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ORIGINAL RESEARCH

Recurrence of Hepatocellular Carcinoma in Patients with Low Albumin-Bilirubin Grade in TACE Combined with Ablation: A Random Forest Cox Predictive Model

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Purpose: The aim of our study was to investigate the relationship between albumin-bilirubin (ALBI) grade and recurrence in patients who underwent TACE sequential ablation. We developed and validated a nomogram to predict low levels of ALBI patients' recurrence.

Patients and Methods: A total of 880 patients undergoing TACE combined ablation at Beijing Youan Hospital from January 2014 to December 2021 were retrospectively enrolled, including 415 patients with L-ALBI (≤-2.6) and 465 patients with high levels (>-2.6) of ALBI (H-ALBI). L-ALBI patients were randomized in a 7:3 ratio into the training cohort (N=289) and validation cohort (N=126). Multivariate Cox regression followed by random survival forest was carried out to identify independent risk factors for prediction nomogram construction. An examination of nomogram accuracy was performed using the C-index, receiver operating characteristic (ROC), calibration curves, and decision curve analysis (DCA) curves. According to the nomogram, the patients were divided into low-risk, intermediate-risk, and high-risk groups. Kaplan-Meier (KM) curves were applied to compare the difference in recurrence-free survival (RFS) among the three groups.

Results: The median RFS in L-ALBI patients was significantly longer than the H-ALBI patients (40.8m vs 20.1m, HR:1.71, 95% CI:1.44–2.04, P<0.0001). The nomogram was composed of five variables, such as age, Barcelona Clinic Liver Cancer (BCLC) stage, globulin, gamma-glutamyl transferase to lymphocyte ratio (GLR), and international normalized ratio (INR). The C-index (0.722 and 0.731) and 1-, 3-, and 5-year AUCs (0.725, 0.803, 0.870, and 0.764, 0.816, 0.798) of the training and validation cohorts proved the good predictive performance of the nomogram. Calibration curves and DCA curves demonstrated good consistency and good clinical utility. There were significant differences in RFS between the low-risk, intermediate-risk, and high-risk groups (P<0.0001).

Conclusion: L-ALBI Patients who underwent TACE combined ablation had better recurrence-free survival than patients with H-ALBI. The nomogram developed and validated in our study had good predictive ability in recurrence for L-ALBI patients.

Keywords: hepatocellular carcinoma, HCC, ablation, nomogram, recurrence, albumin-bilirubin, ALBI

Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 90% of liver cancer and is the sixth leading cause of cancer and the fourth leading cause of cancer-related mortality worldwide, which has caused an enormous burden on global health.[1,2] Despite the decline in incidence, HCC remains the second most common cancer, with 36000 new cases

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reported annually.[3,4] For HCC patients in the early-stage, curative treatments such as resection, ablation, and liver transplantation are recommended. Several studies have reported that the efficacy and safety of ablation therapy are comparable with surgery.[5] Still, disease recurrence after curative therapy remains an issue, and the 5-year recurrence rate of HCC patients after ablation is as high as 50–70%.[6] Transcatheter arterial chemoembolization (TACE) has become the first-choice therapy in patients with intermediate-stage HCC, but the median progression-free survival (PFS) is only five months.[7] Hence prognosis of HCC is still a problem of worldwide major concern.

In comparison with other solid cancers, the treatment and prognosis of HCC depend not only on the tumor biology but also on underlying liver function reserve.[8,9] For decades, the Child-Pugh (CTP) classification system has been widely used to assess patient hepatic function. There have been studies that incorporate Child-Pugh into the nomogram achieved strong survival predictive accuracy.[10] However, clinical assessment of hepatic encephalopathy and ascites is limited by subjectivity.[11] Therefore, a scoring system for serum albumin and bilirubin was developed based on laboratory data from a large international patient cohort, which was simpler and more objective than the CTP classification system.[12,13] The albumin-bilirubin (ALBI) grade was proven to be a reliable model for assessing liver function. Several studies have shown that ALBI grade is superior to CTP classification both in predicting the prognosis of hepatectomy, TACE, and Yi-90 radioembolization.[14–16] Even in patients with early-stage HCC, ALBI grade is associated with recurrence and long-term survival and is sensitive enough to determine outcome. In a recent meta-analysis that described 95 studies exploring the relationship between ALBI and HCC, Bannaga et al reported that ALBI grade was higher than CTP classification and AFP in predicting HCC survival.[17] Patients with the most favorable group (ALBI grade 1) had the highest 5-year OS rate of 77.9–88.5%. The OS rates of ALBI 2 and 3 HCC patients were 38.6%-73.8%.[18] Nevertheless, the predictive role of ALBI grade for HCC patients' recurrence undergoing TACE combined with ablation needs to be further demonstrated.

Although the good predictive performance of ALBI, previous research suggested that the five-year recurrence rate remained high in patients with low levels of ALBI (L-ALBI).[19,20] And postoperative monitoring of L-ALBI patients is easy to ignore because L-ALBI patients have a better prognosis than patients with high levels of ALBI (H-ALBI). Consequently, the aim of our study was to investigate the relationship between ALBI grade and recurrence in patients who underwent TACE sequential ablation. Finally, we developed and validated a nomogram for clinicians to predict L-ALBI patients' recurrence and improve their treatment planning.

Methods and Materials

Patients Selection

This retrospective cohort study reviewed 880 HCC patients who underwent TACE combined with ablation at Beijing Youan Hospital from January 2014 to December 2021. HCC diagnosis was based on the guideline of the American Association for the Study of Liver Diseases (ASSLD).[2,21] The HCC patients were comprised of 415 individuals with low levels (≤-2.6) of ALBI (L-ALBI) and 465 individuals with high levels (>-2.6) of individuals (H-ALBI). L-ALBI patients were randomized in a 7:3 ratio into the training cohort (N=289) and the validation cohort (N=126). The inclusion criteria were like following: (1) Aged 18–75 years. (2) Received TACE combined with ablation and achieved complete ablation. (3) Child-Pugh classification A or B. (4) did not have extrahepatic metastasis or vascular invasion. The exclusion criteria were as follows: (1) received other anti-tumor treatments before ablation. (2) with second primary malignant tumors. (3) 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 and clinicopathological characteristics were collected retrospectively and analyzed. Demographics included age, gender, hypertension, and diabetes. Clinicopathological data was composed of tumor size, tumor number, hemoglobin (Hb), alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), γ-glutamyl transpeptidase (GGT), albumin (ALB), globulin, des-gamma-carboxyprothrombin (DCP),

neutrophil-to-lymphocyte ratio (NLR), prealbumin (Palb), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and gamma-glutamyl transferase to lymphocyte ratio (GLR). The formula for the ALBI score was as follows: (log10 TBIL [μmol/L] × 0.66) − (albumin [g/L] × 0.085).[12]

Therapeutic Procedure

All patients were treated with TACE by two interventional radiologists with more than 5 years of experience. Detailed treatment procedures have been described in previous studies and will not be described in this study. Ablation was performed after TACE within 2 weeks by radiofrequency (RFA) and microwave (MWA). The ablation range completely covered the tumor to the edge of 0.5–1.0cm to prevent marginal residue and recurrence. The detailed protocol of ablation was described in our previous study. Contrast-enhanced CT/MRI was provided to evaluate the tumor response after one month.

Follow-Up

All patients were followed up every three months for the first year, and then every six months thereafter in the outpatient clinic. The contents of follow-ups included liver function, blood tests, and imaging examinations to monitor recurrence. Recurrence was defined as the appearance of a new enhanced lesion with radiographic features. Recurrence-free survival (RFS) was defined as the time from initial treatment to the diagnosis to relapse.

Statistical Analysis

Categorical variables were expressed as number (percentage) and continuous variables were presented as mean±standard deviations. Differences between groups were compared by chi-square tests, *t*-test, and Mann–Whitney test. Survival was estimated by the Kaplan-Meier (KM) curve with the Log rank test. The significance of variables for RFS which were used to construct the nomogram was analyzed by multivariate Cox regression analysis followed by the random survival forest. The prediction ability of the nomogram was assessed by the area under the receiver operating characteristic (ROC) curves (AUCs). The calibration curve and decision curve analysis (DCA) were evaluated to test the calibration performance and clinical utility. Based on the nomogram risk score, patients were categorized into low-risk, medium-risk, and high-risk groups, and the KM curves were generated.

All analyses were performed by SPSS (version 26.0, IBM, Armonk, NY, USA) and R software (version 4.1.3). P-values less than 0.05 were considered to be statistically significant (two-tailed tests).

Result

Baseline Characteristics

A total of 880 HCC patients submitted to TACE combined with ablation in Beijing Youan Hospital were enrolled in our study, including 706 (80.2%) males and 174 (19.8%) females. At the time of diagnosis, 221 (25.1%) patients had hypertension, and 184 (20.9%) patients had diabetes. There were 271 (30.8%) patients with multiple tumor numbers and 312 (35.5%) patients with large tumors (≥30mm). The 880 patients included 415 (46.1%) L-ALBI patients and 465 (53.9%) H-ALBI patients (Table 1).

We randomly allocated L-ALBI patients into a training cohort (N=289) and a validation cohort (N=126), in a 7:3 radio. The clinicopathological features were similar between the training cohort and the validation cohort (Table 2). In the two cohorts, the majority of the patients were male (84.4% vs.80.2%, P=0.355) and the average was over 50 years (55.5±9.53 vs.55.9±9.10, P=0.504). BCLC A had the highest percentage of patients (51.6% vs.55.6%, P=0.746). For characteristics of the tumor, most tumors were solitary (72.0% vs.73.8%, P=0.907) and tumor size was less than 30mm (67.8% vs.66.7%, P=0.790).

The Efficacy of ALBI in HCC Patients Undergoing TACE Combined with Ablation

At July 30, 2023, median follow-up times was 44.1 months in our study. The KM curves showed the mRFS in L-ALBI patients was significantly longer than in H-ALBI patients (40.8m vs.20.1m, P<0.001, HR:1.71, 95% CI:1.44–2.04,

Table 1 Demographics and Clinical Characteristics for HCC Patients

	L-ALBI (N=415)	H-ALBI (N=465)	P-value
Age	55.50±9.40	57.92±8.18	<0.001
Gender			0.050
Male	345 (83.1%)	361 (77.6%)	
Female	70 (16.9%)	104 (22.4%)	
Hypertension			0.197
Yes	113 (27.2%)	108 (23.2%)	
No	302 (72.8%)	357 (76.8%)	
Diabetes			0.478
Yes	82 (19.8%)	102 (21.9%)	
No	333 (80.2%)	363 (78.1%)	
BCLC stage			0.013
0	145 (34.9%)	127 (27.3%)	
A	219 (52.8%)	255 (54.8%)	
B	51 (12.3%)	83 (17.8%)	
Smoking			0.306
Yes	191 (46.0%)	197 (42.4%)	
No	260 (51.0%)	268 (57.6%)	
Drinking			0.368
Yes	144 (34.7%)	147 (31.6%)	
No	307 (65.3%)	318 (68.4%)	
T.S			0.100
<30mm	280 (67.5%)	288 (71.9%)	
≥30mm	135 (32.5%)	177 (38.1%)	
T.N			0.052
Single	271 (72.5%)	308 (66.2%)	
Multiple	144 (27.5%)	157 (33.8%)	
WBC	5.74±2.28	4.63±1.92	<0.001
NLR	3.10±2.68	3.38±2.82	0.136
MLR	0.33±0.20	0.42±0.23	<0.001
RBC	4.49±0.49	3.86±0.58	<0.001
PLR	110.74±49.67	108.9±63.54	0.635
ALT	31.74±20.35	31.05±18.16	0.594
AST	28.14±12.11	35.54±16.94	<0.001
Globulin	27.16±4.64	29.39±5.89	<0.001
GLR	51.28±53.67	85.8±106.8	<0.001
HBsAg	3444.81±3051.17	3478.65±3117.52	0.871
AFP	344.39±1948.59	306.99±1182.90	0.728
INR	1.06±0.09	1.18±0.14	<0.001

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ALBI, Albumin-bilirubin; L-ALBI, patients with low levels of ALBI; H-ALBI, patients with high levels of ALBI; RBC, red blood cell; T.N, tumor number; T.S, tumor size; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLR, gamma-glutamyl transferase to lymphocyte ratio; HBsAg, hepatitis B surface antigen; INR, international normalized ratio; AFP, alpha-fetoprotein.

Figure 1). The 1-, 3-, and 5-year RFS rates of L-ALBI patients were 79.2%, 54.0%, and 39.8%, which were higher than H-ALBI patients (1-year: 67.1%; 3-year: 32.4%; 5-year: 23.4%). Although the L-ALBI patients had a better prognosis, the recurrence remained high and this group of patients was more likely to be overlooked. Therefore, it is necessary to establish a nomogram for L-ALBI patients to predict the recurrence after ablation.

Table 2 Demographics and Clinical Characteristics for Training and Validation Sets

	Training Cohort (N=289)	Validation Cohort (N=126)	P-value
Age	55.5±9.53	55.9±9.10	0.504
Gender			0.355
Male	244 (84.4%)	101 (80.2%)	
Female	45 (15.6%)	25 (19.8%)	
Hypertension			0.775
Yes	77 (26.6%)	36 (28.6%)	
No	212 (73.4%)	90 (71.4%)	
Diabetes			0.217
Yes	52 (18.0%)	30 (23.8%)	
No	237 (82.0%)	96 (76.2%)	
BCLC			0.746
0	104 (36.0%)	41 (32.5%)	
A	149 (51.6%)	70 (55.6%)	
B	36 (12.5%)	15 (11.9%)	
Smoking			0.455
Yes	137 (47.4%)	54 (42.9%)	
No	152 (52.6%)	72 (57.1%)	
Drinking			0.533
Yes	97 (33.6%)	47 (37.3%)	
No	192 (76.4%)	79 (62.7%)	
T.S			0.790
<30mm	196 (67.8%)	84 (66.7%)	
≥30mm	93 (32.2%)	42 (33.3%)	
T.N			0.907
Single	208 (72.0%)	93 (73.8%)	
Multiple	81 (28.0%)	33 (26.2%)	
WBC	5.68±2.21	5.9±2.44	0.347
NLR	3.18±2.85	2.9±2.24	0.364
PLR	113.6±51.72	104.2±44.11	0.076
RBC	4.51±0.50	4.4±0.45	0.094
MLR	0.34±0.21	0.3±0.20	0.215
ALT	31.3±19.89	32.9±21.40	0.464
AST	27.9±12.23	28.6±11.86	0.575
Globulin	27.3±4.76	26.9±4.36	0.420
GLR	52.1±56.32	49.4±47.19	0.646
HBsAg	3424.8±3053.63	3490.6±3057.20	0.840
AFP	356.8±2192.9	315.9±1222.40	0.845
INR	1.1±0.09	1.0±0.09	0.125

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; T.N, tumor number; T.S, tumor size; RBC, red blood cell; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLR, gamma-glutamyl transferase to lymphocyte ratio; HBsAg, hepatitis B surface antigen; INR, international normalized ratio; AFP, alpha-fetoprotein.

Significant Variables of RFS of HCC

The variables were used to build an RFS model in the training cohort. With the increase in the number of random survival forest, the prediction error rate decreased significantly; The error rates tended to be stable when the number of tree was more than 600 (Figure 2A). According to the VIMP method, the importance of variables was ranked, in the order of age, cirrhosis, DCP, BCLC stage, tumor number, tumor size, WBC, NLR, RBC, Hb, PLR, AST, Palb, globulin,

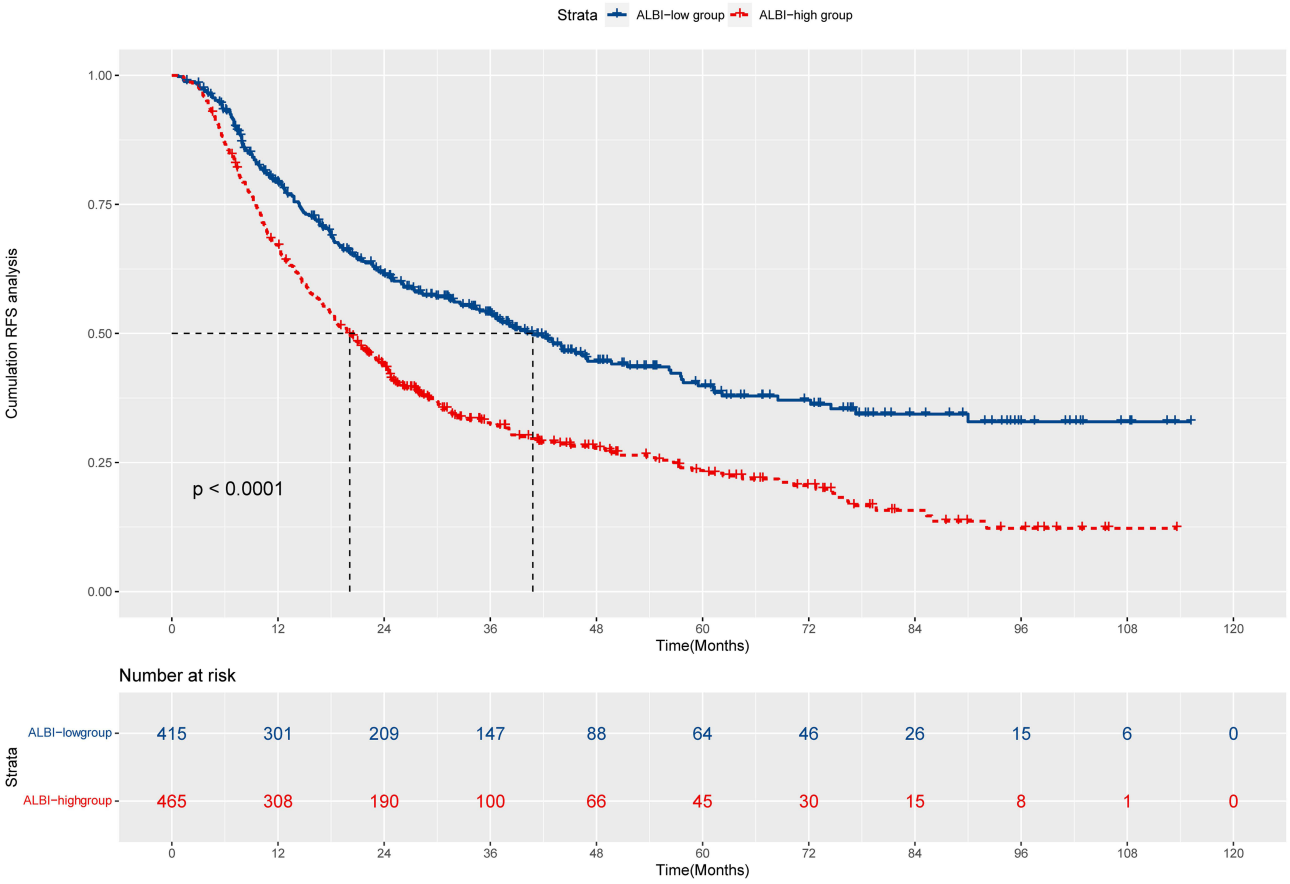

Figure 1 Kaplan-Meier plot of RFS for HCC patients.
Abbreviations: RFS, recurrence free survival; HCC, hepatocellular carcinoma; ALBI, Albumin-bilirubin.

GLR, ALP, PT, INR, AFP and Fibrinogen (Fib) (Figure 2B). Based on the Results of the random survival forest, multivariate survival analysis was performed to reveal the recurrence-related factors (Table 3). The final results obtained were age (HR: 1.03, 95% CI: 1.01–1.04), BCLC stage (HR: 1.67, 95% CI: 1.33–2.09), globulin (HR: 1.04, 95% CI: 1.01–1.08), INR (HR: 11.23, 95% CI: 2.12–59.11) and GLR (HR: 1.00, 95% CI: 1.00–1.01).

Nomogram Construction

The nomogram was constructed based on the prognostic factors identified by the multivariate Cox regression (Figure 3). The C-index was 0.722 (95% CI: 0.68–0.76) and the 1-, 3-, and 5-year AUCs were 0.725, 0.803, and 0.870 in the training cohort (Figure 4). The calibration curves depicted that the predicted outcome was broadly consistent with the actual outcome (Figure 5). Moreover, the decision curve analysis (DCA) testified that the nomogram had a high net benefit (Figure 5).

We calculated the risk scores of HCC patients and divided them into low-risk (N=94), intermediate-risk (N=100), and high-risk (N=95) groups. And there were apparent variances in RFS between the low-risk, intermediate-risk, and high-risk groups (P<0.0001, Figure 6). The median RFS was not reached for the low-risk group with 1-, 3-, and 5-year RFS rates of 90.9%, 80.6%, and 70.3%, respectively. The intermediate-risk group had a median RFS of 44.1 months (95% CI: 32.6–74.5m) with 1-, 3-, and 5-year RFS rates of 76.7%, 55.9%, and 33.4%, respectively. The high-risk group had a median RFS of 18.0 months (95% CI: 14.9–23.9m) with 1-, 3-, and 5-year RFS rates of 66.3%, 28.6%, and 14.0%, respectively.

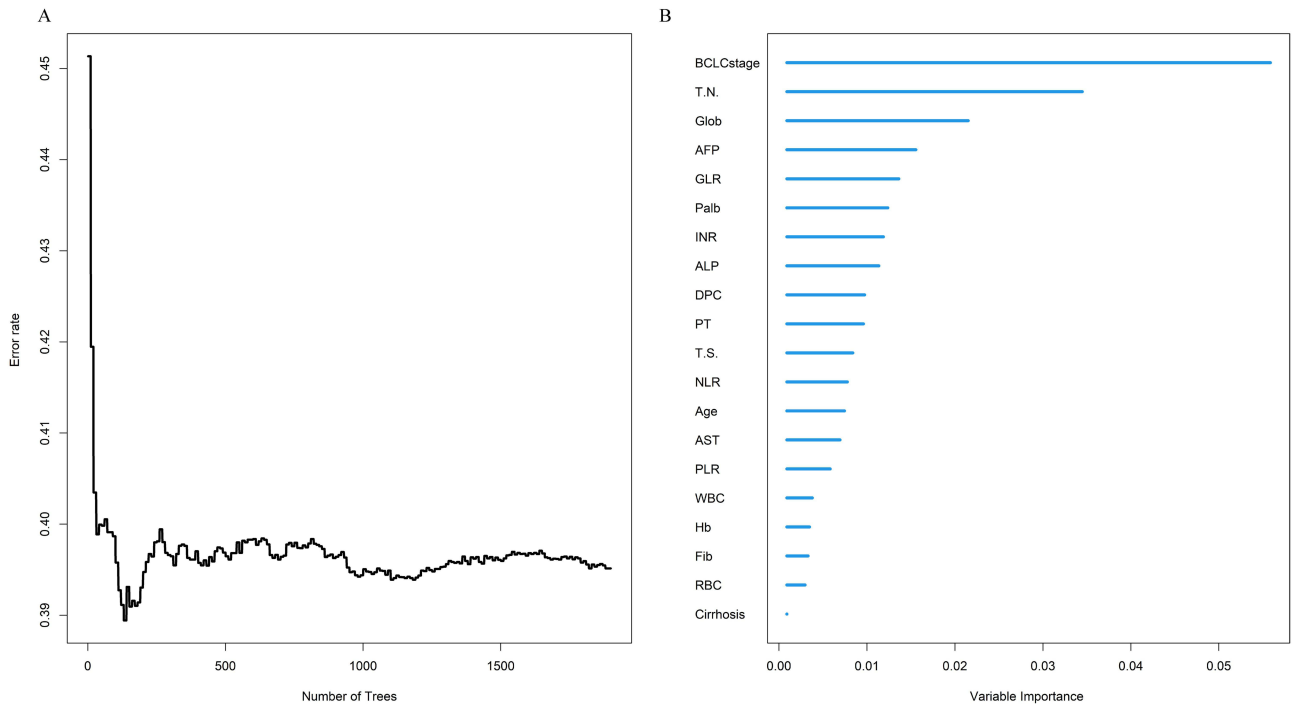

Figure 2 Screening of variables based on random survival forest. (**A**) Error rate of random survival rate forest; (**B**) out-of-bag variable importance ranking.
Abbreviations: DCP, des-gamma-carboxyprothrombin; BCLC, Barcelona Clinic Liver Cancer; T.N, tumor number; T.S, tumor size; RBC, red blood cell; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; PLR, platelet-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLR, gamma-glutamyl transferase to lymphocyte ratio; ALP, alkaline phosphatase; PT, prothrombin time; Fib, fibrinogen; INR, international normalized ratio; AFP, alpha-fetoprotein.

Validate of Nomogram

To validate the performance of the resulting nomogram, we performed internal validation by using an independent validation cohort. In the validation cohort, the C-index was 0.731 (95% CI: 0.67–0.78), with the 1-, 3-, and 5-year AUCs of 0.764, 0.816, and 0.798, and these indicated the validity of the nomogram in predicting RFS (Figure S1). Besides, the calibration curves revealed optimal agreement between the nomogram and the observation and the DCA curves also showed good clinical utility (Figure S2). Patients in the validation cohort were similarly categorized into low-risk (N=48), medium-risk (N=37), and high-risk (N=41) groups, and the KM curves of the three groups were significantly different (P<0.0001, Figure S3). In the validation cohort, the median RFS was not reached for the low-risk group with 1-, 3-, and 5-year RFS rates of 92.6%, 82.2%, and 62.7%, respectively. The intermediate-risk group had a median RFS of 47.8 months (95% CI: 29.2m-NA) with 1-, 3-, and 5-year RFS rates of 86.3%, 49.1%, and 35.8%, respectively. The high-risk group had a median RFS of 23.1 months (95% CI: 15.6–38.7m) with 1-, 3-, and 5-year RFS rates of 68.8%, 26.5%, and 21.2%, respectively.

Discussion

Morbidity and mortality caused by HCC continue to be substantial worldwide.[4,22] Originally developed to evaluate liver function in patients with HCC, the ALBI grade was developed.[19] In our study, we found that L-ALBI patients had a better prognosis than H-ALBI patients treated with TACE sequential ablation (P<0.0001). A nomogram was created and validated to predict recurrence for L-ALBI patients.

The L-ALBI group had a median RFS of up to 40.8 months. But the recurrence rates at 1-, 3-, and 5-year were 79.2%, 53.9%, and 39.8%, respectively, so the recurrence rate remains high. Besides, L-ALBI patients are more likely to be ignored because of the better prognosis. It is necessary to create a nomogram to accurately predict recurrence in this group of patients. In a ratio of 7:3, we divide the L-ALBI patients into the training cohort and the validation cohort in the context of the advantage of eight years of follow-up. The random survival forest and multivariate Cox proportional hazards regression model were performed to screen prognostic variables for RFS in the training cohort. Random survival

Table 3 Multivariate Cox Proportional Hazards Regression to Predict Recurrence Based on Random Survival Forest and Multivariate Cox Regression

Variables	HR (95% CI)	P-value
Age	1.03 (1.01–1.04)	0.008
Cirrhosis	1.27 (0.82–1.95)	0.281
DCP	1.52 (0.79–2.92)	0.207
BCLC stage	1.67 (1.33–2.09)	<0.001
T.N.	1.39 (0.89–2.18)	0.139
T.S.	1.32 (0.87–1.98)	0.192
WBC	0.93 (0.05–1.99)	0.148
NLR	1.03 (0.95–1.12)	0.505
RBC	0.87 (0.65–1.16)	0.342
Hb	0.99 (0.98–1.00)	0.234
PLR	1.00 (0.99–1.00)	0.553
AST	1.00 (0.99–1.02)	0.549
Palb	0.96 (0.92–1.01)	0.131
Globulin	1.04 (1.01–1.08)	0.005
GLR	1.00 (1.00–1.01)	0.009
ALP	1.00 (0.99–1.01)	0.723
PT	0.88 (0.51–1.51)	0.636
INR	11.23 (2.12–59.11)	0.004
Fib	1.02 (0.87–1.19)	0.803
AFP	1.01 (1.00–1.11)	0.885

Abbreviations: DCP, des-gamma-carboxyprothrombin; BCLC, Barcelona Clinic Liver Cancer; T.N, tumor number; T.S, tumor size; RBC, red blood cell; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; Hb, hemoglobin; PLR, platelet-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLR, gamma-glutamyl transferase to lymphocyte ratio; ALP, alkaline phosphatase; PT, prothrombin time; Fib, fibrinogen; INR, international normalized ratio; AFP, alpha-fetoprotein.

forest, a machine learning, takes into account the interactions between variables compared to the univariate Cox regression. According to the accurate screening, a nomogram was established to predict the relapse in L-ALBI patients. The nomogram is used by converting the corresponding predictor value into the corresponding nomogram score and then adding the score value, and the 1-, 3-, and 5-year RFS rates are obtained from the values shown at the intersection points. The C-index, ROC curve, calibration curve, and DCA curve revealed the good predictive performance of the nomogram. Based on the nomogram, patients can be accurately stratified into low-risk, medium-risk, and high-risk groups. In addition, we used an independent validation cohort to internally validate the nomogram, and the results further proved the reliability. With the help of this well-established nomogram, clinicians would be able to make more individualized treatments, control modifiable risk factors, and frequent follow-ups. Therefore, the nomogram can help reduce the recurrence rates and improve the survival rates of patients.

The nomogram includes age, BCLC stage, globulin, GLR, and INR. Several studies have shown that liver weight and portal blood flow velocity are reduced in older patients, which can lead to the liver that is less repairable than in younger patients.[23] Due to the low immunity in the elderly, tumor progression after treatment is faster than in younger patients, leading to a high rate of recurrence and poor prognosis.[24] The BCLC stage, which integrates factors such as liver function, tumor load, and physical condition, is the most widely used staging system for HCC. There is a great deal of heterogeneity among tumors at different stages, and both OS and RFS are related to the stage of BCLC.[25,26] The lymphocytes of the immune system play a critical role in the immune response of the body and contain potent antitumor

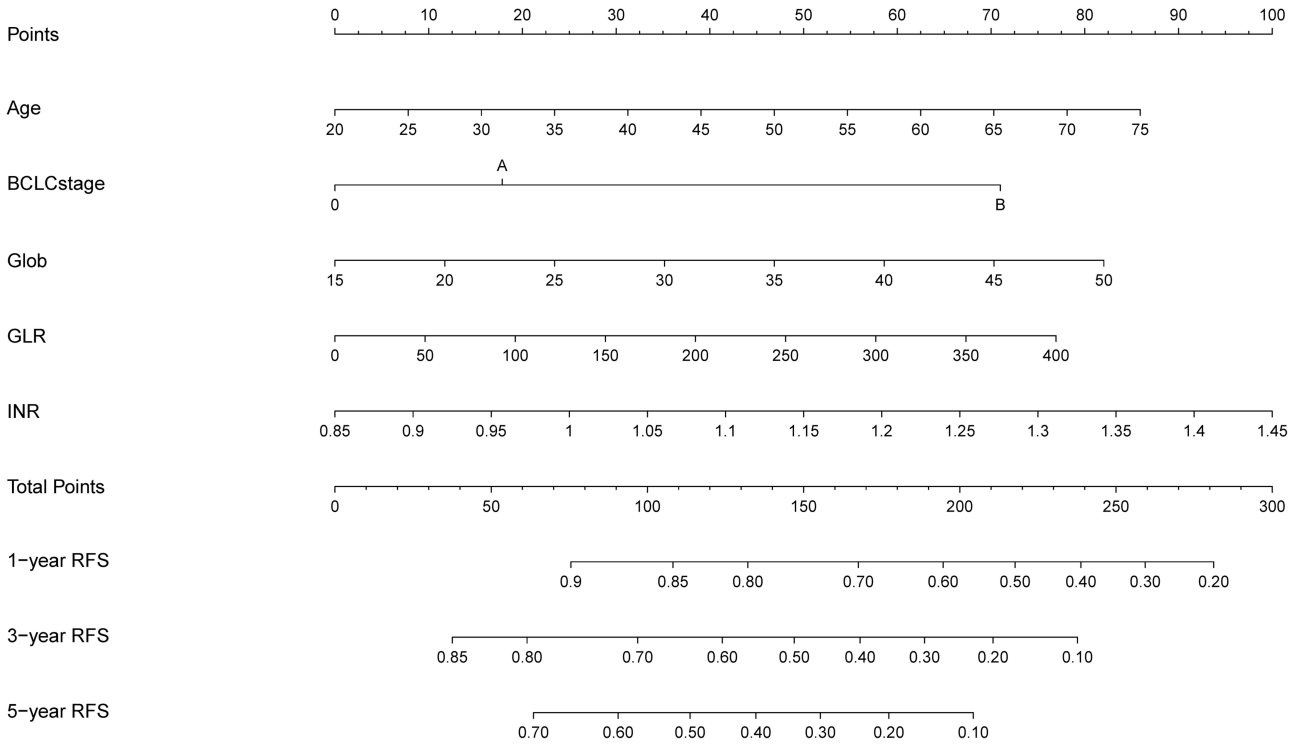

Figure 3 Nomogram, including Age, globulin, GLR, BCLC stage, and INR for 1-, 3-, and 5-year RFS in HCC patients with low levels of ALBI. The nomogram is valued to obtain the probability of 1-, 3-, and 5- years recurrence by adding up the points identified on the points scale for each variable.
Abbreviations: INR, international normalized ratio; GLR, gamma-glutamyl transferase-to-lymphocyte; BCLC, Barcelona Clinic Liver Cancer; Glob, globulin; HCC, hepatocellular carcinoma; RFS, recurrence free survival.

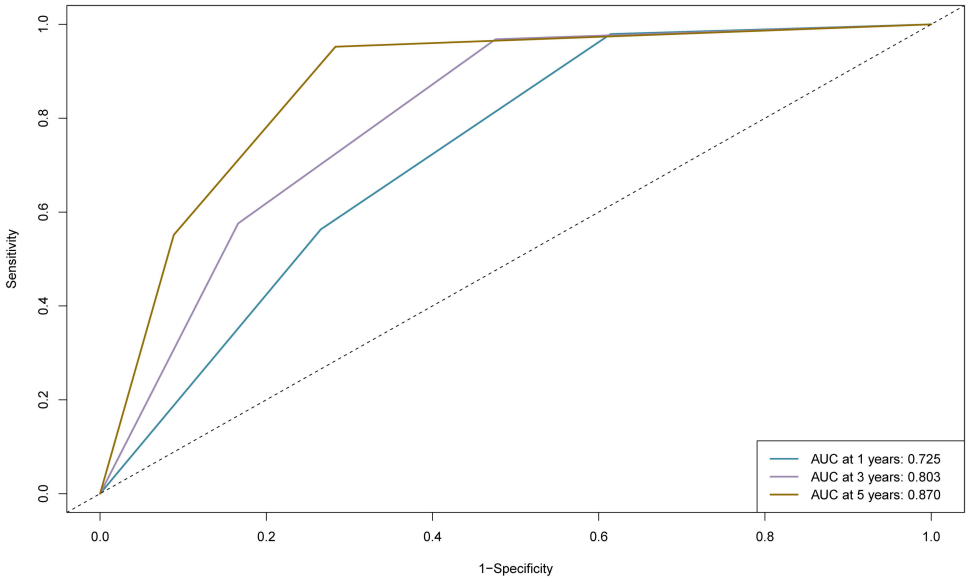

Figure 4 1-, 3-, and 5-year ROC curves of the nomogram in the training cohort.
Abbreviations: ROC, receiver operating characteristics; AUC, area under the curve.

properties.[27] GGT, a cell surface enzyme, has been shown to be a marker for several cancers. In the course of the destruction of hepatocytes, GGT in cells is released into the blood, resulting in an increased concentration of GGT.[28] The increased GLR was independently associated with the poor prognosis of HCC patients and can be a potential indicator of early recurrence.[29–31] INR is an important index of liver synthetic function. As the severity of liver disease worsens, the

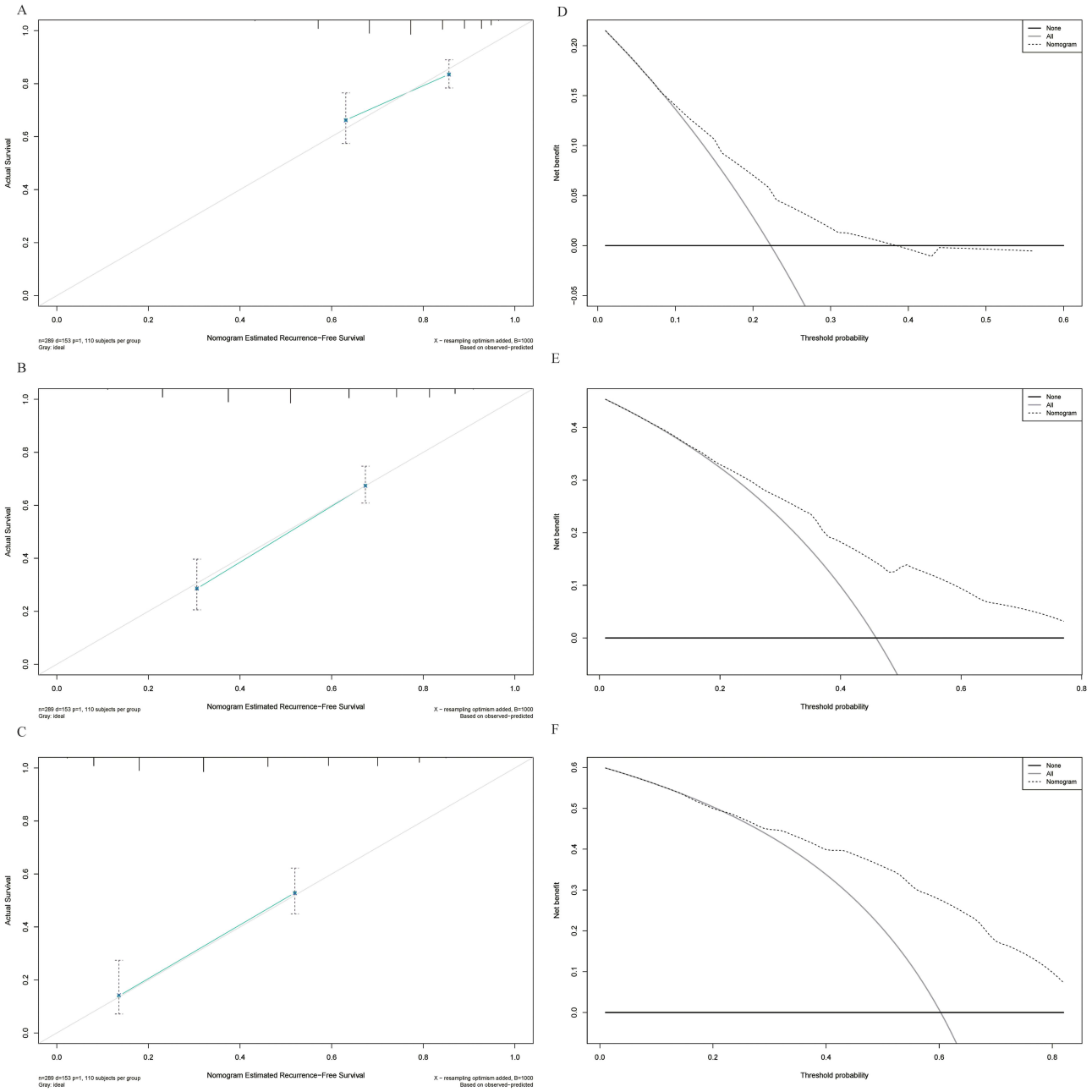

Figure 5 Calibration curves and DCA curves of the nomogram in the training cohort. (**A**) 1-year calibration curves of the nomogram in the training cohort. (**B**) 3-year calibration curves of the nomogram in the training cohort. (**C**) 5-year calibration curves of the nomogram in the training cohort. (**D**) 1-year DCA curves of the nomogram in the training cohort. (**E**) 3-year DCA curves of the nomogram in the training cohort. (**F**) 5-year DCA curves of the nomogram in the training cohort.
Abbreviation: DCA, decision curve analysis.

production of VII factors is also decreased. INR is also recommended for assessing survival in patients with severe liver disease and is included in the MELD score. A study suggested that the high INR to albumin ratio is an independent risk factor for worse DFS and OS in patients with surgically treated HCC.[32] Globulins consist of a variety of pro-inflammatory proteins, including C-reactive protein, α2-macroglobulin, prothrombin, fibrinogen, and serum amyloid A.[33] Primary metabolism of human immunoglobulins is carried out by the liver, and individuals with severe hepatic insufficiency experience decreased immunoglobulin clearance, leading to hyperglobulinemia. A malignancy patient's poor clinical outcome can be attributed to inflammation, which alters tumor cell biological characteristics and destroys immune function.[34,35]

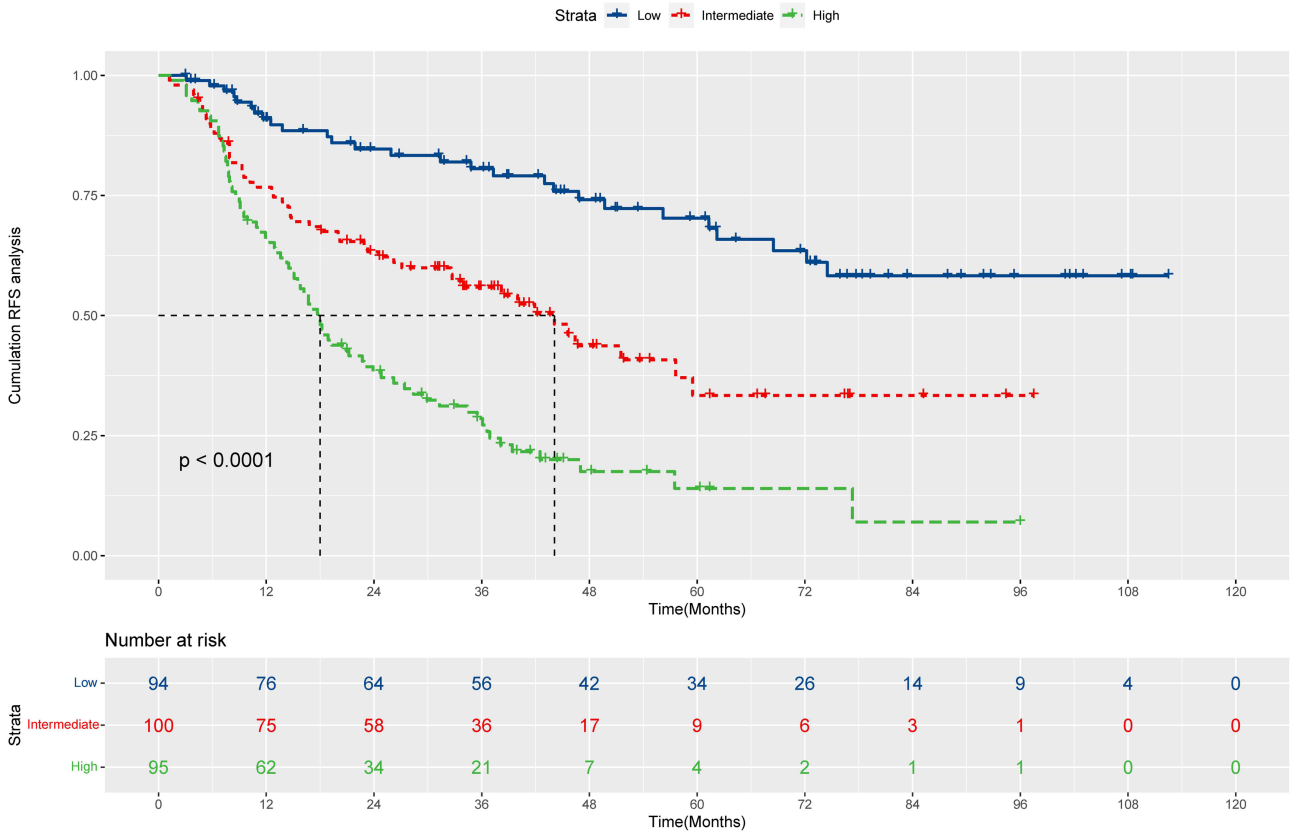

Figure 6 Kaplan-Meier plots of RFS for the low-risk group, intermediate-risk group and high-risk group in the training cohort.
Abbreviation: RFS, recurrence-free survival.

Different treatment modalities of HCC have demonstrated prognostic value of ALBI grade, including liver resection, TACE, and systemic treatment.[36–39] Our study confirmed that ALBI grade could also predict the prognosis of patients with HCC patients underwent TACE combined with ablation. The ALBI score is calculated from objective factors of serum albumin and bilirubin and is based on statistical evidence rather than clinical observation. It was previously illustrated that ALBI grade was more effective than Milan criteria in predicting recurrence after ablation in HCC patients.[40] The incidence of HCC markedly increased with low serum albumin levels.[41] In a basic study, albumin inhibited the growth and invasion of HCC cells.[42] Despite these strengths, the ALBI grade still has limitations. Recurrence rates remained higher in the L-ALBI group, and ALBI alone was not sufficient to predict relapse in HCC patients. The efficacy of surveillance will be decreased because of the better prognosis in the L-ALBI group. Thereby, models for risk assessment in individual patients are still needed.

The BCLC guidelines for the treatment of HCC recommend TACE for patients with intermediate-stage HCC. For early-stage HCC, TACE is able to mark tumors that are not clearly visible on imaging and reduce tumor size by embolizing tumor vessels, shortening ablation time, and increasing the success rate of ablation.[27] The results of several studies indicated improved OS and RFS when TACE and ablation were used in combination for the treatment of HCC, compared with TACE alone.[43–45] On that account, we chose TACE sequential ablation, and further prospective multi-center studies are needed to confirm the efficacy.

However, there were some limitations in our research. Firstly, it was a single-center study, which should be followed up by multicenter studies in the future. Furthermore, as the current study was a retrospective study, there may have been unavoidable selection bias. Nevertheless, we used a follow-up period of up to eight years to explore the impact of ALBI levels in the prognosis of HCC patients after sequential ablation with TACE and created an accurate and reliable nomogram to better guide clinical practice for L-ALBI patients with HCC.

Conclusion

In summary, Patients with low levels of ALBI who underwent TACE combined with ablation had better recurrence-free survival than patients with high levels of ALBI. However, the rates of 1-, 3-, and 5-year RFS rates in L-ALBI patients were 79.2%, 54.0%, and 39.8%, which remained high. Therefore, we created an accurate and reliable nomogram to predict recurrence for L-ALBI patients based on random survival forest and multivariate Cox regression. The nomogram, including age, BCLC stage, GLR, globulin, and INR, demonstrated adequate discrimination ability, which could better guide clinical decisions.

Data Sharing Statement

Data to support the study findings are available on request from the corresponding author.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Beijing You ‘an Hospital and complied with the requirements of the Declaration of Helsinki. As a retrospective study, the requirement for patient written informed 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 conflicts of interest in this work.

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