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ORIGINAL RESEARCH

Preoperative Fibrinogen Albumin Ratio is an Effective Biomarker for Prognostic Evaluation of Gallbladder Carcinoma After Radical Resection: A 10-Year Retrospective Study at a Single Center

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Background: To explore and screen preoperative serum immune response level-related biomarkers with better prognostic ability and developed a prognostic model for decision-making in clinical practice for gallbladder carcinoma (GBC) patients.

Methods: A total of 427 patients who underwent radical resection for GBC in the Department of Hepatobiliary Surgery of the First Affiliated Hospital of Xi'an Jiaotong University from January 2011 to December 2020 were retrospectively analyzed. Time-dependent receiver operating characteristic (time-ROC) was performed to determine the prognostic predictive power of preoperative biomarkers. A nomogram survival model was established and validated.

Results: Time-ROC indicated that the preoperative fibrinogen-to-albumin ratio (FAR) had a better predictive ability for overall survival among preoperative serum immune response level-related biomarkers. Multivariate analysis indicated that FAR was an independent risk factor (P<0.05). The proportion of clinicopathological characteristics of poor prognosis (such as advanced T stage, and N1-2 stage) was significantly higher in high FAR group (P<0.05). Subgroup analyses indicate the prognostic discrimination ability of FAR depended on CA19-9, CA125, liver involvement, major vascular invasion, perineural invasion, T stage, N stage, and TNM stage (all P <0.05). A nomogram model was established based on the prognostic independent risk factors with the C-index of 0.803 (95% *CI*:0.771~0.835) and 0.774 (95% *CI*:0.696~0.852) in the training and testing sets, respectively. The decision curve analysis indicated the nomogram model had a better predictive ability than the FAR and TNM staging system in the training and testing sets.

Conclusion: Preoperative serum FAR has a better predictive ability for overall survival among preoperative serum immune response level-related biomarkers, and it can be used for survival assessment of GBC and guide clinical decision-making.

Keywords: gallbladder carcinoma, fibrinogen to albumin ratio, inflammation, prognosis, nomogram

Introduction

Gallbladder carcinoma (GBC) is the most common malignant tumor of the biliary system and ranks sixth among all digestive tract malignancies, which is characterized by a low early diagnosis rate, a high degree of malignancy, and a poor prognosis.[1,2] The incidence rate of GBC has been increasing worldwide in recent years, and it is (1.00~1.30)/100,000 in China.[3] The incidence, diagnosis, and treatment of GBC have not made major strides in the past 10 years, which has resulted in a stagnant 5-year survival rate for patients. A preoperative assessment of the prognosis of GBC patients can help to select appropriate treatment options for the patient.[4] As a result, developing novel biomarkers is critical for the prognostic assessment of GBC.

Numerous studies have demonstrated that nutritional status and systemic inflammation of patients before surgery influence tumor cell proliferation, apoptosis, and angiogenesis, which can be used to evaluate the prognosis of patients

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with malignant tumors.[5–7] Currently, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), prognostic nutritional index (PNI), platelet-to-albumin ratio (PAR), fibrinogen-to-albumin ratio (FAR), albumin-to-γ-glutamyl transpeptidase ratio (AGR) and albumin-to-alkaline phosphatase ratio (AAPR) were useful tests used to evaluate immune and inflammatory status in patients with malignant tumors, and they had been used to predict the prognosis of GBC patients.[8–15] Nevertheless, there has been no comparative study of the above-mentioned serum biomarkers on the prognostic prediction of patients with GBC after radical resection. In this study, we aimed to explore and screen preoperative serum immune response level-related biomarkers with better prognostic ability and developed a prognostic model for decision-making in the clinical practice of GBC patients.

Methods

Patients and Design

We included all histologically confirmed GBC patients treated at the First Affiliated Hospital of Xi'an Jiaotong University between 2011 and 2020. The inclusion criteria were as follows: (1) postoperative pathologically confirmed GBC; (2) margin status recorded microscopically negative (R0); (3) preoperative serum albumin, lymphocytes, platelets, and other indicators were available; (4) clinicopathological characteristics and follow-up data were all available. The exclusion criteria were as follows: (1) patients with preoperative infection; (2) patients with preoperative severe chronic wasting disease; (3) patients with preoperative coagulation abnormality; (4) patients with preoperative anticoagulation or albumin infusion; (5) patients who received neoadjuvant therapy or other treatments for malignant tumors before surgery; (6) patients died within 30 days after surgery. In total, 427 patients met the inclusion/exclusion criteria and were included in the study. Through January 2022, all included patients were evaluated using the 8th edition AJCC staging system.

Study Variables

Table 1 showed the serological biomarkers variables and calculation methods for this study, and the best cut-off values determined using the X-tile software were also displayed. We defined NLR, PLR, LMR, SII, SIRI, PNI, PAR, FAR, AGR, and AAPR as low-risk and high-risk groups based on optimal cut-off values. Moreover, time-dependent receiver operating characteristic (time-ROC) analysis was performed using R software version 3.6.1 (http://www.r-project.org/) to determine the prognostic predictive power.

Follow-Up

A routine follow-up was performed in outpatient and telephone settings for all patients included in the study. During the first year following surgery, liver function, tumor biomarkers (CEA, CA19-9, CA125), and ultrasound, contrast-enhanced CT or MRI examination were reviewed every 2–3 months, and over a one-year period, follow-ups were conducted once

Table 1 Calculation Method and Cut-off Value of Preoperative Serological Biomarkers

Variables	Calculation Method	Cut-off Value
Neutrophil-to-lymphocyte ratio (NLR)	Neutrophil (10^9/L)/Lymphocyte (10^9/L)	2.2
Platelet-to-lymphocyte ratio (PLR)	Platelet (10^9/L)/Lymphocyte (10^9/L)	155.3
Lymphocyte-to-monocyte ratio (LMR)	Lymphocyte (10^9/L)/Monocyte (10^9/L)	3.8
Systemic immune-inflammation index (SII)	Platelet (10^9/L) *Neutrophil (10^9/L)/Lymphocyte (10^9/L)	399.7
Systemic inflammation response index (SIRI)	Monocyte (10^9/L) *Neutrophil (10^9/L)/Lymphocyte (10^9/L)	0.95
Prognostic nutritional index (PNI)	Albumin (g/L) + 5 * Lymphocyte count (10^9/L)	44.0
Platelet-to-albumin ratio (PAR)	Platelet (10^9/L)/albumin (g/L)	6.25
Fibrinogen-to-albumin ratio (FAR)	Fibrinogen (mg/L)/albumin (g/L)	0.08
Albumin-to-γ-glutamyltransferase ratio (AGR)	Albumin (g/L)/ γ-glutamyltransferase (U/L)	2.03
Albumin-to-alkaline phosphatase ratio (AAPR)	Albumin (g/L)/ alkaline phosphatase (U/L)	0.38

every 3–6 months. The OS was calculated from the date of radical resection until the date of death or the most recent follow-up of the patient, and clinical evidence of recurrence of the tumor. The follow-up ended in January 2022.

Statistical Analysis

All statistical analyses were performed using SPSS version 25. Analyses of categorical variables were conducted using the χ^2 test. Univariate analysis was conducted using the Kaplan-Meier method and Log rank test, and multivariate analysis was conducted using the Cox proportional hazard regression model. The Kaplan-Meier curves were conducted by GraphPad Prism (version 8.0, San Diego, California, USA). Variables with $P<0.05$ were considered statistically significant.

Nomogram Development and Assessment

A training set (N=300) and a testing set (N=127) were created from all included patients in a 7:3 ratio (Baseline characteristics comparison between the training and testing sets shown in Supplementary Table 1). The nomogram prediction model was developed using R software based on the independent variables and an online calculator was developed. The concordance index (C-index), calibration plot, area under ROC (AUC), and decision curve analysis were used to evaluate the performance of the nomogram model.

Results

The study included 427 patients undergoing radical resection for histologically confirmed GBC between 2011 and 2020. The median survival time was 49.0 months, and overall survival rates were 78.0%, 54.8%, and 45.6% at 1, 3, and 5 years, respectively.

Time-Dependent Receiver Operating Characteristic (Time-ROC) Analysis

Time-dependent ROC curves are shown in Figure 1A and B, indicating that FAR outperformed other indicators in training and testing sets as a prognostic biomarker.

An Analysis of the Correlation Between FAR and Clinicopathological Characteristics

The patients with preoperative FAR>0.08 were compared with FAR≤0.08, the proportion of age>60 years, NLR≥2.2, PLR>155.3, LMR≤3.8, SII>399.7, SIRI>0.95, PNI≤44.0, PAR>6.25, AGR≤2.03, AAPR≤0.38, CA19-9>39.0U/mL, CA125>35.0U/mL, TBIL>34.1μmol/L, combined with gallbladder stones, without gallbladder polyps, tumor morphology with infiltrative type, poor tumor differentiation, liver invasion, macrovascular invasion, T stage (stage T3 and T4), N1-2 stage, TNM stage (stage III and IVA) was significantly higher than the latter (Table 2, $P<0.05$).

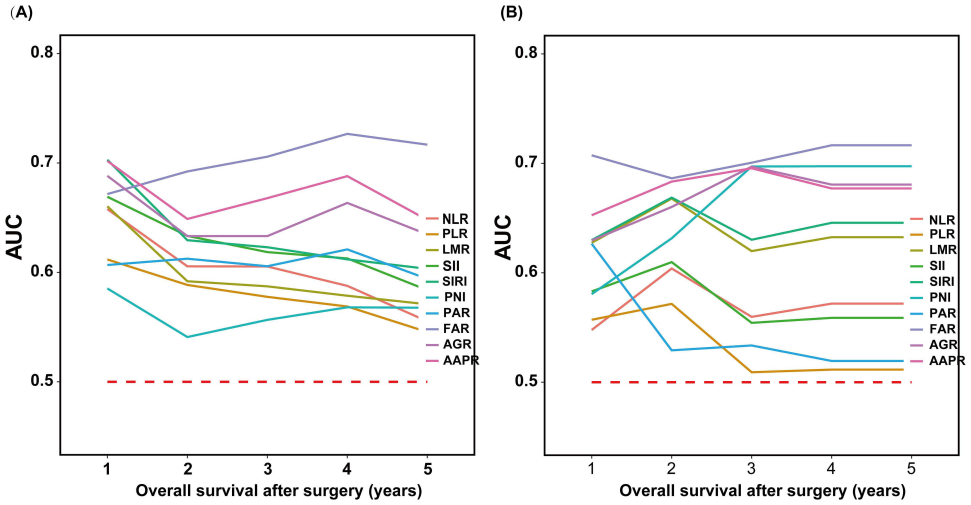

Figure 1 Time-dependent ROC curve of preoperative serum immune response level biomarkers in prognosis prediction after radical resection of gallbladder carcinoma. (**A** and **B**). Time-dependent ROC curve of the training and testing sets.

Table 2 The Relationship of FAR with Clinical Characteristics for GBC After Radical Resection

	FAR		χ^2	*P*	R	*P*
	Low Group	**High Group**				
Sex						
Male	39(29.1)	53(31.9)	0.278	0.598	−0.030	0.599
Female	95(70.9)	113(68.1)				
Age (year)						
≤60	69(51.5)	65(39.2)	4.565	0.033	0.123	0.033
>60	65(48.5)	101(60.8)				
NLR						
<2.2	85(63.4)	51(30.7)	32.012	<0.001	0.327	<0.001
≥2.2	49(36.6)	115(69.3)				
PLR						
≤155.3	82(61.2)	76(45.8)	7.064	0.008	0.153	0.008
>155.3	52(38.8)	90(54.2)				
LMR						
>3.8	102(76.1)	86(51.8)	18.733	<0.001	0.250	<0.001
≤3.8	32(23.9)	80(48.2)				
SII						
≤399.7	70(52.2)	40(24.1)	25.288	<0.001	0.290	<0.001
>399.7	64(47.8)	126(75.9)				
SIRI						
≤0.95	114(85.1)	85(51.2)	38.088	<0.001	0.356	<0.001
>0.95	20(14.9)	81(48.8)				
PNI						
>44.0	100(74.6)	90(54.2)	13.301	<0.001	0.211	<0.001
≤44.0	34(25.4)	76(45.8)				
PAR						
≤6.25	106(79.1)	88(53.0)	22.093	<0.001	0.271	<0.001
>6.25	28(20.9)	78(47.0)				
AGR						
>2.03	66(49.3)	35(21.1)	26.346	<0.001	0.296	<0.001
≤2.03	68(50.7)	131(78.9)				
AAPR						
>0.38	99(73.9)	66(39.8)	34.880	<0.001	0.341	<0.001
≤0.38	35(26.1)	100(60.2)				
CEA (ng/mL)						
≤5.0	113(84.3)	127(76.5)	2.836	0.092	0.097	0.093
>5.0	21(15.7)	39(23.5)				
CA19-9(U/mL)						
≤39.0	108(81.3)	108(65.1)	9.824	0.002	0.181	0.002
>39.0	25(18.7)	58(34.9)				
CA125(U/mL)						
≤35.0	117(87.3)	112(87.5)	16.161	<0.001	0.232	<0.001
>35.0	17(22.7)	54(32.5)				
TBIL (μmol/L)						
≤34.1	128(95.5)	145(87.3)	6.047	0.014	0.142	0.014
>34.1	6(4.5)	21(12.7)				
Unexpected GBC						
No	95(70.9)	112(67.5)	0.407	0.524	0.037	0.525
Yes	39(29.1)	54(32.5)				

(*Continued*)

Table 2 (Continued).

	FAR		χ^2	*P*	R	*P*
	Low Group	High Group				
Gallstones						
No	73(54.5)	55(33.1)	13.810	<0.001	0.215	<0.001
Yes	61(45.5)	111(66.9)				
Gallbladder polyps						
No	114(85.1)	163(98.2)	18.025	<0.001	−0.245	<0.001
Yes	20(14.9)	3(1.8)				
Tumor location						
Neck	17(12.7)	29(17.5)	2.146	0.342	−0.014	0.810
Body and bottom	88(65.7)	96(57.8)				
All gallbladder	29(21.6)	41(24.7)				
Tumor morphology						
Massive type	54(40.3)	49(29.5)	9.094	0.011	0.046	0.430
Infiltrating type	55(41.0)	97(58.4)				
Hybrid type	25(18.7)	20(12.0)				
Tumor differentiation						
Well	27(20.1)	20(12.0)	10.817	0.004	0.188	0.001
Moderate	73(54.5)	75(45.2)				
Poor	34(25.4)	71(42.8)				
Liver involvement						
No	110(82.1)	113(68.1)	7.636	0.006	0.160	0.006
Yes	24(17.9)	53(31.9)				
Major vascular invasion						
No	132(98.5)	155(93.4)	4.714	0.030	0.125	0.030
Yes	2(1.5)	11(6.6)				
Perineural invasion						
No	125(93.3)	149(89.8)	1.164	0.281	0.062	0.282
Yes	9(6.7)	17(10.2)				
Microvascular invasion						
No	126(94.0)	159(95.8)	0.480	0.488	−0.040	0.490
Yes	8(6.0)	7(4.2)				
AJCC 8th edition T stage						
T_{1-2}	41(30.6)	20(12.0)	21.206	<0.001	0.264	<0.001
T_3	91(67.9)	131(78.9)				
T_4	2(1.5)	15(9.0)				
AJCC 8th edition N stage						
N_0	108(80.6)	117(70.5)	4.046	0.044	0.116	0.044
N_{1-2}	26(19.4)	49(29.5)				
AJCC 8th edition TNM stage						
I–II	39(29.1)	18(10.8)	21.590	<0.001	0.267	<0.001
III	93(69.4)	133(80.1)				
IVA	2(1.5)	15(9.0)				

Subgroup Analyses Between Low FAR and High FAR Groups

Forest plots indicated the FAR has an excellent ability to distinguish the prognosis of CA19-9, CA125, liver involvement, major vascular invasion, perineural invasion, T stage, N stage, and TNM stage (Figure 2, all P <0.05).

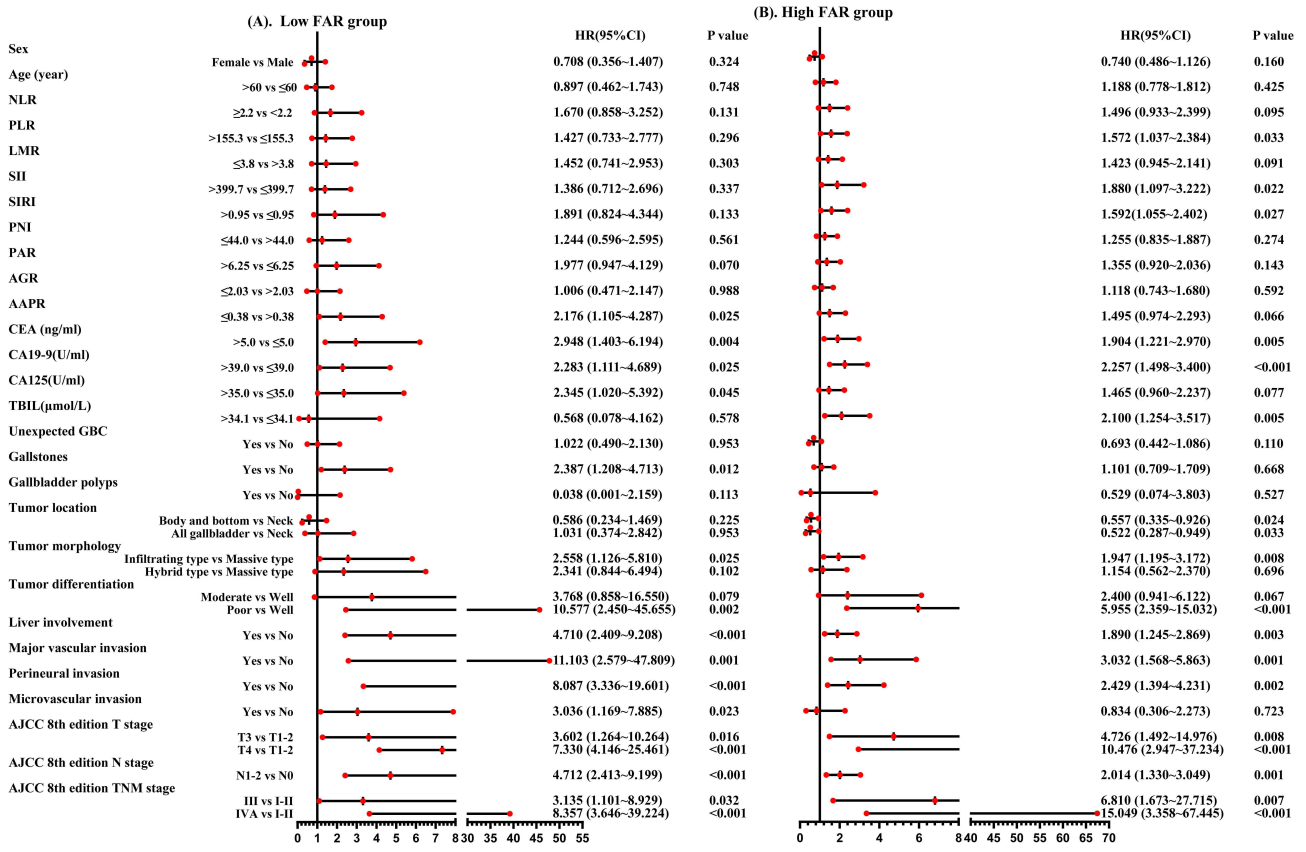

Figure 2 Forest plot of the association between fibrinogen-to-albumin ratio (FAR) and overall survival in the training set. (**A**) Forest plot of low FAR group. (**B**) Forest plot of high FAR group.

Survival Analysis in the Whole Cohort

Univariate analysis showed that the overall survival of patients in the low LMR, PNI, AGR and AAPR, high NLR, PLR, SII, SIRI, PAR and FAR groups were significantly worse than those in the high LMR, PNI, AGR and AAPR, low NLR, PLR, SII, SIRI, PAR and FAR groups ($P<0.05$), which demonstrated that serum biomarkers may be used to predict GBC prognosis. In the testing set, by using the same cut-off value, the overall survival of patients in the low LMR, PNI, AGR and AAPR groups, and the high NLR, SIRI, and FAR groups were worse than the high LMR, PNI, AGR and AAPR groups, and the low NLR, SIRI, and FAR groups ($P<0.05$), while there no statistical difference between the high PLR, SII, PAR and low PLR, SII, PAR groups in overall survival, which was considered to be related to the difference in the overall distribution of patients in the training and testing sets (Supplementary Figure 1 and Figure 2).

The multivariate analysis included only FAR among preoperative immune response level-related markers to avoid multicollinearity, which indicated that FAR was an independent risk factor. Detailed results of the univariate and multivariate analysis are shown in Table 3.

Nomogram Development and Online

A nomogram prediction model for OS was established based on the independent risk factors, including FAR, CEA, CA-125, N stage, major vascular invasion, perineural invasion, and tumor differentiation. The online calculator is available at https://doczj.shinyapps.io/nom_far_gbc/, which is convenient and effective for clinicians. In addition, the online calculator demonstrates that FAR has a good prognostic discrimination ability. Detailed results of the Cox regression are shown on the right-hand side of Table 2, and the nomogram is shown in Figure 3.

Table 3 Univariate and Multivariate Analysis of Prognosis for GBC After Radical Resection

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Sex				
Female vs Male	0.724 (0.506~1.036)	0.077		
Age (year)				
>60 vs≤60	1.192 (0.837~1.696)	0.330		
NLR				
≥2.2 vs <2.2	2.049 (1.146~2.964)	<0.001		
PLR				
>155.3 vs ≤155.3	1.711 (1.206~2.427)	0.003		
LMR				
≤3.8 vs >3.8	1.762 (1.245~2.495)	0.001		
SII				
>399.7 vs ≤399.7	2.164 (1.455~3.220)	<0.001		
SIRI				
>0.95 vs ≤0.95	2.247(1.587~3.181)	<0.001		
PNI				
≤44.0 vs >44.0	1.534 (1.082~2.174)	0.016		
PAR				
>6.25 vs ≤6.25	1.914 (1.349~2.716)	<0.001		
FAR				
>0.08 vs ≤0.08	2.776 (1.878~4.103)	<0.001	1.913(1.268~2.886)	0.002
AGR				
≤2.03 vs >2.03	2.863 (1.822~4.499)	<0.001		
AAPR				
≤0.38 vs >0.38	2.156 (1.516~3.066)	<0.001		
CEA (ng/mL)				
>5.0 vs ≤5.0	2.294 (1.568~3.356)	<0.001	1.572(1.044~2.366)	0.030
CA19-9(U/mL)				
>39.0 vs ≤39.0	2.513 (1.767~3.574)	<0.001		
CA125(U/mL)				
>35.0 vs ≤35.0	2.041 (1.406~2.964)	<0.001		
TBIL (μmol/L)				
>34.1 vs ≤34.1	2.195 (1.347~3.578)	0.002		
Unexpected gallbladder carcinoma				
Yes vs No	0.847 (0.578~1.242)	0.395		
Gallstones				
Yes vs No	1.811 (1.253~2.618)	0.002		
Gallbladder polyps				
Yes vs No	0.078 (0.011~0.560)	0.011		
Tumor location				
Body and bottom vs Neck	0.526 (0.338~0.818)	0.004		
All gallbladder vs Neck	0.654 (0.394~1.087)	0.102		
Tumor morphology				
Infiltrating type vs Massive type	2.259 (1.489~3.429)	<0.001	1.797(1.175~2.748)	0.007
Hybrid type vs Massive type	1.446 (0.808~2.588)	0.214	2.366(1.289~4.342)	0.005
Tumor differentiation				
Moderate vs Well	2.951 (1.338~6.508)	0.007	1.859(0.821~4.209)	0.137
Poor vs Well	8.195 (3.755~17.885)	<0.001	5.096(2.260~11.490)	<0.001
Liver involvement				
Yes vs No	2.749 (1.931~3.914)	<0.001		

(*Continued*)

Table 3 (Continued).

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Major vascular invasion				
Yes vs No	4.794 (2.631~8.735)	<0.001		
Perineural invasion				
Yes vs No	3.799 (2.384~6.054)	<0.001	1.845(1.084~3.141)	0.024
Microvascular invasion				
Yes vs No	1.385 (0.703~2.728)	0.347		
AJCC 8th edition T stage				
T_3 vs T_{1-2}	5.014 (2.333~10.775)	<0.001		
T_4 vs T_{1-2}	16.782 (6.741~41.781)	<0.001		
AJCC 8th edition N stage				
$N_{1\sim2}$ vs N_0	2.850 (2.004~4.054)	<0.001	1.959(1.342~2.860)	<0.001
AJCC 8th edition TNM stage				
III vs I–II	5.383 (2.365~12.248)	<0.001		
IVA vs I–II	18.219 (6.971~47.615)	<0.001		

Nomogram Assessment

The C-index of the nomogram model was 0.803 (95% *CI*:0.771~0.835) and 0.774 (95% *CI*:0.696~0.852) in the training and testing sets, respectively. The AUCs of the nomogram to predict the 1-year, 3-year, and 5-year prognosis were 0.858, 0.858, and 0.837 in the training set, respectively, and the AUCs of the nomogram to predict the 1-year, 3-year, and 5-year prognosis were 0.779, 0.803, and 0.873 in the testing set, respectively (Figure 4A and B).

Further, we also assigned scores to different variable statuses of each patient, stratified them based on X-tile software, and divided patients into a low-risk group with 0–128 points, a medium-risk group with 129–198 points, and a high-risk group with 200–340 points, according to the results, overall survival was statistically significantly different among the three groups ($P<0.0001$, Figure 4C); the testing set also revealed a statistically significant difference in overall survival among the three groups, based on the same stratification method ($P<0.0001$, Figure 4D).

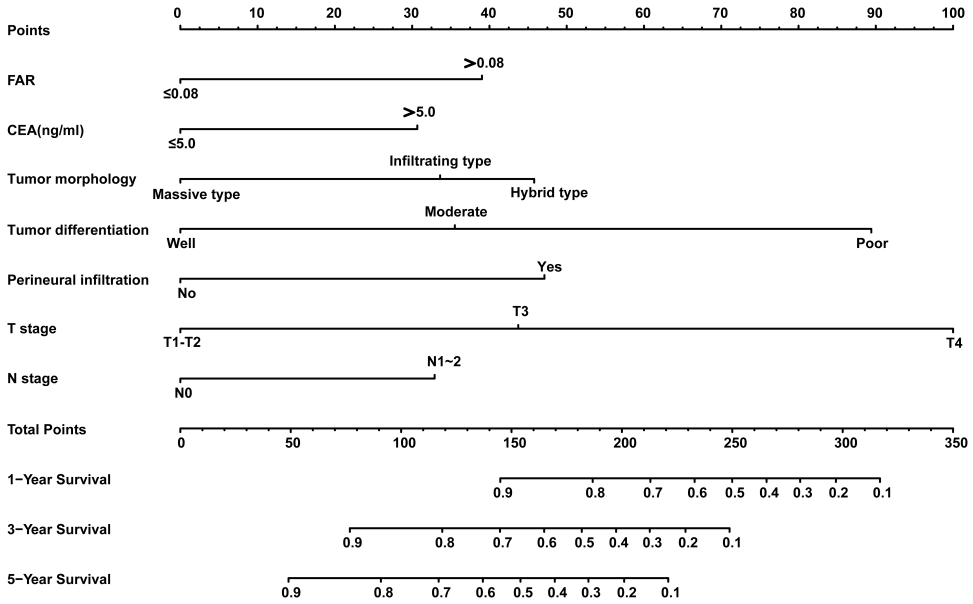

Figure 3 Nomogram prognosis prediction model for gallbladder carcinoma after radical resection.

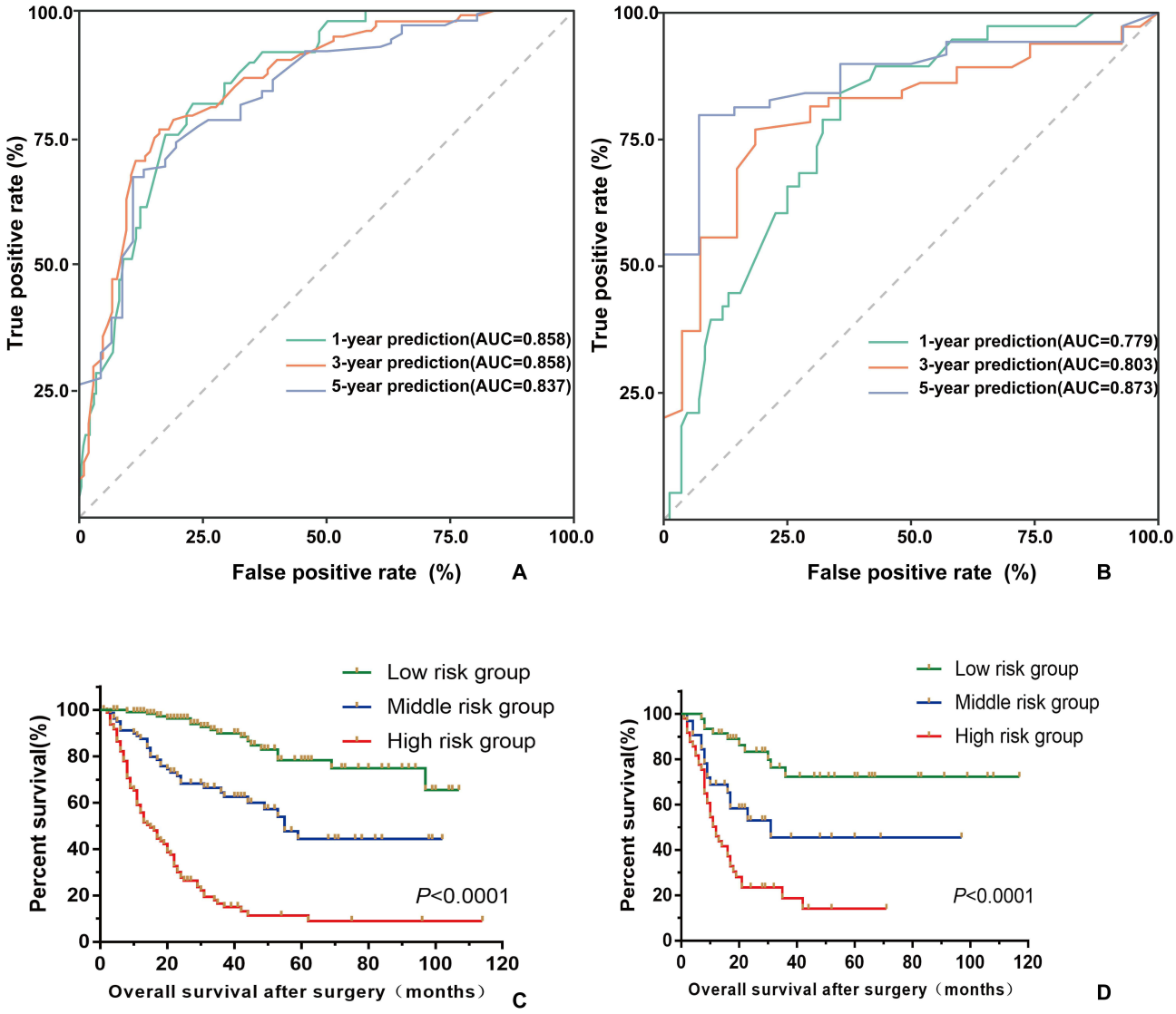

Figure 4 Assessment of nomogram model for predicting overall survival for gallbladder carcinoma after radical resection. (**A** and **B**). ROC curves of nomogram model in the training and testing sets. (**C** and **D**). Survival curves of patients with different risk stratifications in the training and testing sets.

In Figure 5A and B, the calibration plots illustrated that the nomogram model performed better in the training and testing sets, and decision curve analysis demonstrated the nomogram model has a better predictive ability than the FAR and TNM staging system in both training and testing sets (Figure 5C and D).

Discussion

Neutrophils, lymphocytes, monocytes, and platelets are important components in the tumor microenvironment. Malignant tumors trigger a non-specific inflammatory response that is characterized by elevated neutrophil and platelet levels and decreased lymphocytes. Neutrophils in tumor tissue promote tumor proliferation and angiogenesis by secreting TNF-α, VEGF, and interleukin; platelets promote tumor proliferation and differentiation by secreting TNF-β, VEGF, and platelet-derived factors; and monocytes can differentiate into tumor-associated macrophages to promote tumor cell growth, infiltration and angiogenesis, while cytokines are released by lymphocytes and mediate cytotoxic responses to inhibit the growth, proliferation, and metastasis of tumors.[16–19] Therefore, preoperative peripheral blood inflammatory markers can reflect the balance between tumor inflammatory response and immune antitumor function. In this study, the overall survival of patients in the low LMR, high NLR, PLR, SII, SIRI groups were significantly worse than those in the

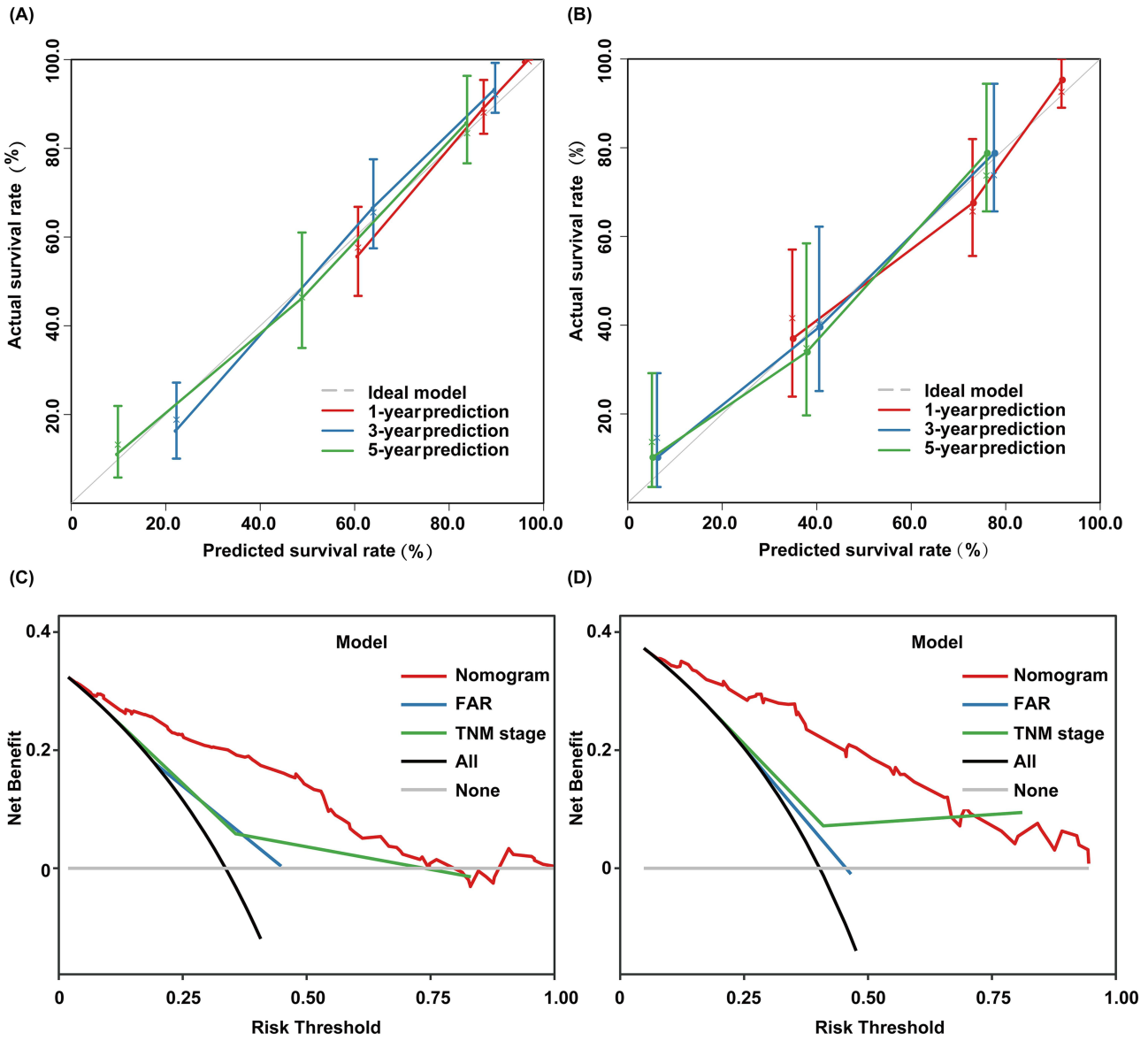

Figure 5 Calibration plot and decision analysis curve of nomogram for predicting overall survival for gallbladder carcinoma after radical resection. (**A** and **B**). Calibration plot of nomogram in the training and testing sets. (**C** and **D**). Decision analysis curve of nomogram in the training and testing sets.

high LMR, low NLR, PLR, SII, SIRI groups, which indicated that serum biomarkers may be used to predict the prognosis of GBC. Based on the biological importance of inflammatory cells within the tumor microenvironment, NLR, PLR, LMR, SII, and SIRI are likely to play a prognostic role, as reported.[8,9]

The serum albumin level is a common serological biomarker of nutrient status and liver function. It has been found that albumin acts as an antioxidant to scavenge reactive oxygen species and nitrogen species that cause systemic inflammation, while inhibiting tumor progression by reducing the phosphorylation of Rb protein in cellular pathways.[20,21] Malignant tumors are often associated with abnormal activation of the coagulation system. Fibrinogen, an important component of the coagulation system, is related to the level of inflammatory response in the body. Several studies have demonstrated that tumor cells can synthesize and secrete fibrinogen into the microenvironment to promote their growth, while platelets can induce fibrinogen aggregation around cancer cells by forming thrombin, which helps to avoid the clearance of natural killer cells.[22,23] γ-GGT is essential for glutathione metabolism and plays a determinant role in protecting against oxidative stress, and the increase of γ-GGT reflects high tumor risk and poor prognosis associated with strong oxidative stress in patients.[24,25] Therefore, the combination of parameters such as albumin, fibrinogen, and γ-

GGT can be effectively used for the prognostic assessment of GBC patients. The study also showed that the overall survival of patients in the low PNI, AGR, AAPR, high PAR, FAR groups were significantly worse than those in the high PNI, AGR, AAPR, low PAR, FAR groups, which indicated the prognostic value of FAR and other biomarkers for GBC.

In this study, a comparison of the prognostic ability of different preoperative biomarkers showed that FAR was superior to the rest of the biomarkers in assessing prognosis. Based on multivariate analysis, FAR was also identified as an independent risk factor; its cut-off value for the prognosis of GBC was 0.08, consistent with the results of Xu et al[13] According to further analysis of the FAR and clinicopathological characteristics of patients, patients with high FAR had a certain correlation with the clinicopathological features of poor prognosis, such as age>60 years, elevated tumor biomarkers, combined with jaundice, poor tumor differentiation, liver invasion, macrovascular invasion, and advanced T stage and lymph node metastasis. The correlation analysis revealed that high FAR levels were positively correlated with poor prognostic characteristics of GBC patients, which would demonstrate that high FAR was associated with poor prognosis. Moreover, the prognostic discrimination ability of FAR depended on CA19-9, CA125, liver involvement, major vascular invasion, perineural invasion, T stage, N stage, and TNM stage.

A single-center analysis of 154 GBC cases by Xu et al[13] evaluated prognostic predictive value of FAR, and they demonstrated that FAR was an independent risk factor for prognosis, but did not validate the prognostic prediction ability of FAR and establish a survival prediction model. The nomogram, as a predictive statistical model for individual patients, has proven to have advantages over the traditional TNM staging system in terms of predicting long-term survival outcomes, which has been proposed as a practical tool to guide cancer treatment.[26–30]

In this study, a nomogram model was developed based on independent risk factors, including FAR, CEA, CA-125, N stage, major vascular invasion, perineural invasion, and tumor differentiation. A good prediction ability was demonstrated by the C-index of our model of 0.803 in the training set and 0.774 in the testing set, which could effectively promote the clinical application of FAR. Sun et al[14] established a nomogram model that considered AGR, T stage, surgical margin, body mass index, and CA19-9 with the C-index of 0.780 and 0.762 in the training and testing set, respectively. Liu et al[8] analyzed 1072 cases from China Gallbladder Cancer Research Group (CRGGC) and established a nomogram prediction model based on SII, T stage, N stage, CA19-9, and surgical margins with the C-index of 0.735 and 0.686 in the training and testing set, respectively. Ma et al[31] also developed a nomogram model based on tumor size, liver invasion, surgical margins, and nerve invasion with the C-index of 0.777. In comparison to the above nomogram models, our nomogram, by incorporating preoperative FAR, had a better predictive ability. Moreover, the predictive power of our nomogram model was significantly higher than that of TNM staging system according to decision curve analysis. In turn, we developed the first online prediction model that will be convenient and effective for clinicians.

There were several limitations in our study, even though preoperative FAR showed some predictive value. The sample size was the largest in a single Chinese center, but it was still relatively small. Furthermore, we failed to validate the prognostic predictive capability of FAR and our nomogram externally. Additionally, no postoperative assessment of recurrence was performed. The development of preoperative non-invasive serological biomarkers with greater prognostic potential needs to be studied in a multicenter, prospective, and large-scale study in the near future, to provide decision support for the clinical diagnosis and treatment of GBC.

Conclusions

In summary, preoperative serum FAR has a better predictive ability for overall survival among preoperative serum immune response level-related biomarkers, and FAR represents an independent risk factor affecting postoperative prognosis. Our novel nomogram established based on FAR can be used in predicting survival probability and stratifying risk to guide clinical decision-making.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by correspondence author, without undue reservation.

Ethics Statement

The study was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No: XJTU1AF2022LSK-089), Xi'an, China. Written informed consent was obtained from all included patients and their families before study enrollment, and adhering to the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest in relation to this work to declare.

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