ORIGINAL RESEARCH

Incorporating Inflammatory Markers and Clinical Indicators into a Predictive Model of Single Small Hepatocellular Carcinoma Recurrence After Primary Locoregional Treatments

Wenying Qiao [iD][1–3,]*, Yiqi Xiong[1,]*, Kang Li[4], Ronghua Jin[2,3], Yonghong Zhang[1,5]

[1]Interventional Therapy Center for Oncology, Beijing You'an Hospital, Capital Medical University, Beijing, 100069, People's Republic of China; [2]National Center for Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, 100015, People's Republic of China; [3]Changping Laboratory, Beijing, 102206, People's Republic of China; [4]Research Center for Biomedical Resources, Beijing You'an Hospital, Capital Medical University, Beijing, 100069, People's Republic of China; [5]Beijing Research Center for Respiratory Infectious Diseases, Beijing, 100006, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yonghong Zhang, Interventional Therapy Center for Oncology, Beijing You'an Hospital, Capital Medical University, 8 Xitoutiao, Youanmenwai Street, Fengtai District, Beijing, People's Republic of China, Tel +86-13810108505, Email zhangyh@ccmu.edu.cn; Ronghua Jin, National Center for Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, 8 Jingshundong Street, Chaoyang District, Beijing, People's Republic of China, Tel +86-13811611118, Email ronghuajin@ccmu.edu.cn

Purpose: We explored the role of tumor size and number in the prognosis of HCC patients who underwent ablation and created a nomogram based on machine learning to predict the recurrence.

Patients and Methods: A total of 990 HCC patients who underwent transcatheter arterial chemoembolization (TACE) combined ablation at Beijing Youan Hospital from January 2014 to December 2021 were prospectively enrolled, including 478 patients with single small HCC (S-S), 209 patients with single large (≥30mm) HCC (S-L), 182 patients with multiple small HCC (M-S), and 121 patients with multiple large HCC (M-L). S-S patients were randomized in a 7:3 ratio into the training cohort (N=334) and the validation cohort (N=144). Lasso-Cox regression analysis was carried out to identify independent risk factors, which were used to construct a nomogram. The performance of the nomogram was evaluated by C-index, receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) curves. Patients in the training and validation cohorts were divided into low-risk, intermediate-risk, and high-risk groups based on the risk scores of the nomogram.

Results: The median recurrence-free survival (mRFS) in S-S patients was significantly longer than the S-L, M-S, and S-L patients (P<0.0001). The content of the nomogram includes age, monocyte-to-lymphocyte (MLR), gamma-glutamyl transferase-to-lymphocyte (GLR), International normalized ratio (INR), and Erythrocyte (RBC). The C-index (0.704 and 0.71) and 1-, 3-, and 5-year AUCs (0.726, 0.800, 0.780, and 0.752, 0.761, 0.760) of the training and validation cohorts proved the excellent predictive performance of the nomogram. Calibration curves the DCA curves showed that the nomogram had good consistency and clinical utility. There were apparent variances in RFS between the low-risk, intermediate-risk, and high-risk groups (P<0.0001).

Conclusion: S-S patients who underwent ablation had the best prognosis. The nomogram developed and validated in the study had good predictive ability for S-S patients.

Keywords: hepatocellular carcinoma, HCC, transcatheter arterial chemoembolization, TACE, ablation, nomogram, recurrence

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related mortality. It is one of the few cancers with an increasing mortality rate.[1,2] Half of the newly diagnosed cases of HCC every year occur in China, posing a serious threat to the lives and health of the Chinese people.[3] With the advancement of

diagnostic techniques, early diagnosis and monitoring of the HCC have extensively improved. Surgical resection, ablation, and liver transplantation are recommended as radical treatments for patients with early-stage liver cancer.[4] Because of decompensated liver function, portal hypertension, and organ shortage, surgical resection, and liver transplantation are limited in many cases.[5,6] As a minimally invasive treatment, ablation has a similar prognosis to surgical resection and exhibits the advantages of fewer complications.[7,8] However, the prognosis of ablation remains unsatisfactory, with a 5-year recurrence rate of 50–70%, which leads to shorter survival of HCC patients.[9] Hence, the recurrence of HCC has become a public health problem that needs urgent attention.

Tumor characteristics such as tumor size and tumor number affect treatment options and prognosis.[10,11] They are also major components of the TNM system and BCLC system. Studies at home and abroad have found that for surgical resection, patients with solitary and small (<30mm) HCC (S-S) have the best prognosis compared to other patients.[12,13] Yet, in patients who underwent ablation, the therapeutic forecast requires further statistics and confirmation.

Precisely due to S-S patients having a better prognosis, the assessment of recurrence in S-S patients is easily overlooked. According to the guidelines, early-stage patients do not need to receive other treatments after radical therapy, which can lead to a further decline in patient follow-up and monitoring efforts.[14] Currently, tumor classification systems such as TNM, Hong Kong Liver Cancer, and Italian liver cancer program have been widely used for treatment selection, but they are not sufficient for predicting relapse. Although predictive markers like AFP, ALBI, NLR, and a number of nomograms are available to predict recurrence in early-stage patients, the nomogram for S-S patients after undergoing ablation is still lacking.[15–17] Therefore, the aim of our study was to confirm the prognosis of S-S patients who underwent ablation and to create a nomogram based on the machine learning approach to more accurately predict the recurrence in order to better guide clinical decisions.

Materials and Methods

Patient Selection

Our study retrospectively evaluated 990 HCC patients who underwent TACE combined ablation at Beijing Youan Hospital from January 2014 to December 2021. The diagnosis of HCC was based on the guideline of America Association for the Study of Liver Diseases (ASSLD).[18,19] HCC patients included 478 patients with single small HCC (S-S), 209 patients with single large (≥30mm) HCC (S-L), 182 patients with multiple small HCC (M-S), and 121 patients with multiple large HCC (M-L). S-S patients were randomized in a 7:3 ratio into the training cohort (N=334) and the validation cohort (N=144). The inclusion criteria were as follows: a) received ablation and achieved complete ablation. b) Aged 18–75 years. c) Child-Pugh classification was class A or B. d) All patients did not receive other antitumor therapy. The Exclusion criteria were as follows: a) advanced HCC. b) with second primary malignant tumors. c) clinical follow-up data incomplete.

Our research was approved by the Medical Ethics Committee of Beijing Youan Hospital and conducted in accordance with the Helsinki Declaration. The requirement for informed consent was waived by the Ethics Commission because the study was based on deidentified data.

Clinicopathologic Characteristics

The demographic, clinical, and pathological information was collected on HCC patients. Demographics included age, gender, cirrhosis, drinking history, smoking history, hypertension, and diabetes. Clinical and pathological data was composed of alpha-fetoprotein (AFP), alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), albumin (ALB), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and gamma-glutamyl transferase to lymphocyte ratio (GLR).

Therapeutic Procedure

All of the patients received TACE combined with ablation, which was conducted by experienced interventional radiologists. Under local anesthesia, percutaneous right femoral artery puncture with a modified Seldinger technique was performed. Through the microcatheter, a mixture of doxorubicin (Pfizer Inc., New York, NY, USA) and lipiodol

(Guerbet, Villepinte, France) was injected into the blood-supply artery of the cancer. The gelfoam or polyvinyl alcohol particles was used to embolize the feeding artery, and the disappearance of the vessel stain was considered the complete embolization. Ablation was performed 1 to 2 weeks after TACE by radiofrequency, microwave, and argon-helium. The ablation area was expanded by 0.5–1cm to determine complete coverage. Otherwise, the procedure was defined as incomplete ablation. The detailed protocol of ablation was described in our previous study. Immediately following ablation, all patients underwent a contrast-enhanced CT to evaluate the success of the ablation and possible complications. Complete ablation was defined as non-enhancement on contrast-enhanced CT with the ablation zone.

Follow-Up

All patients were regularly followed up at the outpatient clinic. Tumor response was assessed by contrast CT or MRI at 4–6 weeks after ablation. Patients were followed up every three months during the first year and every six months thereafter. Follow-up examinations consisted of imaging examinations, liver function, and blood tests to monitor recurrence. Recurrence was confirmed when the imaging results showed an enhanced signal within. Recurrence-free survival (RFS) was defined as the time from initial treatment to the diagnosis to relapse.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviations, and categorical variables were presented as numbers (percentage). Differences between groups were compared by *t*-test, Mann–Whitney, ANOVA, and chi-square tests. Survival rates were calculated by the Kaplan-Meier method and compared with the Log rank test. Multivariate Cox regression analysis followed by lasso regression analysis was carried out to identify independent risk factors, which were used to construct a nomogram to predict recurrence. Prediction ability was measured by receiver-operating characteristic (ROC) curves and areas under the curves (AUC). The calibration of the nomogram was evaluated by the Hosmer-Lemeshow test and displayed by the calibration curves. Decision curve analysis (DCA) was employed to determine the clinical effectiveness by calculating the net benefits for a range of threshold probabilities. According to the nomogram score, patients were divided into low-risk, medium-risk, and high-risk groups, and the Kaplan-Meier curves were generated.

All data were analyzed with SPSS (version 26.0, IBM, Armonk, NY, USA) and R software (version 4.1.3) in this study, and the P-value less than 0.05 was considered statistically significant (two-tailed tests).

Result

Baseline Characteristics

A total of 990 HCC patients who underwent TACE combined ablation in Beijing Youan Hospital were enrolled in the study, including 778 (79.6%) males and 202 (20.1%) females. At the time of diagnosis, 212 (21.4%) patients had diabetes. There were 745 (75.3%) patients with Child-Pugh A and 245 (24.7%) patients with Child-Pugh B. The 990 HCC patients included 478 (48.3%) patients with S-S, 209 (21.1%) patients with S-L, 182 (18.4%) patients with M-S, and 121 (12.2%) patients with M-L (Table 1).

Efficacy

The median follow-up was 4.03 years in this study. The K-M curves indicated a better prognosis in patients with S-S (Figure 1). The mRFS in S-S patients was significantly longer than the S-L, M-S, and M-L patients (3.8 years VS 1.47 years, 1.47 years, and 1.13 years, P<0.0001). However, the 1-, 3-, and 5-year RFS rates for S-S patients were 86.2%, 56.7%, and 40.1%, and the recurrence rate remained high. Consequently, it is necessary to create a nomogram for patients with S-S to identify signs of relapse in order to provide timely treatment.

Next, we randomly divided the patients with S-S into a training cohort (N=334) and a validation cohort (N=161) in a 7:3 ratio. The validation cohort had a similar characteristic as the training cohort (P>0.05). In the two cohorts, the majority of the patients were male (74.9% VS 77.8%, P=0.570), and the average was over 50 years (56.4±9.28 VS 56.1 ±9.04, P=0.697). Most of the patients had cirrhosis (85.9% VS 85.4%, P=0.997), but the majority of Child-Pugh classifications were A (76.4% VS 79.9%, P=0.257), suggesting that patients had good liver function (Table 2).

Table 1 Demographics and Clinical Characteristics for HCC Patients

	S-S (N=478)	S-L (N=209)	M-S (N=182)	M-L (N=121)	P value
Age	56.4±9.21	58.0±8.54	56.4±8.36	56.3±9.16	0.137
Gender					0.029
Male	362 (75.7%)	171 (81.8%)	152 (83.5%)	103 (85.1%)	
Female	116 (24.3%)	38 (18.2%)	30 (16.5%)	18 (14.9%)	
Diabetes					0.154
No	365 (76.4%)	169 (80.9%)	141 (77.5%)	103 (85.1%)	
Yes	113 (23.6%)	40 (19.1%)	41 (22.5%)	18 (14.9%)	
Cirrhosis					0.133
No	68 (14.2%)	28 (13.4%)	14 (7.7%)	18 (14.9%)	
Yes	410 (85.8%)	181 (86.6%)	168 (92.3%)	103 (85.1%)	
Child-Pugh					0.787
A	364 (76.2%)	159 (76.1%)	132 (72.5%)	90 (74.4%)	
B	114 (23.8%)	50 (23.9%)	50 (27.5%)	31 (25.6%)	
Smoking					0.220
No	280 (58.6%)	118 (56.5%)	97 (53.3%)	59 (48.8%)	
Yes	198 (41.4%)	91 (43.5%)	85 (46.7%)	62 (51.2%)	
RBC	4.18±0.65	4.16±0.60	4.14±0.59	4.09±0.62	0.573
Hb	132 (19.9%)	130 (17.9%)	130 (20.2%)	128 (18.9%)	0.279
AST	30.4±12.0	35.3±21.9	32.2±12.8	32.7±13.3	0.001
TBIL	19.6±10.0	19.1±10.2	19.2±10.0	18.2±9.93	0.585
DBIL	6.81±4.75	6.53±4.76	6.16±4.71	6.17±4.14	0.323
ALB	37.7±4.77	37.0±5.22	36.9±4.03	36.5±4.58	0.039
Globulin	28.1±5.15	28.3±5.49	28.1±5.32	29.5±6.01	0.069
Palb	146±58.7	129±59.2	130±50.9	129±61.0	<0.001
Bile.acid	22.8±28.7	21.1±24.9	24.4±34.0	17.9±25.0	0.226
PT	12.6±1.65	12.6±1.45	12.5±1.29	12.5±1.36	0.784
INR	1.12±0.15	1.11±0.12	1.10±0.11	1.10±0.12	0.367
APTT	33.8±4.46	33.4±4.49	34.2±4.35	33.4±5.42	0.351
Fib	2.63±0.81	3.19±1.16	2.67±0.70	3.10±1.00	<0.001
AFP	160±668	430±2055	236±1161	803±2715	<0.001

Abbreviation: S-S, patients with single small tumor; S-L, patients with single and large tumor; M-S, patients with multiple small tumor; M-L, patients with multiple large tumor; RBC, red blood cell; Hb, hemoglobin; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; Palb, prealbumin; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrous protein; AFP, alpha-fetoprotein.

The Prediction Model Was Built Based on the Lasso-Cox Regression

Independent Prognostic Factors of RFS

Lasso regression was used to screen the parameters, and the variation characteristics of the coefficient of these variables were shown in Figure 2A. The model exhibited outstanding performance and the least number of independent variables when λ was 0.026 (Figure 2B). The screened variables included age, gender, hypertension, diabetes, antiviral, smoking, drinking, family, cirrhosis, AFP, RBC, MLR, GLR, Alb, and INR. These variables were incorporated into multivariate Cox regression analysis to identify independent prognostic factors associated with recurrence. The final Results obtained were age (HR: 1.02, 95% CI: 1.01–1.04), RBC (HR: 0.93, 95% CI: 0.87–0.99), MLR (HR: 2.57, 95% CI: 1.17–5.65), INR (HR: 3.01, 95% CI: 1.19–7.62) and GLR (HR: 1.00, 95% CI: 1.00–1.01) (Table 3).

Develop the Nomogram

The nomogram was established based on the independent predictors found by the Lasso-Cox regression analysis (Figure 3). In the training cohort, the C-index was 0.704 (95% CI: 0.67–0.74), with AUCs of 0.726, 0.800, and 0.780

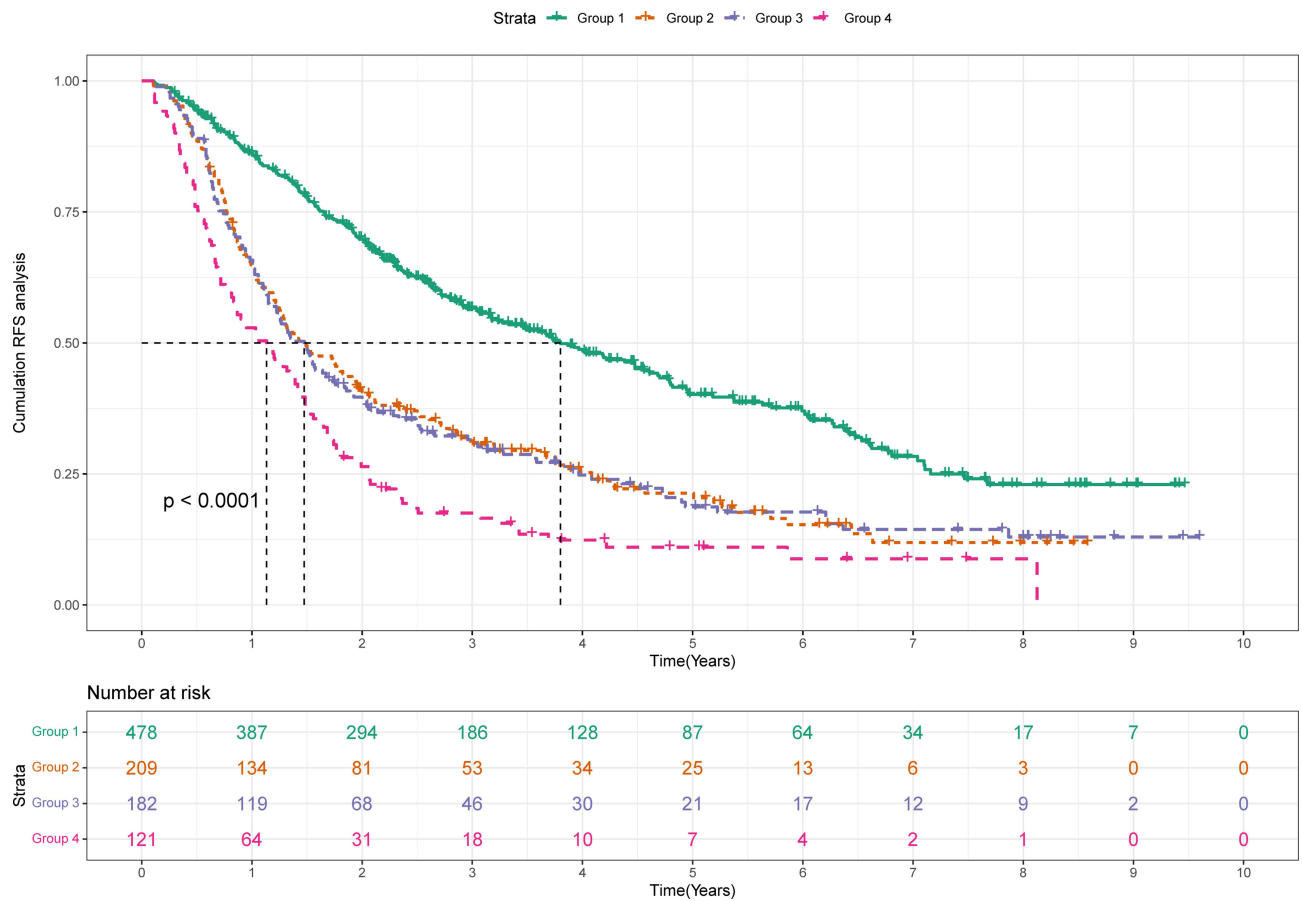**Figure 1** Kaplan-Meier plot of RFS for HCC patients.
Notes: Group 1, patients with single small tumor; Group 2, patients with single large tumor; Group 3, patients with multiple small tumors; Group 4, patients with multiple large tumors.

at 1-, 3-, and 5-year, and these indicated the validity of the nomogram in predicting RFS (Figure 4). The calibration curve showed optimal agreement between the predicted and observed outcomes (Figure 5). Moreover, the 1-, 3-, and 5-year DCA curves testified that the nomogram had a high net benefit (Figure 6).

Table 2 Demographics and Clinical Characteristics for Training and Validation Sets

	Training Cohort (N=334)	Validation Cohort (N=144)	P value
Age	56.4±9.28	56.1±9.04	0.697
Gender			0.570
Male	250 (74.9%)	112 (77.8%)	
Female	84 (25.1%)	32 (22.2%)	
Diabetes			0.732
No	257 (76.9%)	108 (75.0%)	
Yes	77 (23.1%)	36 (25.0%)	
Cirrhosis			0.997
No	47 (14.1%)	21 (14.6%)	
Yes	287 (85.9%)	123 (85.4%)	
Child-Pugh			0.257
A	249 (74.6%)	115 (79.9%)	
B	85 (25.4%)	29 (20.1%)	

(Continued)

Table 2 (Continued).

	Training Cohort (N=334)	Validation Cohort (N=144)	P value
Smoking			1.000
No	196 (58.7%)	78 (58.3%)	
Yes	138 (41.3%)	60 (41.7%)	
RBC	4.16±0.66	4.21±0.62	0.440
Hb	131.2±20.11	132.3±19.51	0.550
AST	30.8±12.10	29.5±11.83	0.312
TBIL	20.0±10.25	18.7±9.51	0.195
DBIL	6.9±4.92	6.4±4.30	0.199
ALB	37.6±4.91	37.9±4.43	0.371
PT	12.7±1.74	12.4±1.42	0.048
INR	1.13±0.15	1.10±0.12	0.050
APTT	33.9±4.42	33.3±4.54	0.153
Fib	2.65±0.84	2.58±0.75	0.367

Abbreviation: RBC, red blood cell; Hb, hemoglobin; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; Palb, prealbumin; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrous protein; AFP, alpha-fetoprotein.

Patients were divided into three groups according to the score of the nomogram: low-risk group, medium-risk group, and high-risk group. And there were apparent variances in RFS (NA, 4.01 years, and 2.04 years) between the low-risk (N=89), medium-risk (N=144), and high-risk (N=101) groups (P<0.0001) (Figure 7). The 1-, 3-, and 5-year RFS rates were 94.0%, 78.9%, and 65.9% in the low-risk group and 76.2%, 31.9%, and 19.1% in the high-risk group.

Validate the Nomogram

Internal validation was conducted to verify the reliability and stability of the nomogram. In the validation cohort, the C-index was 0.71 (95% CI: 0.66–0.76), and 1-,3-, and 5-year AUCs were 0.752, 0.761, and 0.760, both indicating good discrimination (Figure S1). Besides, all calibration curves demonstrated good consistency, and the DCA curves also showed that the nomogram had good clinical utility (Figures S2 and S3). Patients in the validation cohort were similarly categorized into low-risk, medium-risk, and high-risk groups, and the low-risk group (NA) also had a significantly higher
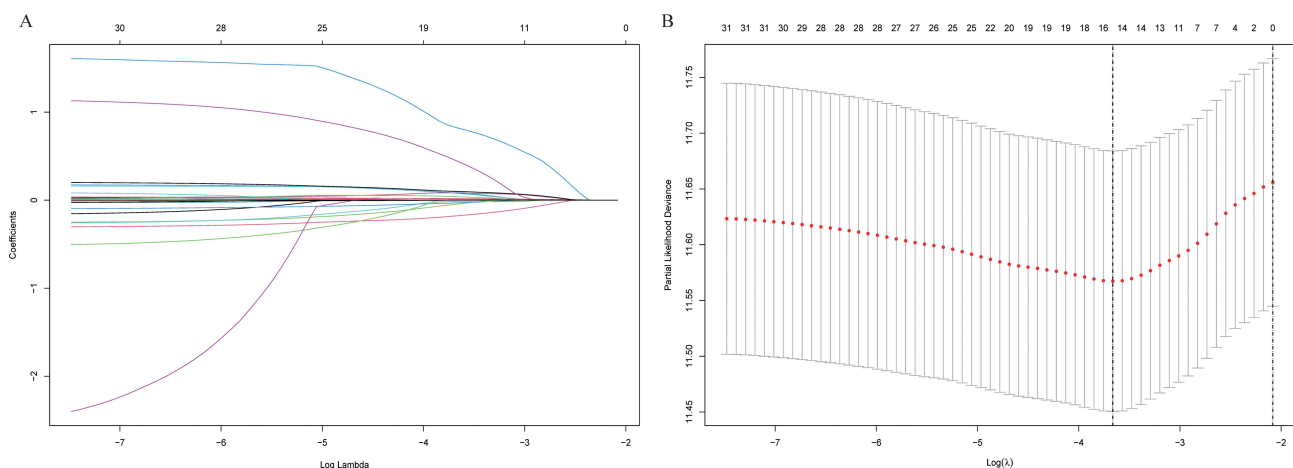

Figure 2 Screening of variables based on Lasso regression. (**A**) The variation characteristics of the coefficient of variables. (**B**) the selection process of the optimum value of the parameter λ in the Lasso regression model by cross-validation method.

Table 3 Cox Proportional Hazards Regression to Predict Recurrence Based on Lasso Regression

Variables	HR (95% CI)	P value
Age	1.02 (1.01–1.04)	0.001
Gender	0.76 (0.53–1.08)	0.129
Hypertension	0.84 (0.64–1.08)	0.218
Diabetes	1.18 (0.89–1.56)	0.248
Antiviral	1.22 (0.95–1.56)	0.116
Smoking	1.11 (0.84–1.47)	0.468
Drinking	1.14 (0.79–1.64)	0.464
Family	1.99 (0.78–3.29)	0.992
Cirrhosis	1.08 (0.73–1.58)	0.718
AFP	1.02 (0.004–2.05)	0.122
RBC	0.93 (0.87–0.99)	0.017
MLR	2.57 (1.17–5.64)	0.019
GLR	1.00 (1.00–1.01)	0.002
Alb	0.98 (0.78–1.24)	0.852
INR	3.01 (1.19–7.62)	0.020

Abbreviations: RBC, red blood cell; ALB, albumin; INR, international normalized ratio; MLR, monocyte-to-lymphocyte; GLR, gamma-glutamyl transferase-to-lymphocyte.

RFS than the high-risk and medium-risk groups (2.3 and 4.8 years) (P<0.0001) (Figure S4). The 1-, 3-, and 5-year RFS rates were 95.8%, 77.8%, and 64.4% in the low-risk group and 76.3%, 35.4%, and 23.2% in the high-risk group. These proved that the nomogram could distinguish patients at high risk of recurrence.
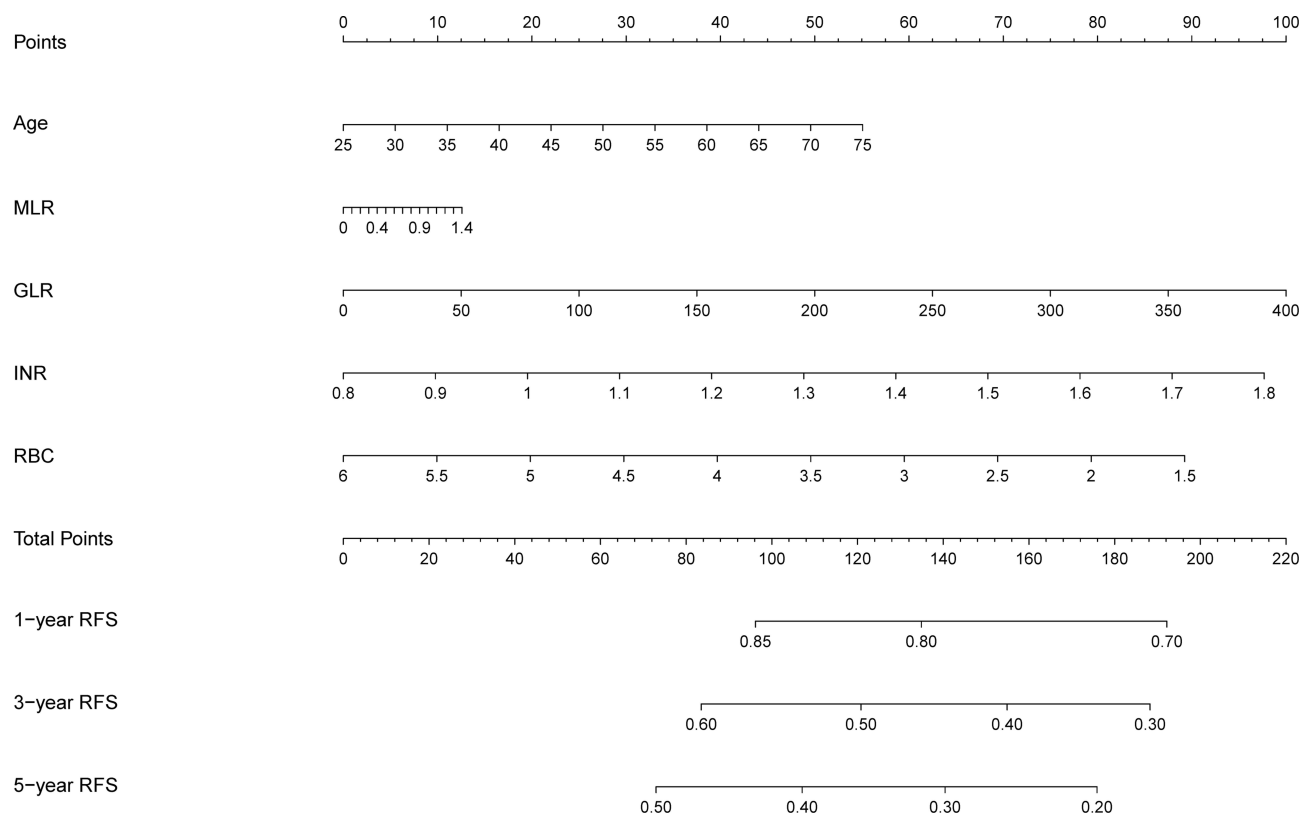

Figure 3 Nomogram, including Age, MLR, GLR, RBC, and INR for 1-, 3-, and 5- years recurrence free survival (RFS) in HCC patients with high HBsAg levels in AFP. The nomogram is valued to obtain the probability of 1-, 3-, and 5- years recurrence by adding up the points identified on the points scale for each variable.
Abbreviations: RBC, red blood cell; INR, international normalized ratio; MLR, monocyte-to-lymphocyte; GLR, gamma-glutamyl transferase-to-lymphocyte.
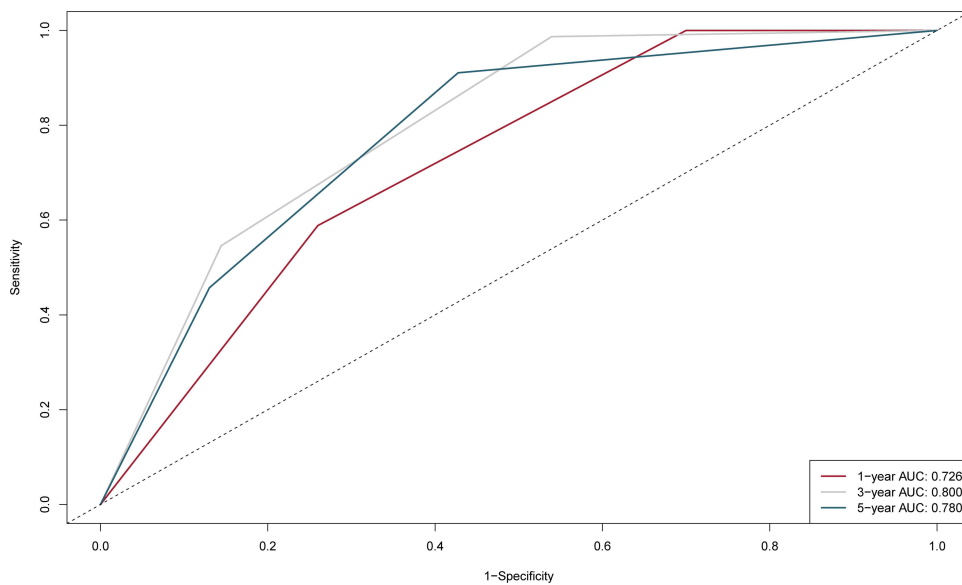
Figure 4 1-, 3-, and 5-year ROC curves of the nomogram in the training cohort.
Abbreviation: ROC, receiver operating characteristics.
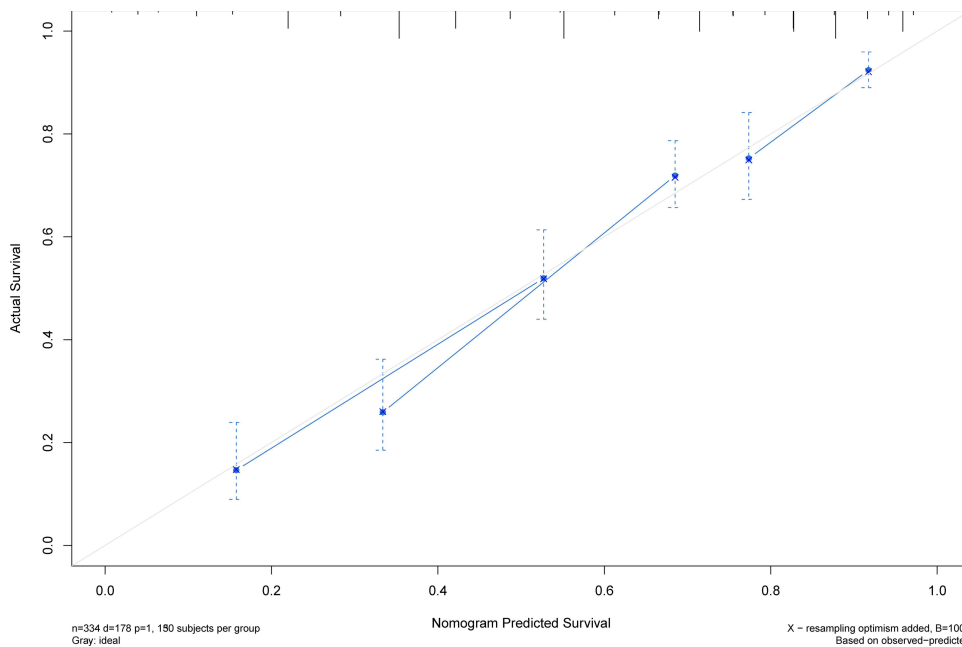

Figure 5 1-, 3-, and 5-year calibration curves of the nomogram in the training cohort.

Discussion

HCC is one of the most frequent and fatal malignancies, which seriously threatens human health.[20,21] The size and number of tumors are important for staging and play a key role in prognosis.[22–24] Our study further explored the role of tumor size and number in tumor progression and prognosis of the HCC patients who underwent ablation and found that patients with single small HCC had the best prognosis. In addition, we created a nomogram by Lasso-Cox regression to predict the prognosis of S-S patients accurately.

Tumor burden, measured as maximum tumor size and number of tumors, has been incorporated as a common element in many prognostic models of HCC.[25] Previous studies have revealed that tumor burden is closely associated with patient
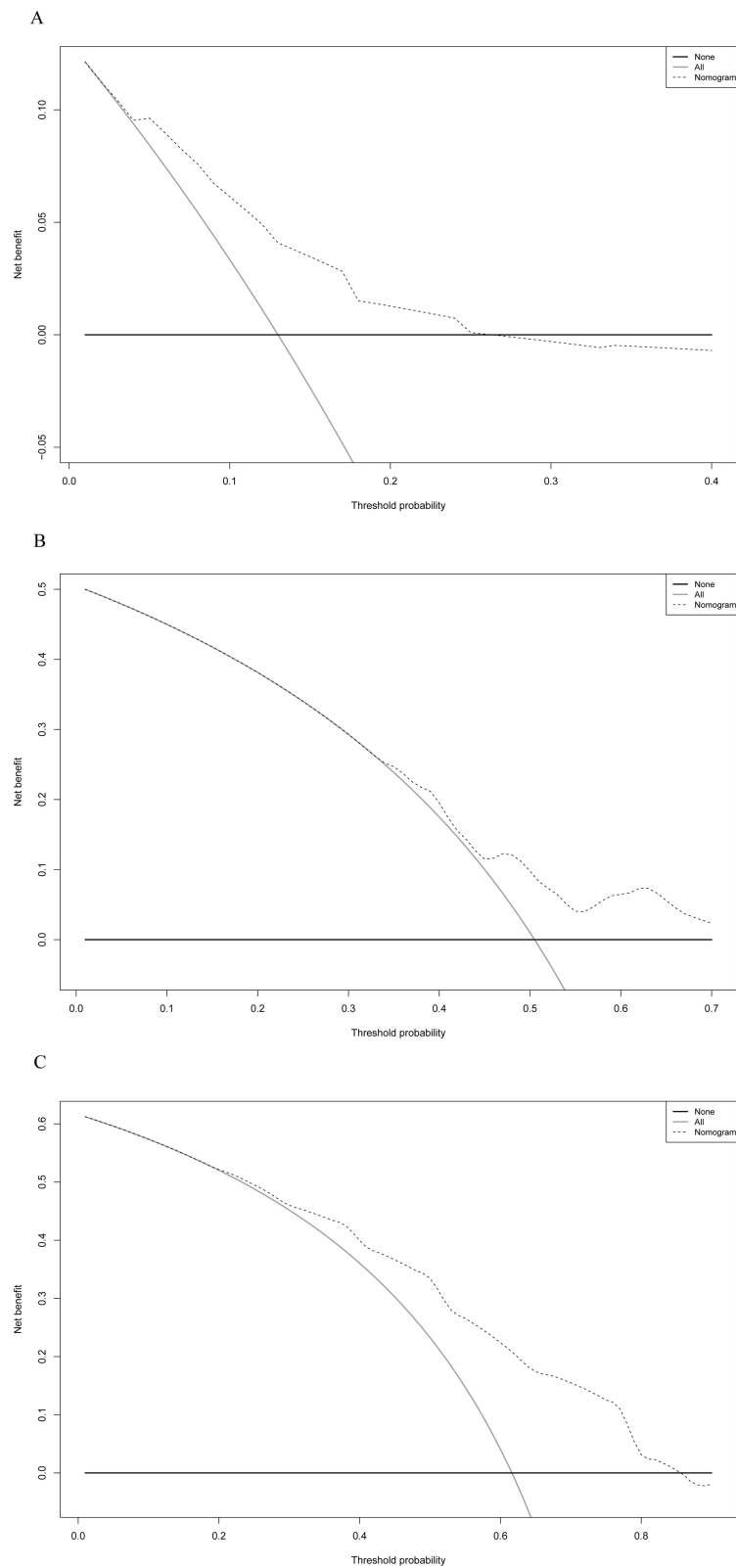
A

B

C

Figure 6 1-, 3-, and 5-year DCA curves of the nomogram in the training cohort. (**A**) One-year decision curve analysis in the training cohort. (**B**) Three-year decision curve analysis in the training cohort. (**C**) Five-year decision curve analysis in the training cohort.
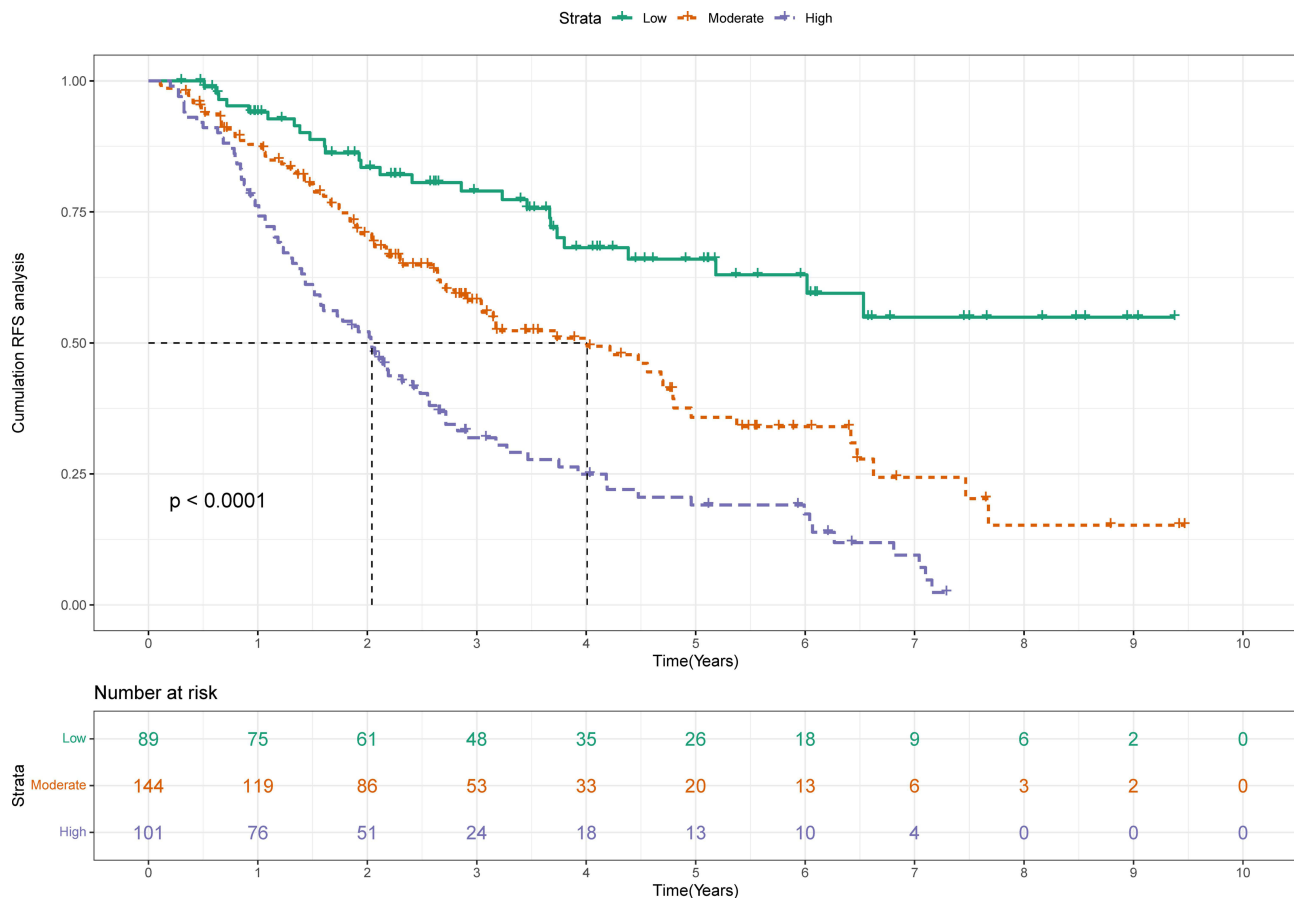**Abbreviation**: DCA, decision curve analysis.

Figure 7 Kaplan-Meier plots of RFS for the low-risk group, intermediate-risk group and high-risk group in the training cohort.
Abbreviation: RFS, recurrence-free survival.

survival and recurrence.[26–29] However, tumor recurrence is still common, even in HCC patients without aggressive features. Furthermore, it might have been insufficient to predict the recurrence of HCC using only tumor burden in all patients with HCC. The results of the study in our center indicated that S-S patients had a better prognosis, with a mRFS of 3.85 years. Because of the good prognosis, monitoring of this group of patients after ablation can be untimely. Furthermore, S-S patients do not require further treatment after radical therapy, which makes follow-up more difficult. However, the rates of 1-, 3-, and 5-year RFS were 86.3%, 56.7%, and 40.2%, respectively. Due to the high recurrence, we need to create a nomogram to predict the population at high risk of recurrence in patients with S-S to help clinicians guide clinical decisions.

Several studies have suggested that liver weight and portal blood flow velocity are reduced in older patients, which can lead to less reparability of the liver in younger patients.[30] Tumor progression after treatment is faster in the elderly than in younger patients because of low immunity, resulting in a high recurrence rate and poor prognosis.[15] As a classic inflammation-associated cancer, approximately 90% of the liver cancer burden is caused by viral hepatitis, excessive drinking, and non-alcoholic fatty liver disease (NAFLD).[31,32] Both the immune microenvironment and inflammatory marker are part of the systemic inflammatory response and exert a fundamental role in tumor initiation, progression, and metastasis.[33,34] MLR is the ratio of monocytes to lymphocytes. Monocytes accumulate at sites of inflammation and differentiate into M1 and M2 macrophages as inflammation occurs. Activated circulating monocytes can secrete a variety of pro-inflammatory factors, which are involved in tumor development.[35–37] Lymphocyte, which possesses potent anticancer activities, plays critical roles in host immune responses and anti-tumor immunity.[38] Tumor invasion and the release of inflammatory factors are responsible for the destruction of hepatocytes, which is characterized by an increase of GGT in peripheral blood.[39] GLR could be used as a potential prognostic marker of early recurrence and prognosis, and higher GLR is associated with poor outcomes.[40–42] INR is

a good measure of hepatic synthetic function. A large cohort study including 2509 HCC patients showed that low INR levels had shorter RFS and OS compared to high INR levels.[43] The incidence of MVI was also found to be significantly higher in HCC patients with low INR levels than normal or high INR levels.[44] RBC could inhibit tumor growth and metastasis by removing circulating immune complexes.[45] Normal RBCs improve the killing effect on tumor cells by increasing the activity of the lymphocyte-activated killer cells and the NK cells through the release of natural killer cell-activating factors.[46]

The nomogram contains five variables screened by Lasso-Cox regression, including age, MLR, GLR, INR, and RBC. The scores on the nomogram are obtained by drawing a vertical line through the position of the corresponding total score so that it intersects the three lines predicting recurrence, and the values shown at the intersection were predicted RFS at 1, 3, and 5 years. The C-index of the nomogram for training and validation cohorts was 0.704 and 0.71, respectively. The correction and ROC curves verified the predictive performance of the nomogram. The DCA curves revealed that the nomogram had a high positive net benefit, which implied good clinical application potential. Patients in the training and validation cohorts were categorized into low-risk, intermediate-risk, and high-risk groups based on the scores of the nomogram, and there was a statistically significant difference in RFS among the three groups (P<0.0001), suggesting that our nomogram had good ability to differentiate S-S patients.

TACE could mark tumors that are not clearly visualized on imaging and reduce tumor size by embolizing tumor vessels, reducing ablation time, and increasing the success rate of ablation.[16] The previous investigation of our team and foreign reports confirmed that the combination therapy with TACE and ablation is superior to TACE alone or ablation alone in RFS and OS.[47,48] Simultaneous examination of comprehensive patient features covering demographics, liver function, and inflammatory markers was a major strength of our study. Compared with single-factor analysis, Lasso regression can minimize the multicollinearity in variables.

Our study still had some limitations. First, this was a retrospective cohort study. Thus, further investigation in a prospective clinical trial is warranted. Secondly, as a single-center study, there was a potential selection bias of the patients in the cohort. Because of the long span in our study, there are differences in ablation between periods and medical teams. As such, the results of the present study need external validation to be verified further. Nevertheless, we used up to eight years of follow-up to create an accurate and reliable nomogram to better guide clinical practice for this group of HCC patients with single and small HCC.

Conclusion

In summary, patients with single small HCC had the best prognosis. However, the rates of 1-, 3-, and 5-year RFS were 86.3%, 56.7%, and 40.2% in patients with S-S. For S-S patients, we created an accurate and reliable nomogram to predict recurrence based on the Lasso-Cox regression analysis. The nomogram, including age, MLR, GLR, RBC, and INR, demonstrated adequate discrimination ability, which could better guide clinical decisions.

Data Sharing Statement

All relevant data are available within the manuscript and its Supplementary Material Files. Further enquiries can be directed to the corresponding author (Yonghong Zhang, zhangyh@ccmu.edu.cn).

Ethics Statement

The study protocol was approved by the Ethics Committee of Beijing Youan Hospital and conducted following the ethical principles outlined in the Helsinki Declaration of 1964 and its subsequent amendments, or other ethical standards with equivalent requirements. As a retrospective study as well as to ensure patient confidentiality, the identities of the individuals included in this study were anonymized using computer-generated ID numbers, and thus, patient consent was waived.

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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 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 report no competing interests in this work.

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