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ORIGINAL RESEARCH

Establishing and Externally Validating a Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score-Based Nomogram for Predicting Early Recurrence in BCLC Stage 0/A Hepatocellular Carcinoma Patients After Radical Liver Resection: A Multi-Center Study

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Purpose: Early recurrence (ER) is associated with poor prognosis in hepatocellular carcinoma (HCC). In this study, we developed and externally validated a nomogram based on the hemoglobin, albumin, lymphocytes, and platelets (HALP) score to predict ER for patients with BCLC stage 0/A HCC who underwent radical liver resection.

Patients and Methods: A total of 808 BCLC stage 0/A HCC patients from six hospitals were included in this study, and they were assigned to a training cohort (n = 500) and an external validation cohort (n = 308). We used univariate and multivariate Cox regression analysis to identify the independent risk factors for disease-free survival (DFS). We also established and externally validated a nomogram based on these risk predictors. The nomogram was evaluated using the area under the receiver operating characteristic curve (AUC), the concordance index (C-index), the calibration curve, decision curve analysis (DCA), and Kaplan–Meier analysis.

Results: Multivariate COX regression showed that HBV DNA ≥10,000 IU/mL (P < 0.001), HALP score ≤38.20 (P < 0.001), tumor size (P = 0.003), clinically significant portal hypertension (P = 0.001), Edmondson-Steiner grade (III–IV) (P = 0.007), satellite nodules (P < 0.001), and MVI (P = 0.001) were independent risk factors for post-operative tumor recurrence. The AUC of our nomogram for predicting the 2-year and 5-year DFS was 0.756 and 0.750, respectively, in the training cohort and 0.764 and 0.705, respectively, in the external validation cohort. We divided the patients into low-, intermediate- and high-risk groups according to the risk score calculated by the nomogram. There were statistically significant differences in the DFS and overall survival (OS) among the three groups of patients (P < 0.001).

Conclusion: We developed and externally validated a new nomogram, which is accurate and can predict ER in BCLC stage 0/A HCC patients after curative liver resection.

Keywords: early recurrence, hepatocellular carcinoma, HALP score, nomogram, Barcelona Clinic of Liver Cancer staging system, disease-free survival

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Introduction

As of 2022, primary liver cancer was the sixth most diagnosed cancer and the third leading cause of cancer-related death in the world, with about 865,000 new cases and 757,948 deaths.[1] 75–85% of primary liver cancer is hepatocellular carcinoma (HCC).[1] For patients with Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC, hepatectomy is the most effective treatment method.[2,3] However, even after active surgical treatment, the prognosis of HCC patients remains poor due to high recurrence rates. The 5-year recurrence rate after radical hepatectomy is as high as 50–70%.[4,5] Recurrence within two years of liver resection (LR) is defined as early recurrence (ER).[6] Compared with late recurrence, patients with ER have poor tumor biology and worse prognoses.[6,7] Therefore, identifying the risk factors for HCC recurrence, especially ER, and providing early post-operative adjuvant therapy for high-risk patients will be beneficial in improving their prognoses. Currently, multiple nomograms exist to predict HCC recurrence. However, they encompass a broad spectrum of tumor stages, including advanced stages such as BCLC stage C and TNM stage IV, leading to imprecise prognostic predictions for patients with early-stage HCC.[8–11] Hence, there is a pressing need to develop a specialized prediction model specifically for patients with BCLC stage 0/A HCC.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a new composite biomarker index defined as hemoglobin × albumin × Lymphocytes / platelets, first proposed by Chen et al in 2015 to predict the prognosis of gastric carcinoma patients.[12] Since then, many researchers have proved that the HALP score is an effective predictor of the overall prognosis of various tumors, such as colorectal cancer,[13] bladder cancer,[14] and gastrointestinal stromal tumors.[15] It is often used to evaluate patients' inflammatory responses and nutritional status. In general, a low HALP score before treatment is associated with a reduced survival rate of cancer patients.[16] Recently, Zhou et al found that a low preoperative HALP score indicates a poor prognosis in HCC patients who underwent LR,[17] suggesting that the HALP score can predict the postoperative recurrence of HCC.

In this study, we aimed to confirm the clinical significance of a low HALP score in predicting the postoperative recurrence of HCC. We then developed and externally validated a novel nomogram based on the HALP score to predict ER in BCLC stage 0/A HCC patients who underwent LR. The results of this study may help guide individualized treatments and improve patient outcomes.

Materials and Methods

Patients Included

We retrospectively selected the patients included in this study. Data for the training cohort originated from patients who underwent treatment at the Tongji Hospital, affiliated to Tongji Medical College of Huazhong University of Science and Technology, from February 2015 to September 2018. The external validation cohort data was from patients treated at the West China Hospital, Taihe Hospital, Huangshi Central Hospital, Jingzhou Central Hospital, and Xiangyang Central Hospital from July 2013 to June 2023. This study was approved by the Institutional Ethics Committees of all six hospitals. The identities of all included patients were anonymized before the analysis. Therefore, the requirement for informed consent was waived.

Data for all BCLC stage 0/A HCC patients who underwent LR in the above hospitals during the period were reviewed. The inclusion criteria were as follows: (1) age 14–75 years; (2) no history of other malignant diseases; (3) no previous treatment for HCC before liver resection; and (4) Child-Pugh class A or selected class B preoperative liver function. The exclusion criteria were as follows: (1) incomplete baseline data; (2) without R0 resection; and (3) combined HCC and intrahepatic cholangiocarcinoma (ICC). A total of 808 BCLC stage 0/A HCC patients met the inclusion criteria and were included in this study. Of the 808 patients, 500 were included in the training group, and 308 were in the external validation group. The flow chart of the patient selection process for the training and external validation groups is presented in Figure 1.

Data Collected

We retrospectively collected the clinical and pathological data of all BCLC stage 0/A HCC patients included in this study. The variables collected included age, sex, HBV DNA load, HBsAg, alpha-fetoprotein (AFP) concentration, total

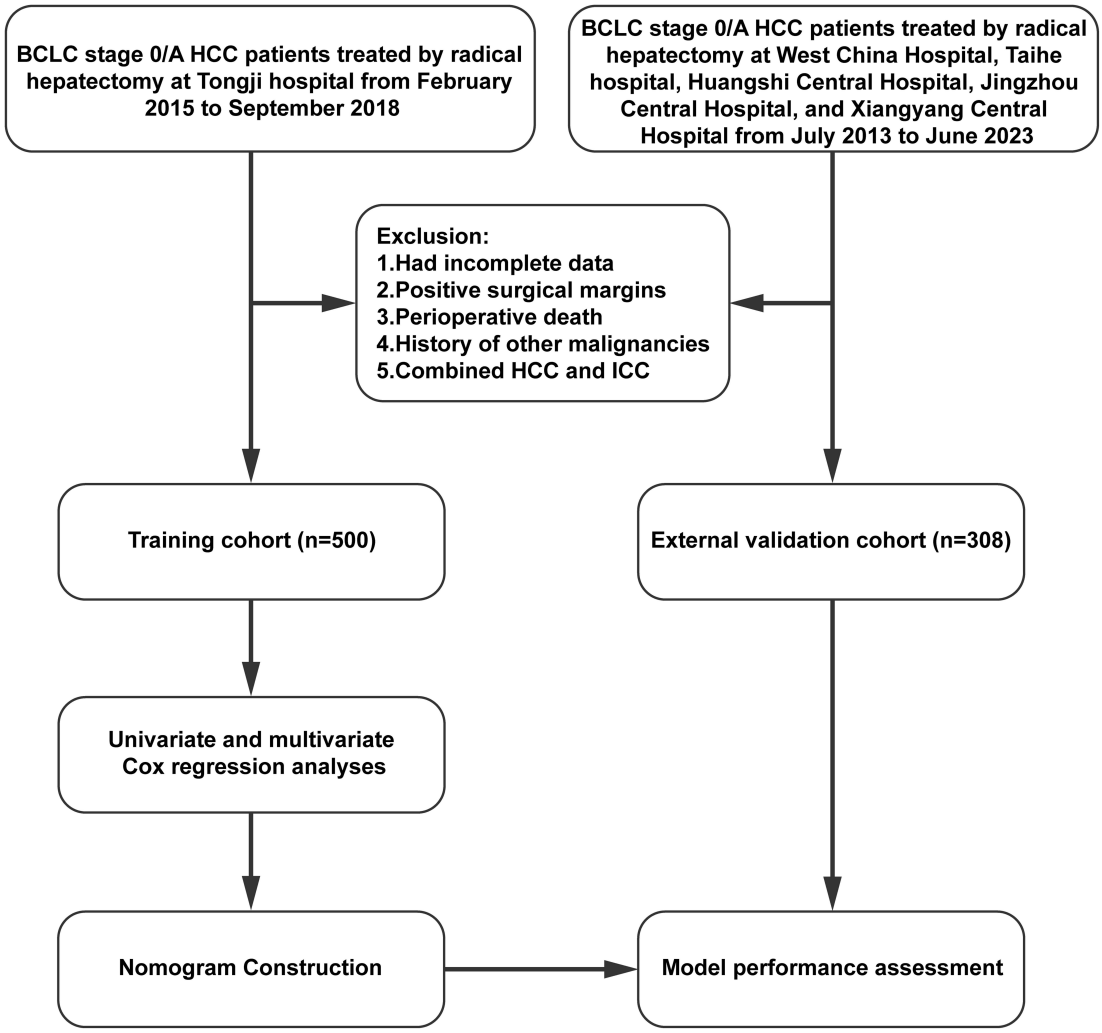

Figure 1 Flowchart showing the patient selection process, construction, and external validation of the nomogram.

bilirubin (TB), albumin (ALB), lymphocyte count, hemoglobin, platelet count, number of tumors, tumor size, surgical approach, resection method, estimated blood loss (EBL), operation time (OT), blood transfusion, cirrhosis, Edmondson-Steiner grade, microvascular invasion (MVI), and satellite nodules. All laboratory test results were obtained within one week leading up to the operation. In this study, clinically significant portal hypertension (CSPH) was defined as gastroesophageal varices detected by gastroscopy, or platelet count <10,000 cells/mL and splenomegaly (maximum diameter >12 cm based on CT scan).[18] The albumin-bilirubin (ALBI) score was calculated by 0.66 * Log10 [TBIL (μmol/L)] - 0.085 * [ALB (g/L)]. Patients with ALBI ≤ −2.60 were classified as ALBI grade 1, those with −2.60 < ALBI ≤ −1.39 were classified as ALBI grade 2, and those with ALBI > −1.39 were classified as ALBI grade 3.[19] We calculated the HALP score by hemoglobin(g/L) * albumin(g/L) * Lymphocyte(*10^9/L) / platelet(*10^9/L).[12] We used the R package survminer to calculate the optimal cut-off values.[20] The cut-off thresholds for HBV DNA and the HALP score were 10,000 IU/mL and 38.20, respectively.

Follow-Up

Follow-up visits were scheduled one month after discharge, every two months within the first year, and every three months thereafter. The follow-up included liver function tests, serum AFP levels, and abdominal ultrasound. Enhanced abdominal CT or enhanced abdominal MRI was performed every six months. Disease-free survival (DFS) was defined as

the time interval between surgery and detection of tumor recurrence. All tumor relapses were diagnosed through CT or MRI. Early recurrence was defined as recurrence within two years after LR.

Statistical Analysis

Continuous variables were represented by means and standard deviations, or medians and interquartile ranges (IQR). Categorical variables were reported as counts and percentages. Independent risk factors were identified using multivariate Cox regression analyses. The nomogram was constructed from the independent risk factors of recurrence identified by the Cox regression analysis. The area under the receiver operating characteristic (ROC) curve and the concordance index (C-index) were used to assess the discrimination performance of the model in predicting DFS. The calibration plot and decision curve analysis (DCA) were used to evaluate the calibration of the nomogram and the net benefit, respectively. We used the X-tile software (version 3.6.1; Yale University, New Haven, CT, USA) to group the patients by risk. Afterwards, the patients were divided into the low-, intermediate- and high-risk groups based on their risk scores. Then, DFS and OS curves were plotted using the Kaplan–Meier method and compared using the Log rank test.

Univariate and multivariate Cox regression analyses were performed using SPSS 26.0 (IBM Corp., Armonk, New York, USA). The nomogram, ROC curves, C-index, calibration curve, DCA, and survival figures were prepared or performed using R software version 4.2.1 (R Project for Statistical Computing, Vienna, Austria). Bilateral $P < 0.05$ was considered to be statistically significant.

Results

Baseline Characteristics

A total of 808 BCLC stage 0/A HCC patients who received radical LR were included in this study according to the inclusion and exclusion criteria. Of these, 500 patients were in the training cohort, and 308 were in the external validation cohort. All patients in this study had R0 liver resection, and most had well-preserved liver function (Child-Pugh class A). Based on the follow-up data and diagnostic criteria, 171 (34.2%) patients in the training cohort and 92 (29.9%) patients in the external validation cohort experienced early recurrence. Male patients were predominant in both cohorts (85.6% and 86.7% respectively). The average ages were 53.23 and 54.09 in the training and external validation cohorts, respectively. Microvascular invasion was detected in 109 (21.8%) patients in the training cohort and 67 (21.8%) patients in the external validation cohort. The demographic, clinical, pathological, and imaging characteristics of the BCLC stage 0/A HCC patients in the training and external validation cohorts are shown in Table 1.

Risk Factors Selection

Univariate Cox regression analysis showed that gender, age, number of tumors, surgical approach, resection method, EBL, operation time, blood transfusion, and cirrhosis had no significant relationship with recurrence in patients with BCLC stage 0/A HCC ($P > 0.05$ for all variables, Table 2). However, HBV DNA load ≥10,000 IU/mL ($P < 0.001$), positive HBsAg ($P = 0.009$), AFP level ≥400 ng/mL ($P < 0.001$), ALBI grade 2 ($P = 0.002$), HALP score ≤38.20 ($P < 0.001$), tumor size ($P < 0.001$), BCLC stage A ($P = 0.001$), CSPH ($P = 0.002$), Edmondson-Steiner grade (III–IV) ($P < 0.001$), satellite nodules ($P < 0.001$) and MVI ($P < 0.001$) were associated with relapse of HCC.

Multivariate Cox regression analysis showed that HBV DNA load ≥10,000 IU/mL [hazard ratio (HR) = 1.820; 95% confidence interval (CI), 1.357–2.440; $P < 0.001$], HALP score ≤38.20 (HR = 1.963; 95% CI, 1.414–2.726; $P < 0.001$), tumor size (HR = 1.080; 95% CI, 1.026–1.138; $P = 0.003$), CSPH (HR = 1.793; 95% CI, 1.274–2.524; $P = 0.001$), Edmondson-Steiner grade (III–IV) (HR = 1.457; 95% CI, 1.110–1.914; $P = 0.007$), satellite nodules (HR = 1.935; 95% CI, 1.349–2.777; $P < 0.001$) and MVI (HR = 1.642; 95% CI, 1.209–2.229; $P = 0.001$) were independent risk factors for post-operative recurrence of BCLC stage 0/A HCC patients (Table 2).

Development and Validation of a Novel Nomogram for Predicting the DFS

Based on the independent risk factors from the multivariate analysis, we constructed a nomogram for predicting the 2-year and 5-year DFS of BCLC stage 0/A HCC patients (Figure 2A). Higher total scores calculated using the nomogram

Table 1 Baseline Characteristics of BCLC Stage 0/A HCC Patients Who Underwent Hepatectomy in the Training and External Validation Cohorts

Variables		Training Cohort (n=500)	External Validation Cohort (n=308)
Gender			
	Male	428 (85.6%)	267 (86.7%)
	Female	72 (14.4%)	41 (13.3%)
Age (years)			
	<60	344 (68.8%)	201 (65.3%)
	≥60	156 (31.2%)	107 (34.7%)
HBV DNA (IU/mL)			
	<10,000	356 (71.2%)	216 (70.1%)
	≥10,000	144 (28.8%)	92 (29.9%)
HBsAg			
	Negative	87 (17.4%)	51 (16.6%)
	Positive	413 (82.6%)	257 (83.4%)
AFP (ng/mL)			
	<400	353 (70.6%)	214 (69.5%)
	≥400	147 (29.4%)	94 (30.5%)
TBIL (μmol/L)		12.80 (9.60–16.50)	14.15 (10.60–17.80)
ALB (g/L)		40.90 (38.30–43.78)	42.85 (40.20–44.98)
Lymphocyte (×10^9/L)		1.55 (1.22–1.88)	1.44 (1.15–1.86)
Hemoglobin (g/L)		143.00 (133.00–153.00)	144.00 (132.25–153.00)
Platelet (×10^9/L)		153.50 (119.00–197.00)	134.00 (102.25–179.00)
ALBI grade			
	1	349 (69.8%)	248 (80.5%)
	2	151 (30.2%)	60 (19.5%)
	3	0 (0%)	0 (0%)
HALP score			
	>38.20	413 (82.6%)	262 (85.1%)
	≤38.20	87 (17.4%)	46 (14.9%)
Tumor size (cm)		3.80 (2.50–5.60)	4.10 (2.80–6.70)
Number of tumors			
	Solitary	480 (96.0%)	298 (96.8%)
	Multiple	20 (4.0%)	10 (3.2%)
BCLC stage			
	0	62 (12.4%)	27 (8.8%)
	A	438 (87.6%)	281 (91.2%)
CSPH			
	Negative	428 (85.6%)	250 (81.2%)
	Positive	72 (14.4%)	58 (18.8%)
Surgical approach			
	OLR	222 (44.4%)	189 (61.4%)
	MILR	278 (55.6%)	119 (38.6%)
Resection method			
	NAR	335 (67.0%)	186 (60.4%)
	AR	165 (33.0%)	122 (39.6%)
EBL (mL)			
	<200	205 (41.0%)	113 (36.7%)
	≥200	295 (59.0%)	195 (63.3%)
OT (min)			
	<180	204 (40.8%)	111 (36.0%)
	≥180	296 (59.2%)	197 (64.0%)

(*Continued*)

Table 1 (Continued).

Variables		Training Cohort (n=500)	External Validation Cohort (n=308)
Blood transfusion			
	No	459 (91.8%)	290 (94.2%)
	Yes	41 (8.2%)	18 (5.8%)
Cirrhosis			
	No	113 (22.6%)	132 (42.9%)
	Yes	387 (77.4%)	176 (57.1%)
E-S grade			
	I–II	282 (56.4%)	184 (59.7%)
	III–IV	218 (43.6%)	124 (40.3%)
Satellite nodules			
	Negative	449 (89.8%)	281 (91.2%)
	Positive	51 (10.2%)	27 (8.8%)
MVI			
	Negative	391 (78.2%)	241 (78.2%)
	Positive	109 (21.8%)	67 (21.8%)

Abbreviations: HBV DNA, hepatitis B virus DNA; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; TBIL, total bilirubin; ALB, albumin; ALBI, albumin-bilirubin grade; HALP, hemoglobin, albumin, lymphocyte, and platelet score; BCLC, Barcelona Clinic of Liver Cancer; CSPH, clinically significant portal hypertension; OLR, open liver resection; MILR, minimally invasive liver resection; NAR, non-anatomical anatomical resection; AR, anatomical resection; EBL, estimated blood loss; OT, operation time; E-S, Edmondson-Steiner grade; MVI, microvascular invasion.

Table 2 Univariate and Multivariate Cox Regression Analysis of Independent Risk Factors Associated with Disease-Free Survival (DFS) in the Training Cohort

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	Reference			
Female	0.689 (0.461–1.029)	0.069		
Age (years)				
<60	Reference			
≥60	1.125 (0.857–1.476)	0.397		
HBV DNA (IU/mL)				
<10,000	Reference		Reference	
≥10,000	1.857 (1.425–2.420)	< 0.001	1.820 (1.357–2.440)	< 0.001
HBsAg				
Negative	Reference		Reference	
Positive	1.655 (1.134–2.415)	0.009	1.492 (0.997–2.231)	0.051
AFP (ng/mL)				
<400	Reference		Reference	
≥400	1.691 (1.292–2.213)	< 0.001	1.296 (0.969–1.734)	0.080
ALBI grade				
1	Reference		Reference	
2	1.529 (1.171–1.997)	0.002	1.087 (0.817–1.446)	0.565
HALP score				
>38.20	Reference		Reference	
≤38.20	2.151 (1.594–2.903)	< 0.001	1.963 (1.414–2.726)	< 0.001

(*Continued*)

Table 2 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tumor size (cm)	1.139 (1.092–1.188)	< 0.001	1.080 (1.026–1.138)	0.003
Number of tumors				
Solitary	Reference			
Multiple	1.695 (0.987–2.909)	0.056		
BCLC stage				
0	Reference		Reference	
A	2.375 (1.429–3.947)	0.001	1.407 (0.818–2.417)	0.217
CSPH				
Negative	Reference		Reference	
Positive	1.677 (1.215–2.316)	0.002	1.793 (1.274–2.524)	0.001
Surgical approach				
OLR	Reference			
MILR	1.052 (0.812–1.363)	0.701		
Resection method				
NAR	Reference			
AR	0.960 (0.729–1.265)	0.774		
EBL (mL)				
<200	Reference			
≥200	1.203 (0.924–1.568)	0.170		
OT (min)				
<180	Reference			
≥180	1.202 (0.923–1.565)	0.173		
Blood transfusion				
No	Reference			
Yes	1.013 (0.634–1.620)	0.956		
Cirrhosis				
No	Reference			
Yes	1.372 (0.983–1.916)	0.063		
E-S grade				
I–II	Reference		Reference	
III–IV	1.623 (1.255–2.097)	< 0.001	1.457 (1.110–1.914)	0.007
Satellite nodules				
Negative	Reference		Reference	
Positive	2.458 (1.741–3.470)	< 0.001	1.935 (1.349–2.777)	< 0.001
MVI				
Negative	Reference		Reference	
Positive	2.272 (1.716–3.006)	< 0.001	1.642 (1.209–2.229)	0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; HBV DNA, hepatitis B virus DNA; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; TBIL, total bilirubin; ALB, albumin; ALBI, albumin-bilirubin grade; HALP, hemoglobin, albumin, lymphocyte and platelet score; BCLC, Barcelona Clinic of Liver Cancer; CSPH, clinically significant portal hypertension; OLR, open liver resection; MILR, minimally invasive liver resection; NAR, non-anatomical anatomical resection; AR, anatomical resection; EBL, estimated blood loss; OT, operation time; E-S, Edmondson-Steiner grade; MVI, microvascular invasion.

were associated with poorer prognoses. The area under the ROC curve (AUC) values for our nomogram for predicting the 2- and 5-year DFS were 0.756 and 0.750 in the training cohort and 0.764 and 0.705 in the external validation cohort, respectively (Figure 2B and C). The C-index of discrimination for predicting the training cohort's 2- and 5-year DFS rates was 0.708 (95% CI: 0.677–0.740). For the external validation cohort, the C-index was 0.705 (95% CI: 0.657–0.752). The calibration curve showed that the predicted 2- and 5-year recurrence probabilities were similar to the actual

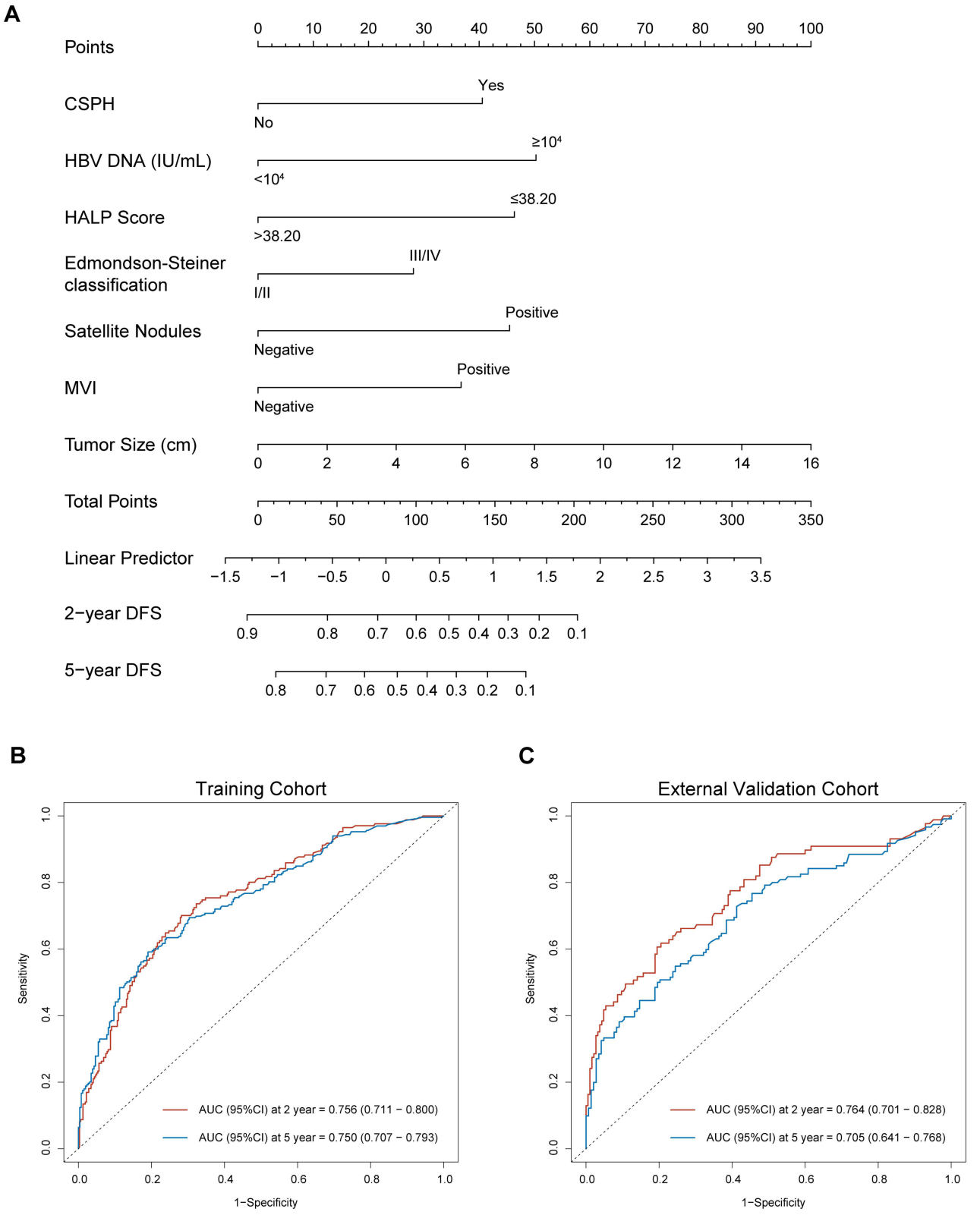

Figure 2 (**A**) The nomogram model for predicting 2-year and 5-year DFS. (**B**) The 2-year and 5-year receiver operating characteristic (ROC) curve of DFS in the training cohort. (**C**) The 2-year and 5-year ROC curves of DFS in the external validation cohort.

probabilities in the training and external validation datasets (Figure 3A–D). The DCA for the nomogram showed high net benefits in the reasonable threshold probabilities in the training and external validation datasets (Figure 4A–D).

Furthermore, according to the total risk scores calculated from the nomogram prediction model, we used the X-tile software to divide the training and external validation cohorts into low-, intermediate- and high-risk groups. As shown in Figure 5A–D, patients in the low-risk groups had the best DFS and OS, while those in the high-risk groups had the worst DFS and OS. This indicated that our nomogram had excellent stratification ability.

Discussion

Radical liver resection significantly improves the survival of HCC patients. However, high postoperative recurrence rates (reaching 50%-70%) remain a major limiting factor for long-term survival in HCC patients.[4,21] Therefore, implementing adjuvant therapy for individuals at high risk of postoperative recurrence has become crucial in enhancing the long-term

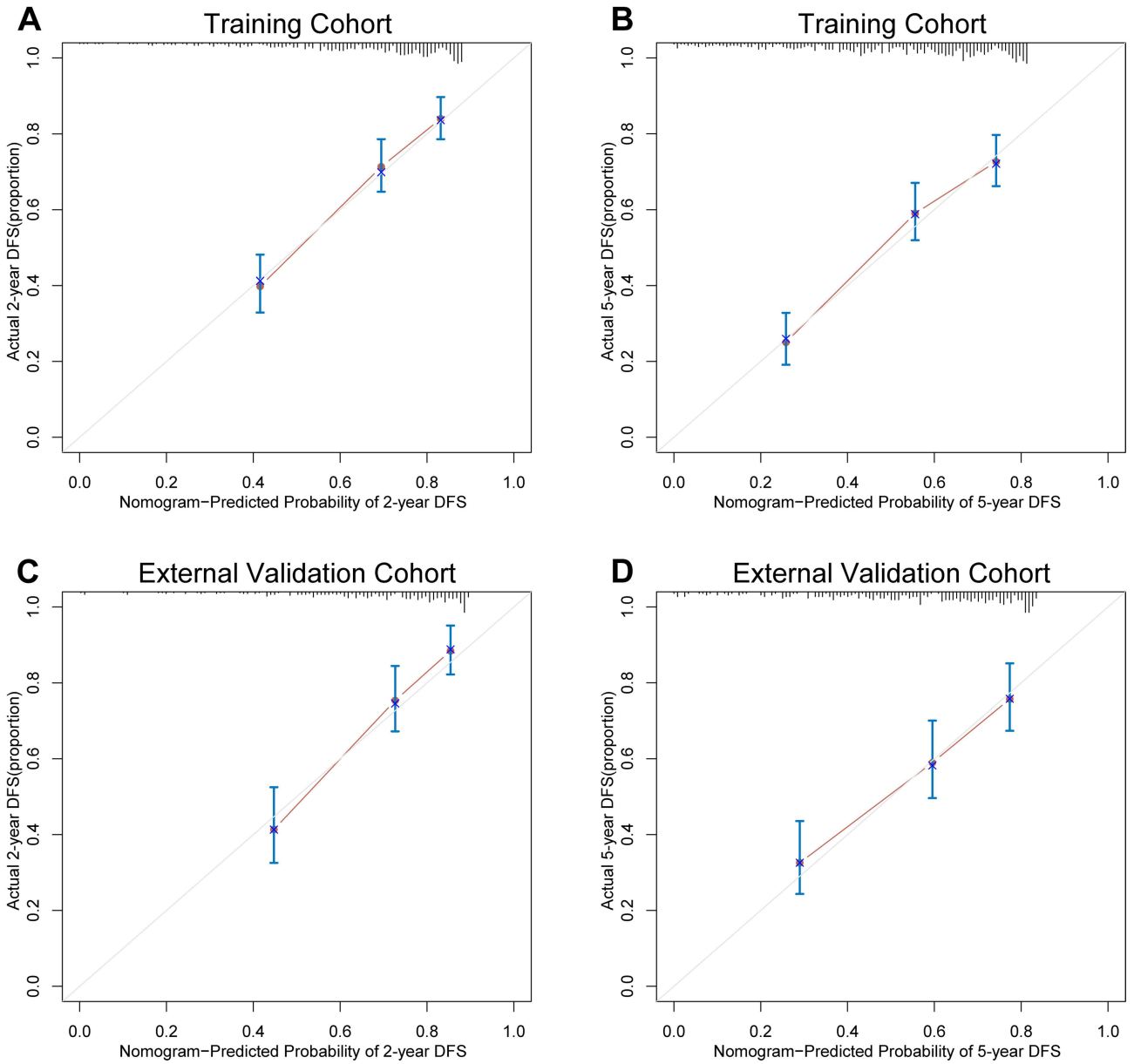

Figure 3 Calibration curve for predicting the 2-year DFS (**A**) and the 5-year DFS (**B**) in the training cohort and the 2-year DFS (**C**) and the 5-year DFS (**D**) in the external validation cohort.

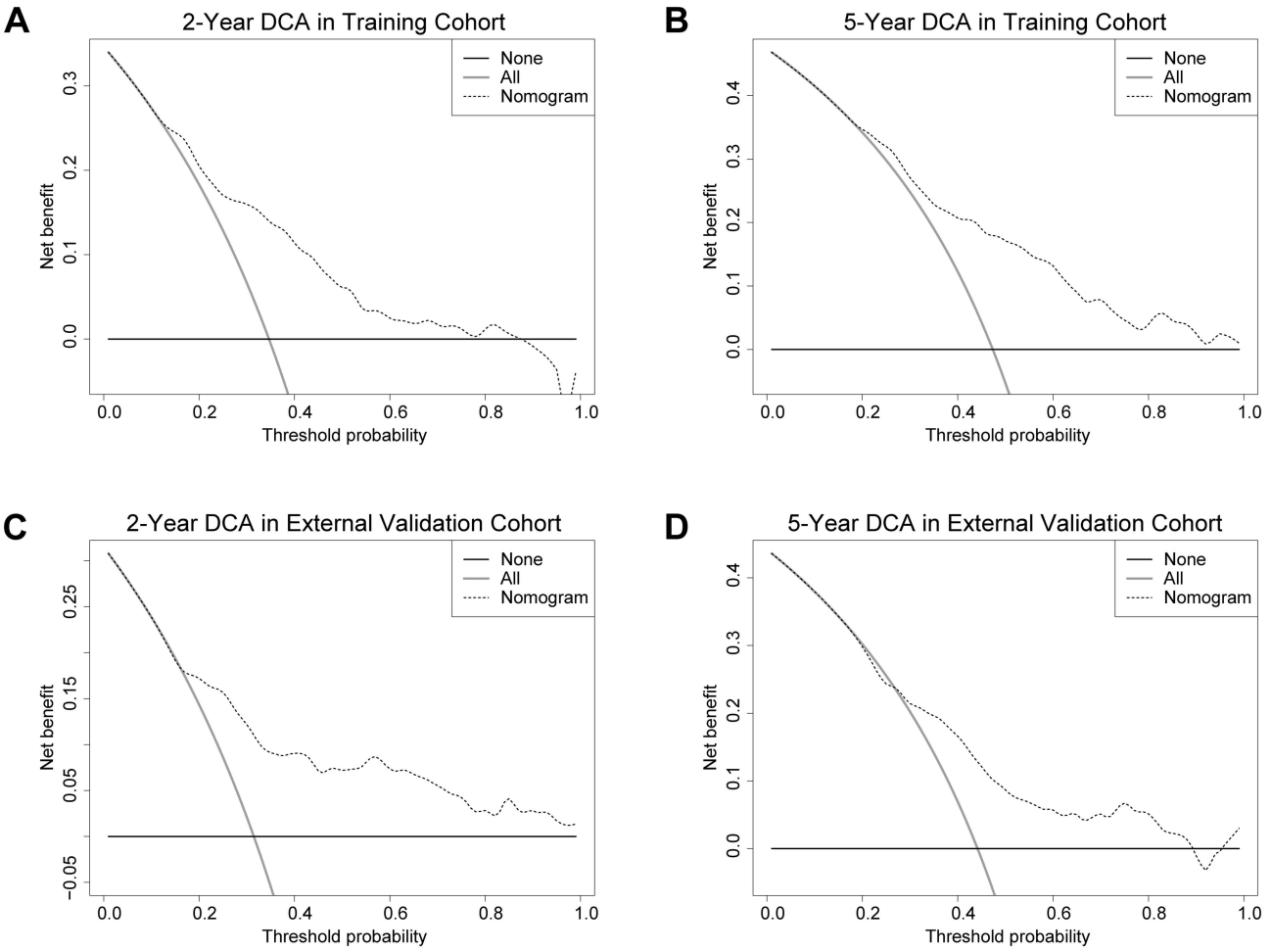

Figure 4 DCA plots for the nomogram in predicting the 2-year DFS (**A**) and the 5-year DFS (**B**) in the training cohort and the 2-year DFS (**C**) and the 5-year DFS (**D**) in the external validation cohort.

survival of these patients.[22] The first Phase 3 study reporting positive Results for adjuvant treatment of HCC demonstrated improved recurrence-free survival in patients receiving atezolizumab plus bevacizumab compared to active surveillance in those at high risk of recurrence after liver resection or ablation.[23] Additionally, preliminary results from an ongoing study at our center on adjuvant therapy after radical liver resection indicate that the 2-year disease-free survival rates for the adjuvant anti-PD-1 and adjuvant TACE groups are 60.3% and 42.6%, respectively. These results suggest that postoperative adjuvant therapy can delay recurrence and extend overall survival for a considerable number of patients. Therefore, it is essential to identify the patients with high recurrence risk in advance to enable the implementation of effective preventive measures.

Patients with BCLC stage 0/A HCC are the primary candidates for liver resection.[24] However, due to the varying criteria for patient selection, existing prognostic models often encompass a wide range of tumor stages, including advanced stages such as BCLC stage C and TNM stage IV, which has made it challenging to use a single model to accurately evaluate the prognosis of patients with early-stage HCC.[9,11,25] Therefore, developing a specialized model to predict the prognosis of BCLC stage 0/A HCC patients is of great significance.

Currently, the commonly used staging systems like BCLC stage and Tumor-Node-Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) primarily consider factors such as tumor size, number, and MVI.[24,26] Because the postoperative recurrence of HCC is influenced by numerous factors, including nutritional and immune status, portal hypertension, HBV DNA load, Edmondson-Steiner grade, satellite nodules, etc;[18,27–30] the ability to perform individualized assessments of patients using the common staging systems is limited.

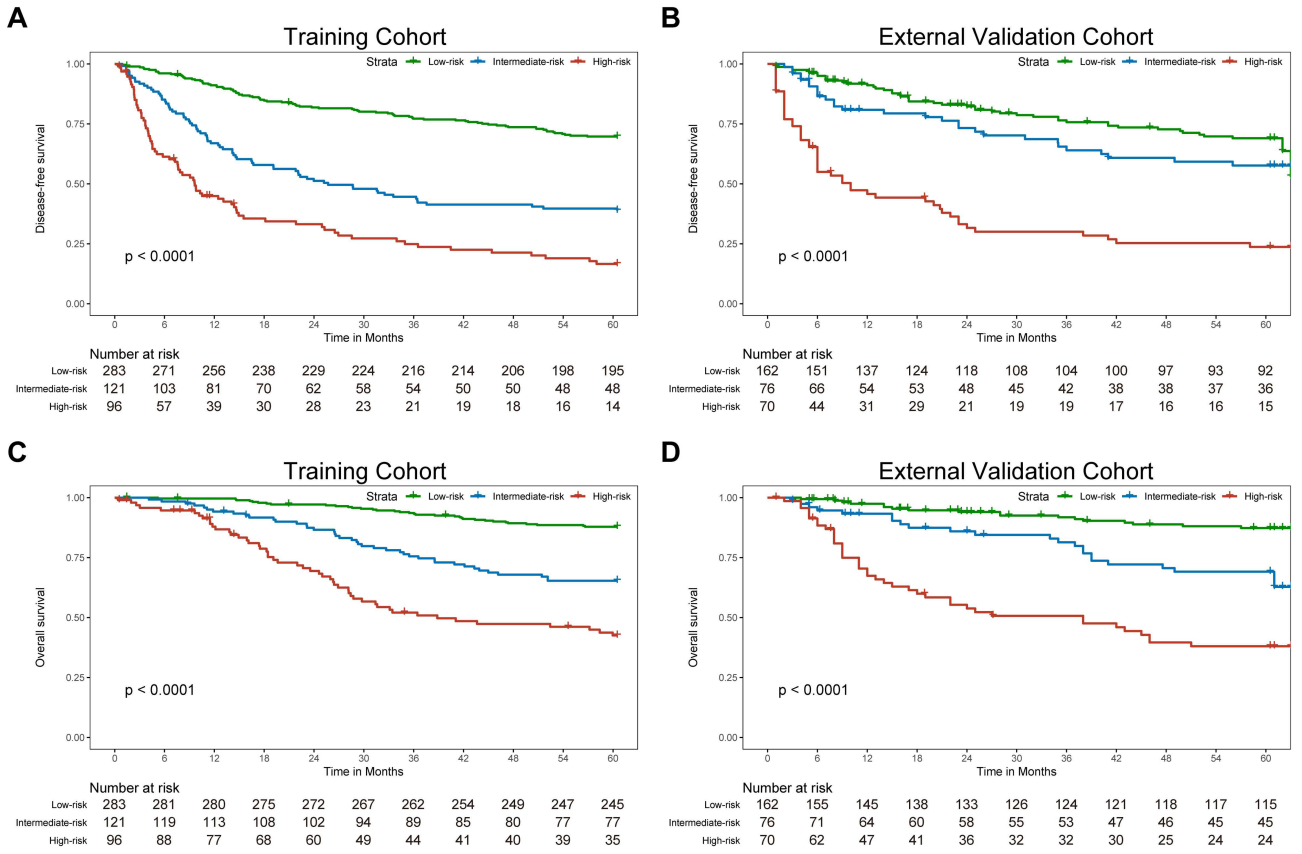

Figure 5 The Kaplan-Meier survival curves for low-, intermediate- and high-risk groups of BCLC stage 0/A HCC patients after radical liver resection based on our nomogram calculated risk scores. The disease-free survival Kaplan-Meier survival curves in the training cohort (**A**) and the external validation cohort (**B**). The overall survival Kaplan-Meier survival curves in the training cohort (**C**) and the external validation cohort (**D**).

Previous prognostic models mainly focused on tumor-related variables and did not consider other conditions, such as the nutritional and immune status of the patients or liver cirrhosis. The HALP score is a new comprehensive marker of the nutritional and immune status that is an important risk biomarker for a variety of digestive system cancers, including gastric cancer,[12,31] esophageal squamous cell carcinoma (ESCC),[32,33] colorectal cancer,[34,35] and intrahepatic cholangiocarcinoma.[36,37] However, since the HALP score was only developed in 2015, original studies exploring the utility of this novel index in HCC are still lacking.[12,16] Recently, Zhou et al[17] and Toshida et al[30] reported that a low HALP score (<54.132; ≤45.6) is an independent predictor of poor OS in HCC patients (HR = 1.708; HR = 1.66). In this study, multivariate COX regression analysis also showed that a low HALP score (≤38.20) is an independent risk factor for recurrence in BCLC stage 0/A HCC patients after surgery (HR = 1.85). Here, we developed and externally validated a novel nomogram that includes the HALP score that effectively predicted ER in postoperative BCLC stage 0/A HCC patients.

Although a low HALP score is an unfavorable prognostic factor for HCC, the specific mechanism by which it affects the prognosis of HCC remains unclear. We have tried to explain this phenomenon by analyzing the four components of the HALP score. Clinical studies suggest that low hemoglobin levels are associated with poor survival in HCC patients.[38] This is likely due to tumor hypoxia caused by anemia, which might increase the invasiveness of cancer. For example, hypoxia-inducible factor (HIF) can activate vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which play a key role in tumor angiogenesis.[39] Albumin usually reflects the body's nutritional status and inflammation level.[17] Studies have shown that the reduction of albumin promotes the migration and invasion of HCC cells by increasing urokinase plasminogen activator surface receptor (uPAR) and matrix metalloproteinase 2 (MMP2) and 9 (MMP9).[40] Lymphocytes have powerful anti-tumor immune functions and can inhibit tumor development. Elevated lymphocyte levels are associated with a good tumor prognosis.[41] In addition, clinical studies have found that

inflammatory markers composed of lymphocytes can predict the prognosis of patients with HCC.[42–44] Cancer cell-platelet interactions are an important component of cancer metastasis.[45] Midorikawa et al[46] believed that high platelet counts are associated with poor prognoses in patients with hepatocellular carcinoma without cirrhosis. From the roles of the individual components of the score described above, it makes logical sense that lower HALP scores should be associated with worse oncological outcomes, which is consistent with the current literature.

Cirrhosis plays a crucial role in the occurrence of HCC, with approximately 70–90% of HCC patients having cirrhosis.[47] CSPH is an important prognostic indicator in patients with cirrhosis, and it results from increased intrahepatic vascular resistance caused by the dysregulation of liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs).[48,49] There is still controversy over whether preoperative CSPH affects the surgical outcomes of HCC patients with compensated liver cirrhosis.[50] Cortese et al[51] analyzed HCC patients with Child-Pugh class A liver function who underwent liver resection and found no significant difference in OS and DFS between the CSPH and non-CSPH groups. Lopez et al[52] also reported no statistically significant difference in the perioperative and long-term prognosis between the CSPH and non-CSPH groups. However, Xia et al[18] found that in patients with BCLC stage A HCC, the CSPH group had worse OS and recurrence-free survival (RFS) than the non-CSPH group (HR = 2.340; HR = 2.577). A systematic review and meta-analysis found that CSPH negatively impacted the long-term prognosis of HCC patients after partial hepatectomy.[53] Another systematic review and meta-analysis evaluated the impact of CSPH on the prognosis of HCC patients with compensated liver cirrhosis who underwent surgical treatment and found that CSPH significantly increased the 3- and 5-year postoperative mortality.[50] Qin et al[54] investigated the predictive ability of ALBI grade plus CSPH (ALBI-P score) in patients with HCC after LR. Multivariate analysis showed that the ALBI-P score was an independent risk factor for postoperative recurrence (HR = 1.441) and death (HR = 1.332). These studies highlight the potential value of CSPH in predicting the postoperative recurrence of HCC. In this study, there were 72 cases (14.4%) with preoperative CSPH in the training group and 58 cases (18.8%) with preoperative CSPH in the external validation group. Multivariate Cox regression analysis showed that CSPH (HR = 1.793) is an independent risk factor for relapse after LR in patients with BCLC stage 0/A HCC.

Consistent with previous reports,[22,27–29] the results of multivariate Cox regression analysis in this study showed that HBV DNA load ≥10,000 IU/mL, tumor size, Edmondson-Steiner grade (III–IV), satellite nodules, and MVI were independent risk factors for postoperative recurrence in patients with BCLC stage 0/A HCC. HBV DNA load reflects the level of viral replication, which is a key driver of liver injury and HCC development, and higher levels negatively impact the prognosis.[55] MVI refers to the presence of micrometastatic HCC emboli within hepatic vessels, detectable only under a microscope, and is a critical factor for early HCC recurrence and poor prognosis.[56] Edmondson-Steiner grade is a globally recognized and long-established histological classification standard for HCC. Generally, the poorer the differentiation, the stronger the tumor's proliferation ability and angiogenic activity.[57] Satellite nodules are macroscopic or microscopic tumor cell nests located around or near the main tumor, sharing similar histological characteristics with the primary tumor. They are significant predictors of postoperative recurrence.[58] The impact of tumor size on prognosis is primarily due to the increased invasiveness of larger tumors. Studies have shown that when the tumor diameter exceeds 5 cm, the incidence of intrahepatic metastasis and portal vein invasion significantly increases.[59]

In this study, we established a nomogram model that included the HALP score and evaluated its ability to predict early recurrence in patients with early-stage HCC after undergoing radical liver resection. The model underwent multi-center external validation. The probability of early recurrence can be estimated for each patient based on the risk score calculated using our nomogram. The model demonstrated excellent discrimination in both the training and external validation cohorts, with 2-year AUCs of 0.756 and 0.764, respectively. Kaplan-Meier survival curves indicated that this model could effectively identify patients at high risk of recurrence, and it also had good applicability in the external cohort of this study. Currently, the efficacies of transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), radiotherapy, and molecular targeted therapy in the adjuvant treatment of HCC are being studied.[60] Therefore, our nomogram can help to identify patients at high risk of recurrence after radical liver resection and enable these patients to benefit from adjuvant therapy.

Our study has several limitations. Firstly, this is a retrospective study; therefore, the conclusions require further validation. Secondly, the nomogram was derived from BCLC stage 0/A HCC patients who underwent liver resection and

may not be applicable to HCC patients with other BCLC stages or those who received other treatments. Finally, the mechanism by which the HALP score predicts the prognosis of HCC patients needs to be further studied.

Conclusion

In Conclusion, we developed and externally validated a novel nomogram based on the HALP score that can predict the DFS after hepatectomy in BCLC stage 0/A HCC patients. This model exhibited a good predictive ability and can assist doctors in making personalized treatment decisions for BCLC stage 0/A HCC patients.

Abbreviations

ER, early recurrence; HCC, hepatocellular carcinoma; HALP, hemoglobin, albumin, lymphocyte and platelet score; BCLC, Barcelona Clinic of Liver Cancer; DFS, disease-free survival; ROC, receiver operating characteristic; C-index, concordance index; DCA, decision curve analysis; HBV DNA, hepatitis B virus DNA; MVI, microvascular invasion; AUC, area under the receiver operating characteristic curve; OS, overall survival; LR, liver resection; ICC, intrahepatic cholangiocarcinoma; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; TBIL, total bilirubin; ALB, albumin; EBL, estimated blood loss; OT, operation time; E-S, Edmondson-Steiner grade; CSPH, clinically significant portal hypertension; ALBI, albumin-bilirubin grade; CT, computed tomography; MRI, magnetic resonance imaging; IQR, interquartile ranges; HR, hazard ratio; CI, confidence interval; OLR, open liver resection; MILR, minimally invasive liver resection; NAR, non-anatomical anatomical resection; AR, anatomical resection.

Data Sharing Statement

The datasets used and analyzed in this study can be obtained from the corresponding author upon reasonable request.

Ethics Statement

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki.

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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 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 report no conflicts of interest in this work.

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