Am J Cancer Res 2026;16(5):1966-1976
www.ajcr.us /ISSN:2156-6976/ajcr0171260

Original Article

Preoperative nomogram for predicting microvascular invasion and stratifying recurrence risk in early-stage hepatocellular carcinoma

Zhi-Cheng Guo[1*], Lian Li[1,4*], Zhang-Neng Yu[1], Kun-Peng Wang[1], Dong Li[1], Jin-Ting Jiang[5], Fan He[1], Li-Tian Zhang[1], Jia-Wu Yan[1], Liang-Liang Xu[1], Hua Zhang[2,3], Ming Zhang[1]

[1]Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China; [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children of MOE, West China Second University Hospital, Sichuan University, Chengdu 610041, Sichuan, China; [3]Key Laboratory of Chronobiology (Sichuan University), National Health Commission of China, Chengdu 610041, Sichuan, China; [4]Department of Cardiovascular Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China; [5]West China School of Medicine, Sichuan University, Chengdu 610041, Sichuan, China. [*]Equal contributors.

Received January 5, 2026; Accepted May 6, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: Microvascular invasion (MVI) is a key determinant of early recurrence and poor prognosis in hepatocellular carcinoma (HCC). However, it can only be diagnosed pathologically after surgery, making reliable preoperative prediction challenging. We aimed to establish and validate a practical preoperative model to predict MVI and risk of recurrence in patients with early-stage HCC. A total of 1,196 patients with BCLC 0-A stage HCC who underwent curative liver resection were retrospectively analyzed. Preoperative clinical and radiological variables were evaluated to identify independent predictors of MVI using multivariate logistic regression. A nomogram was constructed and internally validated to estimate the individual probability of MVI, and disease-free survival (DFS) was compared between the risk groups derived from the nomogram. MVI was pathologically confirmed in 327 of the 1,196 patients (27.3%). In the training and validation cohorts, the nomogram incorporating alpha-fetoprotein (AFP), tumor size, neutrophil-to-lymphocyte ratio (NLR), prothrombin time (PT) and age achieved concordance indexes of 0.72 (95% CI, 0.68-0.75) and 0.73 (95% CI, 0.67-0.79), respectively, with good calibration performance. Patients stratified into the high-risk group based on the nomogram-derived score exhibited significantly shorter DFS than those in the low-risk group ($P < 0.001$), thereby substantiating the model's prognostic utility. Overall, the proposed nomogram model exhibited satisfactory performance in predicting MVI Preoperatively and stratifying recurrence risk in patients with early-stage HCC, thus facilitating individualized risk assessment and treatment planning.

Keywords: Hepatocellular carcinoma, microvascular invasion, nomogram, recurrence risk

Introduction

Liver cancer is the third leading cause of cancer-related mortality worldwide [1]. Hepatocellular carcinoma (HCC) accounts for approximately 90% of all liver cancers and is a critical global health burden [2]. In clinical practice, the Barcelona Clinic Liver Cancer (BCLC) staging system is widely used for treatment strategy decisions and prognostic assessment of HCC patients. For patients with stage 0-A BCLC, hepatic resection remains the cornerstone of curative therapy and is generally associated with favorable long-term outcomes [3]. However, the presence of microvascular invasion (MVI) has been identified as one of the most significant pathological factors of early recurrence and poor survival in HCC. MVI has been demonstrated to considerably increase the probability of post-operative recurrence, thereby jeopardizing survival outcomes, even in cases where complete macroscopic tumor removal has been achieved [4, 5].

MVI has been shown to have a significant impact on the post-operative prognosis of HCC

https://doi.org/10.62347/VPSW2871

patients with BCLC stage 0-A. Preoperative assessment of MVI potentially holds substantial practical value for planning the extent of liver resection and perioperative treatment strategies. For instance, evidence indicates that anatomical resection confers superior disease-free survival (DFS) compared with non-anatomical resection in patients with MVI [6, 7]. Of particular significance is the ability to identify patients at high risk of MVI prior to surgery. This facilitates the selection of candidates for neoadjuvant therapies aimed at mitigating MVI and reducing the risk of early postoperative recurrence [8]. Nevertheless, the gold standard for MVI diagnosis is pathological examination of resected specimens, which cannot be performed preoperatively [9]. Consequently, this standard cannot be applied to the preoperative and intraoperative decision-making processes. Therefore, the development of precise pre-operative instruments for evaluating the risk of MVI is clinically valuable. This facilitates the implementation of individualized preoperative treatments and surgical strategies, thereby ensuring optimal oncological outcomes [10].

The present study specifically focused on patients with BCLC stage 0-A HCC who underwent curative resection. We developed and validated a preoperative nomogram model to predict the probability of MVI in early-stage patients using routinely available clinical and radiological variables. The patients were stratified into high- and low-risk groups based on their nomogram-derived risk scores. This study was performed to further examine their associations with postoperative recurrence. We believe that this preoperative model will provide significant supplementary information for individualized prognostic assessment and formulation of preoperative treatment strategies. Additionally, the model simultaneously guided the extent of intraoperative resection and margin selection based on the predicted risk of MVI.

Patients and methods

Ethics statement

This retrospective study was conducted in accordance with the Declaration of Helsinki and associated ethical standards. Ethical approval was obtained from the Ethics Committee of the West China Hospital, Sichuan University (Approval No. 20251994). The requirement for written informed consent was waived due to the retrospective nature of the study. All data were de-identified prior to analysis. The study was registered with the Chinese Clinical Trial Registry (ChiCTR2500114739).

Patients

A total of 1,196 HCC patients who underwent curative liver resection at the West China Hospital, Sichuan University, between January 2012 and December 2020 were retrospectively analyzed. Patients were randomly assigned into a training cohort (n = 835) and a validation cohort (n = 361) in a 7:3 ratio using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria). The training cohort was used for nomogram construction and internal validation, whereas the validation cohort was used for external validation.

The inclusion criteria were as follows: (1) pathologically confirmed HCC classified as BCLC stage 0-A [3]; (2) curative (R0) liver resection; and (3) availability of complete clinicopathological and follow-up data. Patients were excluded if they had a history of other primary malignancies, received any preoperative anticancer treatments such as transcatheter arterial chemoembolization (TACE) or radiofrequency ablation (RFA), or had severe liver diseases other than hepatitis B or C infection.

Data collection and follow-up

The clinical data of HCC patients were collected as follows: (1) demographic characteristics, including age and sex; (2) tumor-related factors, including maximum tumor diameter, tumor number, and vascular invasion, which were assessed by preoperative contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), and further confirmed pathologically for capsule invasion, satellite nodules, and tumor differentiation; (3) tumor staging, classified according to the BCLC classification; (4) laboratory tests, including routine blood tests, liver and renal function tests, hepatitis B and C immunology, hepatitis B virus (HBV) DNA load, and serum α-fetoprotein (AFP) levels. All laboratory data were obtained during the first examinations performed after hospital admission.

All surgical specimens were subjected to routine pathological examination, with particular attention to the presence of MVI. Briefly, MVI was defined as the presence of a tumor in the portal vein, hepatic vein, or a large capsular vessel of the surrounding hepatic tissue lined by endothelium that was visible only by microscopy [10].

After liver resection, patients were followed up every 3 months during the first 2 years using CT or MRI, and every 6 months thereafter. DFS was defined as the interval between the date of surgery and the first documented recurrence or death from any cause.

Statistical analysis

Continuous variables with normal distributions were expressed as means ± standard deviation and compared using Student's t-test. Continuous variables with non-normal distributions were expressed as medians with interquartile ranges and compared using the Mann-Whitney U test. Categorical variables were expressed as numbers (percentage) and compared using the χ^2 or Fisher's exact tests. Independent predictors of MVI were identified using univariate and multivariate logistic regression in the training cohort, and a nomogram was constructed based on multivariate analysis. Model discrimination and calibration were assessed using the concordance index (C-index) and the area under the receiver operating characteristic (ROC) curve. Calibration was evaluated using calibration plots with 1,000 bootstrap resamples and further assessed by the Hosmer-Lemeshow goodness-of-fit test. Internal validation was performed using bootstrap resampling with 1,000 repetitions. The optimal cutoff value was determined using the Youden index, and the corresponding sensitivity, specificity, predictive values, and likelihood ratios were calculated. Kaplan-Meier survival analysis with the log-rank test was used to compare DFS between subgroups stratified by pathological MVI status and risk groups defined using the cut-off value. Decision curve analysis was performed to evaluate the clinical utility of the model. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients baseline characteristics

During the study period, 1,605 patients underwent liver resection for HCC at West China Hospital. After applying the inclusion and exclusion criteria, 1,196 patients were enrolled in this study. These patients were randomly assigned into a training group (n = 835) or validation cohort (n = 361) (Figure S1).

The baseline clinicopathological characteristics of the patients are summarized in **Table 1**. The distribution of demographic features, liver function, tumor-related variables, and laboratory indices were comparable between the training and validation cohorts, with no statistically significant differences. Overall, the majority of patients were male (83.3%) and hepatitis B surface antigen-positive (87.3%). Most patients (95.1%) presented with a single tumor. Pathological MVI was detected in 327 patients (27.3%): 228 (27.3%) in the training cohort and 99 (27.4%) in the validation group.

Development and validation of an MVI-predictive nomogram

All variables employed in this analysis were derived from preoperative assessments. Tumor-related features, including maximum tumor diameter and number, were evaluated using preoperative CT or MRI results.

The results of the univariate logistic regression analysis are summarized in **Table 2**. Variables significantly associated with MVI in the univariate analysis included age, white blood cell count (WBC), prothrombin time (PT), AFP, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), tumor size, and BCLC stage.

For the multivariate logistic regression analysis (**Table 3**), outcomes are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). In this model, age < 60 years (0.62 [0.42-0.92]), prolonged prothrombin time (PT) ≥ 12.8 s (1.85 [1.24-2.75]), elevated serum AFP level ≥ 400 ng/mL (2.51 [1.80-3.51]), neutrophil-to-lymphocyte ratio (NLR) ≥ 3 (2.40 [1.60-3.62]), and tumor size ≥ 5 cm (2.26 [1.58-3.23]) were identified as independent predictors of MVI. In contrast, WBC, PLR, and

Table 1. Patient characteristics of HCC patients in the training and validation cohorts

Variables	Overall (n = 1,196)	Train (n = 835)	Validation (n = 361)	*P value*
Male, n (%)	996 (83.3)	691 (82.8)	305 (84.5)	0.461
Age (years)	50.18 (42.68-60.00)	50.20 (43.00-60.30)	50.00 (42.00-59.26)	0.579
HBsAg, n (%)				0.832
Positive	1,044 (87.3)	730 (87.4)	314 (87.0)	
Negative	152 (12.7)	105 (12.6)	47 (13.0)	
HCV, n (%)				0.720
Present	7 (0.6)	4 (0.5)	3 (0.8)	
Absent	1,189 (99.4)	831 (99.5)	358 (99.2)	
HBV-DNA (IU/mL), n (%)				0.345
< 2,000	598 (50.0)	410 (49.1)	188 (52.1)	
≥ 2,000	598 (50.0)	425 (50.9)	173 (47.9)	
AFP (ng/mL)				0.475
< 400	804 (67.2)	556 (66.6)	248 (68.7)	
≥ 400	392 (32.8)	279 (33.4)	113 (31.3)	
WBC (10^9/L)	5.19 (4.15-6.34)	5.19 (4.12-6.39)	5.16 (4.21-6.28)	0.963
NEU (10^9/L)	3.04 (2.37-3.97)	3.05 (2.37-3.98)	3.04 (2.32-3.95)	0.526
LYM (10^9/L)	1.45 (1.15-1.85)	1.44 (1.14-1.84)	1.49 (1.17-1.90)	0.267
PLT (10^9/L)	123.0 (87.0-168.5)	124.0 (86.0-170.0)	122.0 (87.0-167.0)	0.956
ALT (U/L)	38.0 (27.0-55.0)	38.0 (27.0-55.0)	38.0 (26.0-55.0)	0.472
AST (U/L)	36.0 (28.0-51.0)	37.0 (28.0-52.0)	35.0 (27.0-48.0)	0.079
TB (μmol/L)	13.8 (10.5-18.2)	13.8 (10.5-18.3)	13.8 (10.6-18.0)	0.803
ALB (g/L)	41.9 (39.2-44.6)	41.8 (39.1-44.5)	42.3 (39.2-44.7)	0.297
PT (s)	11.9 (11.2-12.6)	11.8 (11.2-12.6)	12.0 (11.3-12.8)	0.100
AAR	0.95 (0.77-1.23)	0.96 (0.77-1.23)	0.93 (0.76-1.19)	0.306
NLR	2.07 (1.57-2.74)	2.08 (1.61-2.76)	2.03 (1.50-2.70)	0.109
PLR	82.00 (59.66-111.51)	82.38 (60.18-113.00)	80.68 (59.44-108.96)	0.402
PNI	49.63 (46.13-53.15)	49.45 (45.95-52.70)	50.10 (46.70-53.70)	0.056
APRI	0.78 (0.51-1.23)	0.80 (0.52-1.25)	0.73 (0.47-1.20)	0.073
FIB4	2.53 (1.67-4.10)	2.54 (1.68-4.18)	2.48 (1.63-3.76)	0.269
ALBI				0.560
1	882 (73.7)	612 (73.3)	270 (74.8)	
2	312 (26.1)	222 (26.6)	90 (24.9)	
3	2 (0.2)	1 (0.1)	1 (0.3)	
Tumor size (cm), n (%)				0.899
< 5	656 (54.8)	459 (55.0)	197 (54.6)	
≥ 5	540 (45.2)	376 (45.0)	164 (45.4)	
Tumor number, n (%)				0.956
Single	1,137 (95.1)	794 (95.1)	343 (95.0)	
Multiple	59 (4.9)	41 (4.9)	18 (5.0)	
BCLC stage, n (%)				0.341
0	100 (8.4)	74 (8.9)	26 (7.2)	
A	1,096 (91.6)	761 (91.1)	335 (92.8)	
Differentiation, n (%)				0.600
Grade I+II	762 (63.7)	528 (63.2)	234 (64.8)	
Grade III+IV	434 (36.3)	307 (36.8)	127 (35.2)	
Satellite, n (%)				0.849
Present	129 (10.8)	91 (10.9)	38 (10.5)	
Absent	1,067 (89.2)	744 (89.1)	323 (89.5)	

Liver capsule invasion, n (%)				0.957
Present	532 (44.5)	371 (44.4)	161 (44.6)	
Absent	664 (55.5)	464 (55.6)	200 (55.4)	
Pathological MVI, n (%)				0.966
Present	327 (27.3)	228 (27.3)	99 (27.4)	
Absent	869 (72.7)	607 (72.7)	262 (72.6)	

Data are presented as median (interquartile range) or n (%). Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HBV-DNA, Hepatitis B Virus Deoxyribonucleic Acid; AFP, alpha fetal protein; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ALB, albumin; PT, prothrombin time; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; APRI, aspartate aminotransferase to platelet ratio index; FIB4, fibrosis-4 index; ALBI, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; MVI, microvascular invasion.

Table 2. Univariate logistic regression analysis of MVI presence based on preoperative data in the training cohort

Variable	Comparison	OR (95% CI)	*P value*
Gender	Male vs. Female	1.50 (0.98-2.3)	0.065
Age (years)	< 60 vs. ≥ 60	0.61 (0.43-0.88)	0.008*
HBsAg	Positive vs. Negative	1.37 (0.84-2.22)	0.203
HCV	Present vs. Negative	0.40 (0.05-3.34)	0.397
HBV-DNA (IU/mL)	< 2000 vs. ≥ 2000	0.91 (0.66-1.25)	0.563
WBC (10^9/L)	< 4 vs. ≥ 4	1.57 (1.07-2.31)	0.022*
PLT (10^9/L)	< 100 vs. ≥ 100	1.08 (0.78-1.48)	0.645
TB (μmol/L)	< 28 vs. ≥ 28	0.86 (0.41-1.79)	0.690
ALB (g/L)	< 40 vs. ≥ 40	0.85 (0.62-1.16)	0.303
PT (s)	< 12.8 vs. ≥ 12.8	1.63 (1.13-2.33)	0.008*
AFP (ng/mL)	< 400 vs. ≥ 400	2.60 (1.90-3.56)	< 0.001*
AAR	< 1 vs. ≥ 1	1.25 (0.92-1.68)	0.153
NLR	< 3 vs. ≥ 3	2.67 (1.89-3.78)	< 0.001*
PLR	< 150 vs. ≥ 150	1.71 (1.22-2.40)	0.002*
PNI	< 45 vs. ≥ 45	1.26 (0.87-1.83)	0.228
APRI	< 1 vs. ≥ 1	1.18 (0.86-1.61)	0.298
FIB4	< 3.25 vs. ≥ 3.25	0.96 (0.7-1.31)	0.786
ALBI	Grade 1 vs. Grade 2/3	1.03 (0.73-1.44)	0.886
Tumor size (cm)	< 5 vs. ≥ 5	2.66 (1.95-3.64)	< 0.001*
Tumor number	Single vs. Multiple	0.89 (0.44-1.79)	0.734
BCLC stage	0 vs. A	2.64 (1.33-5.24)	0.005*

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HBV-DNA, Hepatitis B Virus Deoxyribonucleic Acid; WBC, white blood cell; PLT, platelet; TB, total bilirubin; ALB, albumin; PT, prothrombin time; AFP, alpha fetal protein; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; APRI, aspartate aminotransferase to platelet ratio index; FIB4, fibrosis-4 index; ALBI, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; MVI, microvascular invasion. *P < 0.05 was considered statistically significant.

BCLC stage did not show independent significance in the multivariate model.

These independent predictors were subsequently incorporated into a nomogram to estimate the risk of MVI (**Figure 1**). The corresponding point assignments for each variable are provided in Table S1. In the training cohort, the nomogram demonstrated good discriminatory ability, with a C-index of 0.72 (95% CI, 0.68-0.75), which was consistent with the area under the curve (AUC) of 0.72 (Figure S2A). In the validation group, the C-index was 0.73 (95% CI, 0.67-0.79), with a comparable AUC of 0.73 (Figure S2B) (Table S2). Internal validation using bootstrap resampling (1,000 repetitions) demonstrated stable model performance, with a bootstrap-corrected C-index of 0.707. Calibration plots showed good agreement between predicted probabilities and observed outcomes in both cohorts (Figure S3). This was further supported by the Hosmer-Lemeshow goodness-of-fit test (χ^2 = 3.20, df = 6, P = 0.783), indicating adequate model calibration. Using a cutoff value of 0.34, the model showed moderate sensitivity (52.6% in the training cohort and 55.6% in the validation cohort) and relatively good specificity (77.6% and 79.4%, respectively). The negative predictive value was 81.3% in the training cohort and 82.5% in the validation cohort, suggesting that the model may be particularly useful for identifying patients unlikely to have MVI. Detailed results are shown in Table S2.

Table 3. Multivariate logistic regression analysis of MVI presence based on preoperative data in the training cohort

Variable	Comparison	OR (95% CI)	*P value*
Age (years)	< 60 vs. ≥ 60	0.62 (0.42-0.92)	0.016*
WBC (10^9/L)	< 4 vs. ≥ 4	1.27 (0.83-1.93)	0.267
PT (s)	< 12.8 vs. ≥ 12.8	1.85 (1.24-2.75)	0.002*
AFP (ng/mL)	< 400 vs. ≥ 400	2.51 (1.80-3.51)	< 0.001*
NLR	< 3 vs. ≥ 3	2.40 (1.60-3.62)	< 0.001*
PLR	< 150 vs. ≥ 150	0.84 (0.55-1.28)	0.423
Tumor size (cm)	< 5 vs. ≥ 5	2.26 (1.58-3.23)	< 0.001*
BCLC stage	0 vs. A	1.54 (0.74-3.21)	0.251

Abbreviations: WBC, white blood cell; PT, prothrombin time; AFP, alpha fetal protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; BCLC, Barcelona Clinic Liver Cancer. *P < 0.05 was considered statistically significant.

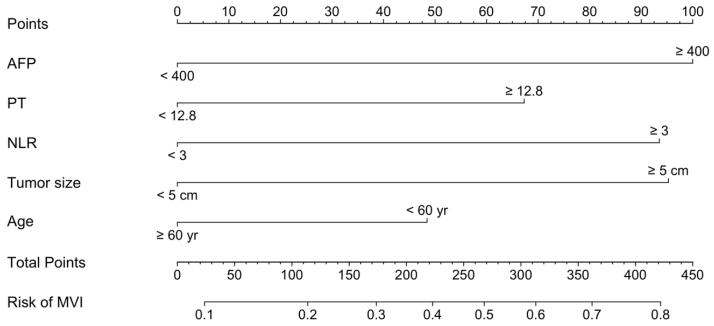

Figure 1. Nomogram to estimate the risk of MVI in patients with BCLC 0-A stage hepatocellular carcinoma. To use the nomogram, locate the value of each predictor on its corresponding axis and draw a vertical line upward to the "Points" axis to obtain the score, sum the scores of all predictors, and then draw a vertical line from the total points axis down to estimate the individual probability of MVI.

Recurrence risk stratification

Using this cutoff value, patients were subsequently stratified into high- and low-risk groups based on this cut-off value. In the validation cohort Kaplan-Meier survival analyses demonstrated that patients with a positive MVI status had a significantly shorter DFS than those without MVI (P < 0.0001; **Figure 2A**). The median DFS was 53.0 months (95% CI, 40.0-88.6) in patients without MVI and 16.0 months (95% CI, 8.9-27.0) in patients with MVI. Similarly, patients in the high-risk group, according to the nomogram score, exhibited markedly poorer DFS than those in the low-risk group (P < 0.0001; **Figure 2B**). The median DFS was 55.0 months (95% CI, 43.0-88.6) in the low-risk group and 16.0 months (95% CI, 11.2-27.0) in the high-risk group. The incidence of MVI was significantly more elevated in the high-risk group than that in the low-risk cohort (50.5% [55/109] vs. 17.5% [44/252], P < 0.001). These findings indicate that both the pathological MVI status and nomogram-based risk stratification are strongly associated with postoperative recurrence.

Decision curve analysis (DCA) was performed to further evaluate the clinical utility of the model. As shown in **Figure 3A**, **3B**, the nomogram provided greater net clinical benefit in predicting recurrence compared with MVI status alone, particularly at 1-year follow-up, within a threshold probability range of approximately 0.15-0.50 for 1-year DFS and 0.30-0.60 for 3-year DFS. These results suggest that the nomogram had superior clinical applicability for individualized recurrence risk estimation after liver resection in patients with HCC.

Discussion

The accurate preoperative assessment of MVI may play a pivotal role in optimizing preoperative treatment strategies and in formulating targeted surgical plans for HCC patients. Firstly, preoperative identification of patients with a high probability of MVI may facilitate the selection of candidates for neoadjuvant interventions designed to improve DFS or long-term oncologic prognosis [8]. Second, in clinical practice, estimating the probability of MVI prior to surgery could assist surgeons in determining individualized surgical plans, such as adequate resection margins, extent of hepatic resection, and anatomical or non-anatomical resection approaches, to reduce the risk of early recurrence [6, 7]. Consequently, the development of a reliable model for preoperative MVI prediction would be of considerable clinical value, as it could provide objective support for surgical and perioperative decision-making in early-stage, resectable HCC.

In the present study, MVI was identified in approximately 28% of patients with early-stage

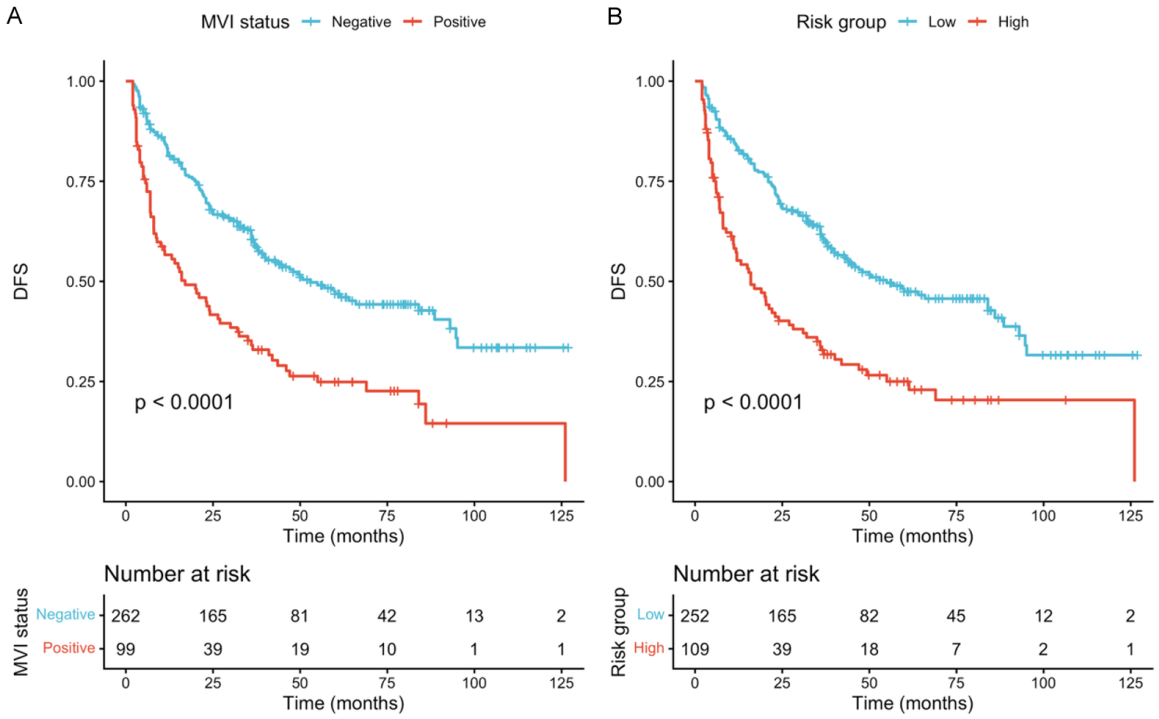

Figure 2. Kaplan-Meier analysis of DFS according to MVI status and nomogram-based risk stratification in the validation cohort. A: DFS stratified by MVI status. B: DFS stratified by the nomogram-based risk group. DFS: disease-free survival; MVI: microvascular invasion.

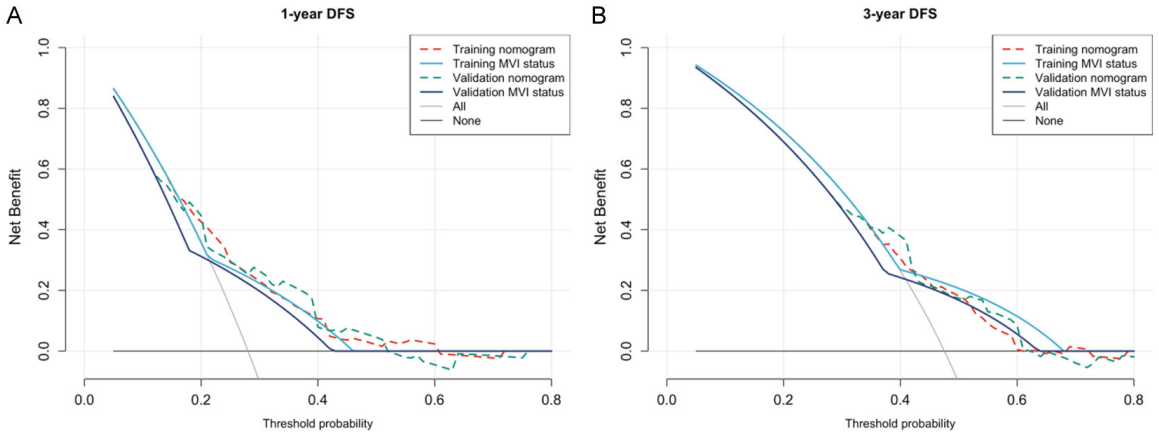

Figure 3. DCA evaluating the clinical utility of the nomogram and MVI status for predicting DFS in the training and validation cohorts. A: DCA for 1-year DFS. B: DCA for 3-year DFS. DCA: decision curve analysis; DFS: disease-free survival; MVI: microvascular invasion.

HCC and was strongly associated with an elevated risk of postoperative recurrence. Preoperative variables, including age, NLR, AFP level, tumor size, and PT, were identified as independent predictors of MVI. Although the BCLC stage was associated with MVI in the univariate analysis, it did not remain independently significant in the multivariate model, possibly due to overlap with tumor burden-related variables such as tumor size. The integration of these preoperative factors resulted in the construction of a predictive model capable of accurately estimating individual MVI risk. Moreover, the model demonstrated the capacity to effectively stratify patients based on their recurrence risk, underscoring its potential clinical

significance in supporting personalized treatment strategies for early-stage HCC.

Although previous research has sought to predict MVI using preoperative imaging features, serum biomarkers, and tumor-related variables, most of these models have included patients beyond early-stage HCC (BCLC stage 0-A), a group in which MVI is more prevalent [11-13]. This may compromise the model specificity and clinical relevance [14]. Furthermore, studies focusing on early-stage HCC cohorts frequently lacked postoperative recurrence risk stratification [10, 15, 16], thus restricting their applicability in individualized clinical decision-making.

Therefore, based on the limitations of the aforementioned two types of studies, we developed a preoperative MVI prediction model specifically tailored to early-stage resectable HCC (BCLC 0-A), incorporated postoperative recurrence risk stratification. This model integrates multi-dimensional preoperative parameters, including demographic features, serologic factors, inflammatory markers, and radiologic tumor features. Collectively, these factors form a comprehensive and biological relevant framework for preoperative MVI assessment.

In terms of predictive performance, previously reported clinical nomograms have demonstrated moderate discrimination (AUC ≈ 0.80) [17], whereas radiomics-based models have achieved higher accuracy, with AUCs often exceeding 0.85-0.90 [18]. In comparison, our model achieved an AUC of approximately 0.73 in the validation cohort. Despite this relatively low discrimination, the reliance of the model on simple and readily available parameters enables a balanced approach that harmonizes interpretability and clinical applicability. This accessible tool facilitates individualized risk estimation, thereby providing a framework to guide peri-operative treatment strategies and surgical planning for early-stage HCC.

To further elucidate the biological rationale underlying the model, we examined key variables incorporated into the prediction framework. Among these, AFP and tumor size are well-established biological features that have been consistently associated with MVI and tumor aggressiveness in HCC. AFP serves as a pivotal biomarker for both diagnosis and prognosis, with elevated or rising levels reflecting aggressive tumor behavior and correlating with vascular invasion, poor differentiation, and an increased risk of recurrence following curative resection [10, 18]. Similarly, tumor size has been demonstrated to be a reliable predictor of MVI, and its occurrence increases in proportion to tumor diameter [4, 17]. Larger tumors have been shown to invade microvessels, indicating advanced local infiltration and more aggressive pathological features [19]. Collectively, these classical parameters provided a robust biological rationale for their incorporation into the model, thereby reinforcing their clinical interpretability.

Furthermore, our findings indicate that younger patients are more likely to exhibit MVI, which aligns with the observations by Zhang and colleagues [20], possibly reflecting the fact that tumors arising in younger patients require greater intrinsic proliferative and invasive potential to develop within a relatively intact physiological environment. However, the association between age and MVI remains unclear. Other studies have reported contradictory findings, indicating that older patients have a higher probability of developing MVI [21]. The presence of such inconsistencies across studies may be indicative of variations in the underlying disease etiology, viral infection status, or molecular profiles among cohorts. This observation highlights the need for further multicenter investigations.

Despite the paucity of studies directly examining the association between coagulation variables and MVI, prolonged PT may indicate impaired hepatic synthesis and coagulation imbalance, which may predispose patients to endothelial injury, microthrombosis, and localized hypoxia, facilitating tumor cell infiltration into microvessels and MVI formation [22, 23]. An elevated NLR reflects systemic inflammation and immune dysregulation. Activated neutrophils release proteolytic enzymes, reactive oxygen species, and proangiogenic cytokines (e.g., IL-8 and VEGF) that disrupt endothelial integrity, promote angiogenesis, and enhance vascular invasion. In contrast, lymphopenia indicates weakened immune surveillance [24-26]. These pathophysiological changes have been demonstrated to play important roles in promoting MVI formation.

The coexistence of prolonged PT and elevated NLR may represent two interconnected aspects of the coagulation-inflammation axis. Inflammatory cytokines (e.g., IL-6, TNF-α) have been shown to impair hepatic synthesis of coagulation factors. Thrombin and fibrin further activate endothelial and immune cells, thereby amplifying inflammation and establishing a hypercoagulable, immunosuppressive microenvironment conducive to MVI formation [27, 28]. Consequently, PT and NLR may serve as complementary indicators of tumor aggressiveness.

Based on these findings, the clinical use of the model can be considered. In the preoperative setting, the nomogram may help guide risk-adapted management in patients with early-stage HCC. Patients classified as low risk are less likely to have MVI and may be suitable for standard surgical approaches with routine follow-up. In contrast, those identified as high risk may benefit from more careful management, such as considering wider resection margins or anatomical resection, along with closer postoperative surveillance. In addition, the model may help identify patients who could potentially be candidates for neoadjuvant therapies, although further prospective validation is required.

The present study has several limitations. Firstly, as a retrospective, single-center study, there is a potential risk of selection bias, and the study population may not fully represent broader clinical settings. Although strict inclusion criteria and internal validation were applied, the findings may still reflect local practice patterns and patient characteristics. Secondly, external validation was not performed. Although the model showed stable performance in the internal validation cohort, its generalizability needs to be further confirmed in independent, multicenter, prospective populations. Thirdly, the nomogram was developed using routinely available clinical and radiological variables. While this improves its practicality, the lack of molecular and advanced imaging features may limit its predictive accuracy. Future studies incorporating these factors may further enhance model performance. Finally, several variables were dichotomized to facilitate clinical use, which may have led to some loss of information. Using continuous variables in future analyses may help to improve the precision of the model.

Conclusion

Collectively, these findings underscore the clinical relevance of integrating routinely available preoperative variables, including tumor features, serum biomarkers, and host-related inflammatory and coagulative indicators, for both preoperative MVI prediction and postoperative recurrence risk stratification in early-stage HCC. The proposed model functions as a pragmatic instrument that links preoperative assessments with postoperative outcomes. This enables clinicians to identify patients at high risk of MVI presence and postoperative recurrence. This information can inform individualized treatments by optimizing surgical plans and guiding neoadjuvant treatment strategies.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 82270648, 82203785, and 82473470), the Key Research and Development Program of the Science and Technology Department of Sichuan Province (Nos. 2024YFFK0310 and 2024YFFK0309), and the Postdoctoral Research Fund of West China Hospital, Sichuan University (No. 2024HXBH073). The funding sources provided support for personnel, postgraduate training, and research-related activities. We would like to thank Editage (www.editage.cn) for English language editing.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Ming Zhang and Liang-Liang Xu, Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China. Tel: +86-18980606723; +86-28-6066-0497; E-mail: zmhxdoctor@wchscu.edu.cn (MZ); Tel: +86-18200560-532; E-mail: perlight145@163.com (LLX); Dr. Hua Zhang, Key Laboratory of Birth Defects and Related Diseases of Women and Children of MOE, West China Second University Hospital, Sichuan University, Chengdu 610041, Sichuan, China. Tel: +86-13096309007; E-mail: huazh0108@126.com

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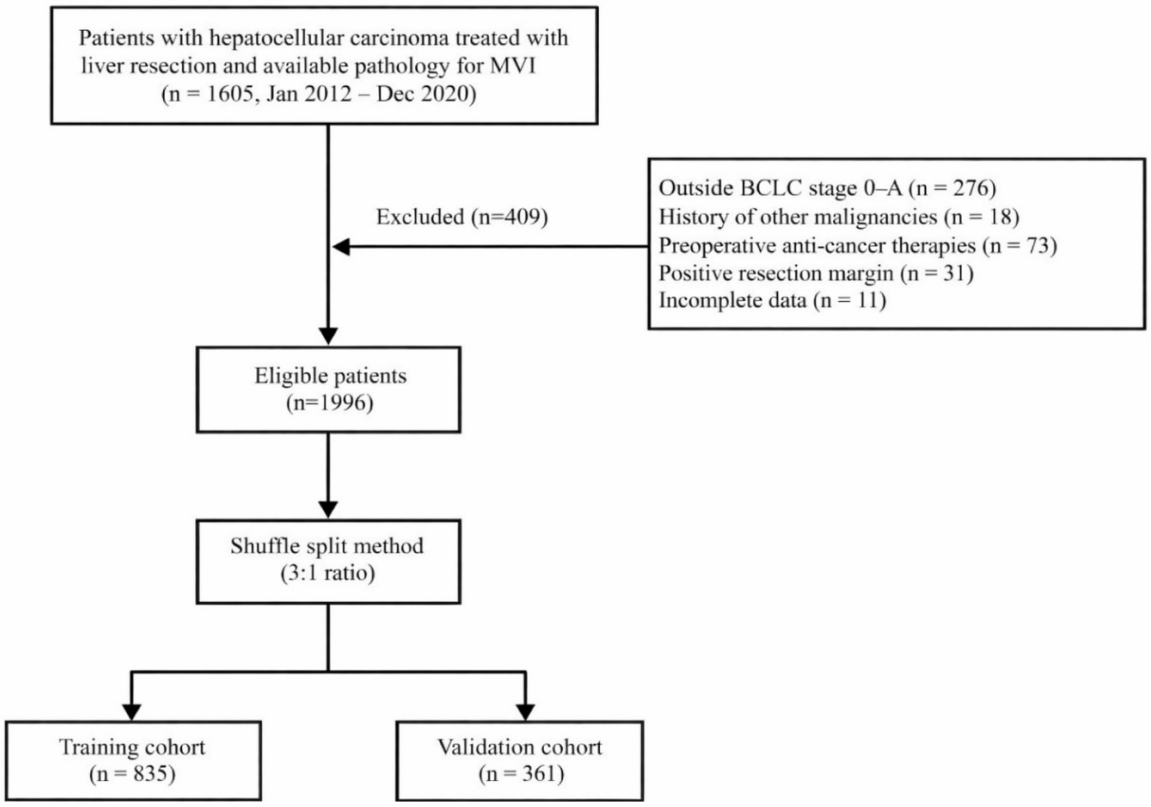

Figure S1. Flow chart of the study.

Table S1. Point assignment for each variable in the nomogram predicting microvascular invasion

Variable	Category	Points
AFP	< 400 ng/mL	0
	≥ 400 ng/mL	100
PT	< 12.8 s	0
	≥ 12.8 s	68
NLR	< 3	0
	≥ 3	95
Tumor size	< 5 cm	0
	≥ 5 cm	97
Age	≥ 60 yr	0
	< 60 yr	50

Points were assigned according to the magnitude of regression coefficients derived from the multivariate logistic regression model. AFP ≥ 400 ng/mL was set as the reference for scaling (100 points), and the scores of other variables were assigned proportionally. The total score corresponds to the predicted probability of MVI as shown in the nomogram. Abbreviations: AFP, alpha-fetoprotein; PT, prothrombin time; NLR, neutrophil-to-lymphocyte ratio; MVI, microvascular invasion.

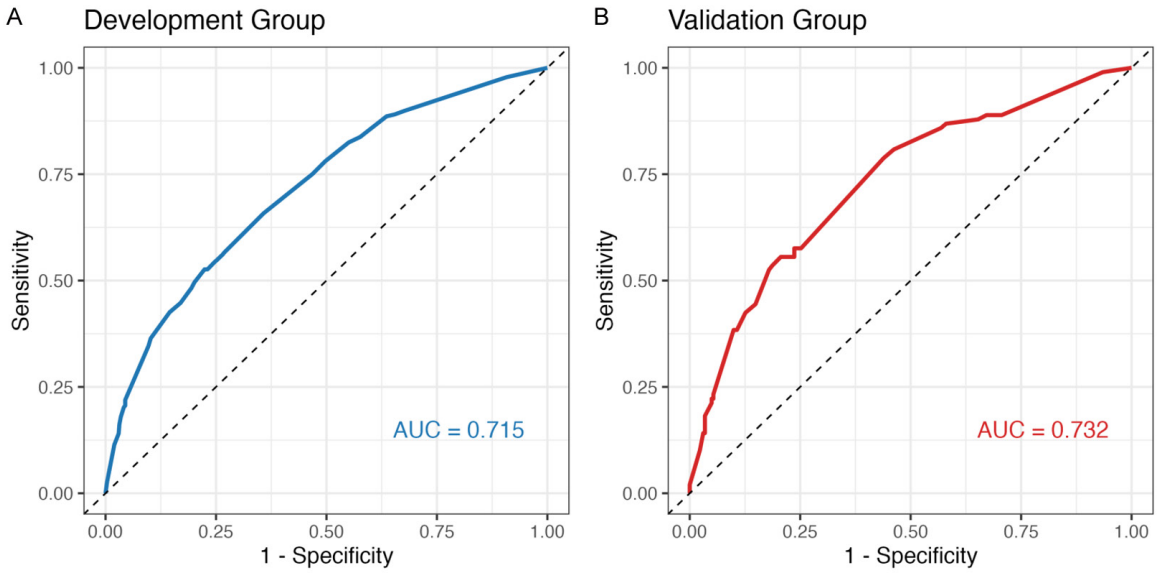

Figure S2. Receiver operating characteristic (ROC) curves of the risk score model for predicting microvascular invasion in (A) the training cohort (AUC = 0.715) and (B) the validation cohort (AUC = 0.732).

Table S2. Accuracy of the prediction score of the nomogram for estimating the risk of MVI presence

Variable	Value (95% CI)	
	Training Cohort	Validation Cohort
Area under ROC curve, concordance index	0.715 (0.68-0.75)	0.732 (0.67-0.79)
Cutoff score	0.34	0.34
Sensitivity, %	52.6% (43.2-84.5)	55.6% (48.5-87.7)
Specificity, %	77.6% (45.4-87.2)	79.4% (49.8-86.9)
Positive predictive value, %	46.9% (35.5-57.2)	50.5% (35.7-61.9)
Negative predictive value, %	81.3% (78.9-89.4)	82.5% (79.8-92.6)
Positive likelihood ratio	2.35 (1.53-3.49)	2.70 (1.61-4.09)
Negative likelihood ratio	0.61 (0.32-0.67)	0.56 (0.23-0.62)

Abbreviations: MVI, microvascular invasion; ROC, receiver operating characteristic.

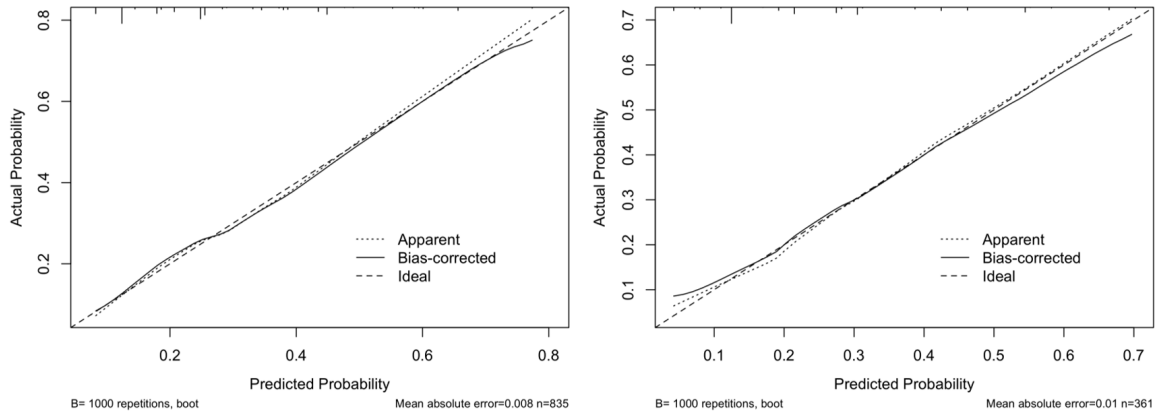

Figure S3. Calibration curves of the nomogram for predicting microvascular invasion (MVI) in hepatocellular carcinoma (HCC) patients undergoing liver resection (LR): training cohort (left panel) and validation cohort (right panel).