.66-0.90)	0.001
Hepatitis B surface antigen								
Negative	Reference		Reference		Reference		Reference	
Positive	1.58 (1.24-2.01)	< 0.001	1.38 (1.07-1.79)	0.014	1.44 (1.19-1.75)	< 0.001	1.31 (1.07-1.61)	0.009
Alpha-fetoprotein, ng/mL								
< 400	Reference		Reference		Reference		Reference	
≥ 400	1.58 (1.32-1.91)	< 0.001	1.26 (1.04-1.52)	0.018	1.38 (1.18-1.63)	< 0.001	1.21 (1.02-1.43)	0.027
Alanine transaminase, IU/L								
≤ 40	Reference		Reference		Reference		Reference	
> 40	1.48 (1.26-1.75)	< 0.001	0.96 (0.79-1.17)	0.69	1.40 (1.21-1.60)	< 0.001	0.92 (0.78-1.08)	0.315
Aspartate transaminase, IU/L								
≤ 40	Reference		Reference		Reference		Reference	
> 40	2.19 (1.87-2.57)	< 0.001	1.31 (1.07-1.60)	0.007	2.08 (1.83-2.37)	< 0.001	1.47 (1.25-1.74)	< 0.001
Prothrombin time, second								
≤ 13	Reference		Reference		Reference		Reference	
> 13	1.41 (1.16-1.70)	< 0.001	1.18 (0.97-1.43)	0.073	1.25 (1.06-1.47)	0.007	1.08 (0.92-1.28)	0.352
Total bilirubin, μmol/L								
≤ 32.4	Reference				Reference			
> 32.4	1.00 (0.52-1.92)	0.992			1.02 (0.59-1.76)	0.953		
Albumin-bilirubin grade								
1	Reference		Reference		Reference		Reference	
2	1.79 (1.51-2.12)	< 0.001	1.28 (1.07-1.60)	0.007	1.45 (1.25-1.68)	< 0.001	1.08 (0.93-1.27)	0.316
Tumor diameter, cm								
< 5	Reference		Reference		Reference		Reference	
≥ 5	3.13 (2.63-3.73)	< 0.001	2.12 (1.74-2.58)	< 0.001	2.48 (2.17-2.85)	< 0.001	1.85 (1.59-2.15)	< 0.001
Number of tumors								
Single	Reference		Reference		Reference		Reference	
Multiple	1.65 (1.37-	< 0.001	1.55 (1.27-	< 0.001	1.87 (1.60-	< 0.001	1.76 (1.50-	< 0.001

	1.99)		1.87)		2.19)		2.07)	
Hypertension								
No	Reference		Reference		Reference		Reference	
Yes	0.74 (0.58-0.94)	0.013	1.01 (0.79-1.30)	0.933	0.82 (0.68-0.98)	0.034	1.02 (0.84-1.24)	0.842
Diabetes								
No	Reference				Reference			
Yes	1.04 (0.78-1.38)	0.792			0.84 (0.65-1.09)	0.191		
Cardiovascular disease								
No	Reference				Reference			
Yes	0.76 (0.39-1.47)	0.413			0.68 (0.38-1.20)	0.18		
Anatomical resection								
No	Reference		Reference		Reference			
Yes	1.21 (1.03-1.41)	0.022	0.96 (0.82-1.14)	0.668	1.10 (0.96-1.26)	0.161		
Major hepatectomy								
No	Reference		Reference		Reference		Reference	
Yes	2.13 (1.76-2.58)	< 0.001	1.23 (1.01-1.51)	0.044	1.86 (1.57-2.20)	< 0.001	1.13 (0.95-1.35)	0.172
Transfusion								
No	Reference		Reference		Reference		Reference	
Yes	1.98 (1.50-2.61)	< 0.001	1.00 (0.76-1.37)	0.987	1.61 (1.24-2.08)	< 0.001	0.90 (0.69-1.18)	0.455
Differentiation								
I-II	Reference		Reference		Reference		Reference	
III-IV	2.00 (1.71-2.34)	< 0.001	1.49 (1.27-1.76)	< 0.001	1.59 (1.40-1.81)	< 0.001	1.27 (1.11-1.45)	< 0.001
Microvascular invasion								
No	Reference		Reference		Reference		Reference	
Yes	2.52 (2.15-2.95)	< 0.001	1.59 (1.34-1.89)	< 0.001	2.21 (1.93-2.53)	< 0.001	1.56 (1.35-1.80)	< 0.001
Cirrhosis								
No	Reference				Reference			
Yes	1.02 (0.87-1.19)	0.825			1.03 (0.90-1.17)	0.667		
Portal vein tumor thrombus								
No	Reference		Reference		Reference		Reference	
Yes	4.08 (3.28-5.07)	< 0.001	2.18 (1.73-2.74)	< 0.001	3.20 (2.60-3.95)	< 0.001	1.91 (1.53-2.38)	< 0.001
Systemic immune-inflammation index/albumin								
Low	Reference		Reference		Reference		Reference	
High	1.93 (1.64-2.26)	< 0.001	1.22 (1.03-1.46)	0.025	1.63 (1.42-1.87)	< 0.001	1.19 (1.03-1.38)	0.022

HR: Hazard ratio; AHR: Adjusted hazard ratio.


A
1-year DCA
5-year DCA
All 3-year DCA
3-year DCA
All 1-year DCA
All 5-year DCA
Net benefit
Risk threshold
B
C
Nomogram
CNLC stage
All
BCLC stage
Milan criteria
None
D
E
F

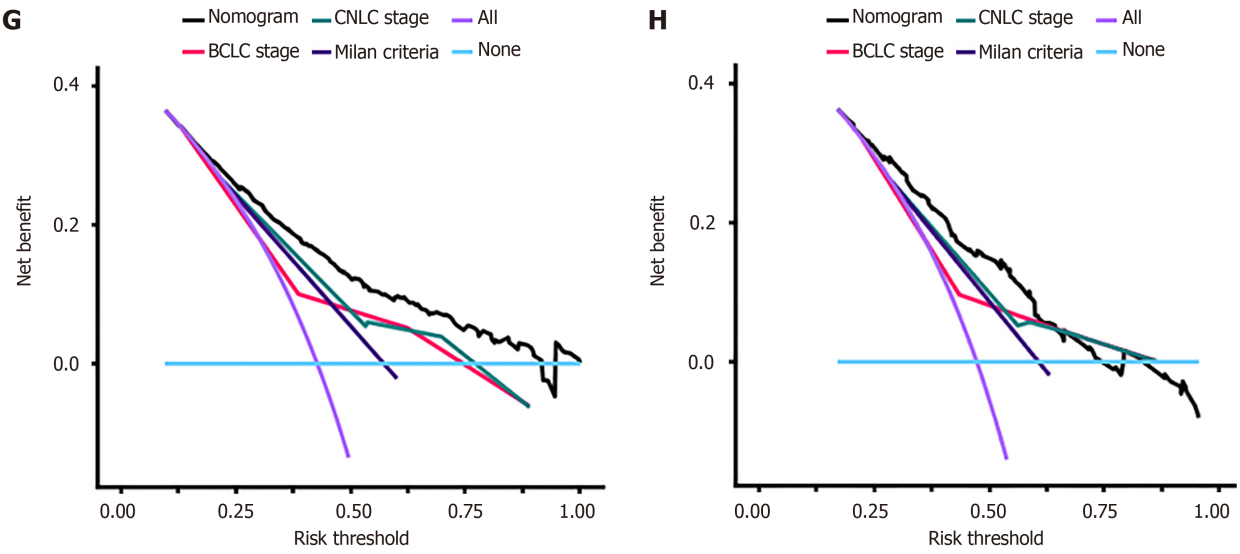


Figure 8 Decision curve analysis for comparing various models. A: Decision curve analysis (DCA) at 1-year, 3-year, and 5-year intervals in the training set; B: DCA at 1-year, 3-year, and 5-year intervals in the validation set; C: DCA at the 1-year interval comparing models in the training set; D: DCA at the 1-year interval comparing models in the validation set; E: DCA at the 3-year interval comparing models in the training set; F: DCA at the 3-year interval comparing models in the validation set; G: DCA at the 5-year interval comparing models in the training set; H: DCA at the 5-year interval comparing models in the validation set. DCA: Decision curve analysis; BCLC: Barcelona Clinic Liver Cancer; CNLC: China Liver Cancer Staging.

However, this study has a few limitations. First, this retrospective study is associated with the risk of selection bias and the presence of unmeasured confounders that could affect the outcomes. These factors limit our ability to establish causality and may impact the generalizability of the results. Second, all patients were from one center, potentially limiting the generalizability of our results. To ensure the robustness and applicability of our nomogram and the SII/ALB cutoff value, external validation is necessary. Third, the majority of our patients (84%) were HBV-positive, which differs from the typical patient populations in Europe, the United States, and Japan. This may limit the applicability of our results to regions with different etiological profiles of HCC. Prospective, multi-center investigations should be conducted to validate the effect of SII/ALB and our nomogram in predicting prognosis across diverse patient populations.

CONCLUSION

SII/ALB is a new factor for independently predicting survival and recurrence in HCC patients undergoing liver resection. Moreover, the nomogram model based on SII/ALB showed good accuracy and discriminative ability for forecasting 5-year OS in HCC patients following liver resection. The simplicity and low cost of SII/ALB make it a promising tool for predicting HCC prognosis.

FOOTNOTES

Author contributions: Chen KL wrote the original draft of the manuscript; Chen KL, Qiu YW, and Yang M conceptualized the study; Chen KL, Qiu YW, Yang M, Wang T, Yang Y, Qiu HZ, Sun T, and Wang WT reviewed and edited the manuscript; all of the authors read and approved the final version of the manuscript to be published.

Supported by The National Natural Science Foundation of China, No. 81770566 and No. 82000599; The NHC Key Laboratory of Echinococcosis Prevention and Control, No. 2021WZK1004; and The Health Commission of the Tibet Autonomous Region, No. 311220432.

Institutional review board statement: The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments, and this study was approved by the Institutional Review Board of West China Hospital of Sichuan University Ethics Committee, No. 2024(189).

Informed consent statement: Patient consent was waived due to the retrospective nature of the study.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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S-Editor: Luo ML
L-Editor: A
P-Editor: Yu HG

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