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ORIGINAL RESEARCH

Lasso-Based Nomogram for Predicting Early Recurrence Following Radical Resection in Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) is a common malignancy with a high recurrence rate following curative resection. This study aimed to identify factors contributing to early recurrence (within 2 years) and develop a Lasso-based nomogram for individualized risk assessment.

Methods: We conducted a retrospective analysis of 206 hCC patients who underwent curative resection at Taizhou Hospital, Zhejiang Province, from January 2019 to August 2022. Patients were randomly divided into training (n=144) and validation (n=62) cohorts. Lasso regression was used to identify potential recurrence risk factors among 17 candidate predictors. A Cox proportional hazards model was constructed based on variables selected by Lasso. Model performance was assessed using receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA).

Results: Five independent predictors of early HCC recurrence were identified: age, serum alanine aminotransferase (ALT) levels, cirrhosis, tumor diameter, and microvascular invasion (MVI). The nomogram demonstrated area under the curve (AUC) values for recurrence-free survival (RFS) of 0.828 (95% confidence interval [CI]: 0.753–0.904) at 1 year, 0.799 (95% CI: 0.718–0.880) at 2 years, and 0.742 (95% CI: 0.642–0.842) at 5 years in the training cohort. The corresponding AUCs in the validation cohort were 0.823 (95% CI: 0.686–0.960), 0.804 (95% CI: 0.686–0.922), and 0.857 (95% CI: 0.722–0.992) at 1, 2 and 5 years, respectively. Calibration curves and DCA confirmed the nomogram's high accuracy and clinical utility.

Conclusion: The Lasso-Cox regression nomogram effectively predicts HCC recurrence within two years post-hepatectomy, providing a valuable tool for personalized postoperative management to improve patient outcomes.

Keywords: hepatocellular carcinoma, microvascular invasion, early recurrence, nomogram, Lasso regression

Introduction

Hepatocellular carcinoma (HCC), a major form of liver cancer, poses a significant global health challenge due to its high morbidity and mortality, ranking fourth in cancer incidence and second in cancer-related deaths in China.[1] Current treatment options for HCC include surgical resection, liver transplantation, transarterial chemoembolization (TACE), radioembolization, and systemic therapies.[2–4] While surgical resection remains the primary curative option, offering potential long-term survival,[5] postoperative recurrence is a major concern, with reported rates of 50–70% within 5 years.[2,6,7]

The molecular mechanisms underlying HCC metastasis and recurrence are complex and not fully understood. Recent studies have highlighted the roles of epithelial-mesenchymal transition (EMT), the tumor immune microenvironment (TIME), and dysregulated signaling pathways such as Wnt/β-catenin, PI3K/AKT, and TGF-β in HCC progression.[4,8] Additionally, non-coding RNAs, including microRNAs and long non-coding RNAs, have been implicated in modulating HCC metastasis at the post-transcriptional level.[9,10] Furthermore, iron deficiency (ID) has been shown to increase SPNS2 expression, promoting HCC metastasis.[11]

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Several clinical and pathological factors predict HCC recurrence after curative resection, including tumor size and number, vascular invasion, tumor differentiation, and serum alpha-fetoprotein (AFP) levels.[7,12] Portal vein invasion, a form of vascular invasion, strongly predicts early recurrence and poor prognosis,[13] while elevated serum AFP levels are associated with increased recurrence risk and reduced survival.[14]

Other recurrence-associated factors include cirrhosis, tumor characteristics, liver function (Child-Pugh score), tumor stage (Barcelona Clinic Liver Cancer System), tumor differentiation, and microvascular invasion (MVI).[15–18] MVI, defined as the presence of tumor cells within endothelium-lined vascular spaces,[19] is strongly linked to intrahepatic metastasis and recurrence.

HCC patients face a poor prognosis, with a five-year survival rate of only 18%.[20] Despite extensive research on recurrence predictors, few studies have specifically examined early recurrence (within two years of curative resection) using the least absolute shrinkage and selection operator (Lasso)-Cox method. Lasso regression, which enables variable selection and regularization, improves model interpretability and prevents overfitting, particularly in high-dimensional data. This retrospective study used the Lasso-Cox approach to identify predictors of early recurrence in post-resection HCC patients. By combining clinical and pathological factors, we aimed to develop a novel tool to guide early treatment strategies.

Materials and Methods

Patients

This study was approved by the Ethics Committee of Taizhou Hospital, Zhejiang Province (KL20241118). HCC patients who underwent curative hepatectomy were enrolled at Taizhou Hospital, Wenzhou Medical University, between January 2019 and August 2022. The patient selection process is outlined in Figure 1. HCC diagnosis was confirmed through postoperative pathology.

Patients eligible for inclusion were those who had undergone curative resection for HCC and had complete clinical data, including sex, age, serum alanine aminotransferase (ALT), albumin (ALB), total bilirubin (TBIL), neutrophil-to-lymphocyte ratio (NEUTLYMPH), prothrombin time (PT), Child-Pugh score, cirrhosis status, number and size of tumors, China Liver Cancer (CNLC) classification, Barcelona Clinic Liver Cancer (BCLC) stage, serum AFP levels, tumor differentiation, presence of MVI, and Ki67 expression.

Exclusion criteria were as follows: (1) Patients with incomplete or missing data on any of the predictive factors studied; (2) Patients with non-HCC liver tumors; (3) Patients who had not undergone curative resection for HCC; (4) Patients who had received preoperative treatments such as transarterial chemoembolization or radiofrequency ablation; (5) Patients with a history of liver transplantation or other liver surgeries; (6) Patients with advanced or metastatic HCC; (7) Patients with a prior history of other malignant tumors; (8) Patients with major comorbidities potentially influencing study outcomes.

Data Collection

Relevant clinical data included demographic and clinical characteristics such as age, gender, cirrhosis status, and CNLC and BCLC staging. Laboratory parameters, including ALB, serum ALT levels, TBIL, NEUTLYMPH, PT, serum AFP levels, and Child-Pugh classification, were recorded. Additionally, histopathological features such as tumor size, tumor count, MVI, and Ki67 expression were assessed.

Follow-up

Postoperative follow-up was conducted quarterly during the first three years, biannually from the third to fifth year, and annually thereafter. Follow-up assessments included physical examinations, AFP tests, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans of the thoracic and abdominal regions. Data on tumor recurrence, including the time to recurrence, were collected through telephone follow-ups and electronic medical records, with recurrence timing recorded to the nearest month. The primary study endpoint was recurrence-free survival (RFS), defined as the time from surgery to the first recurrence or metastasis.

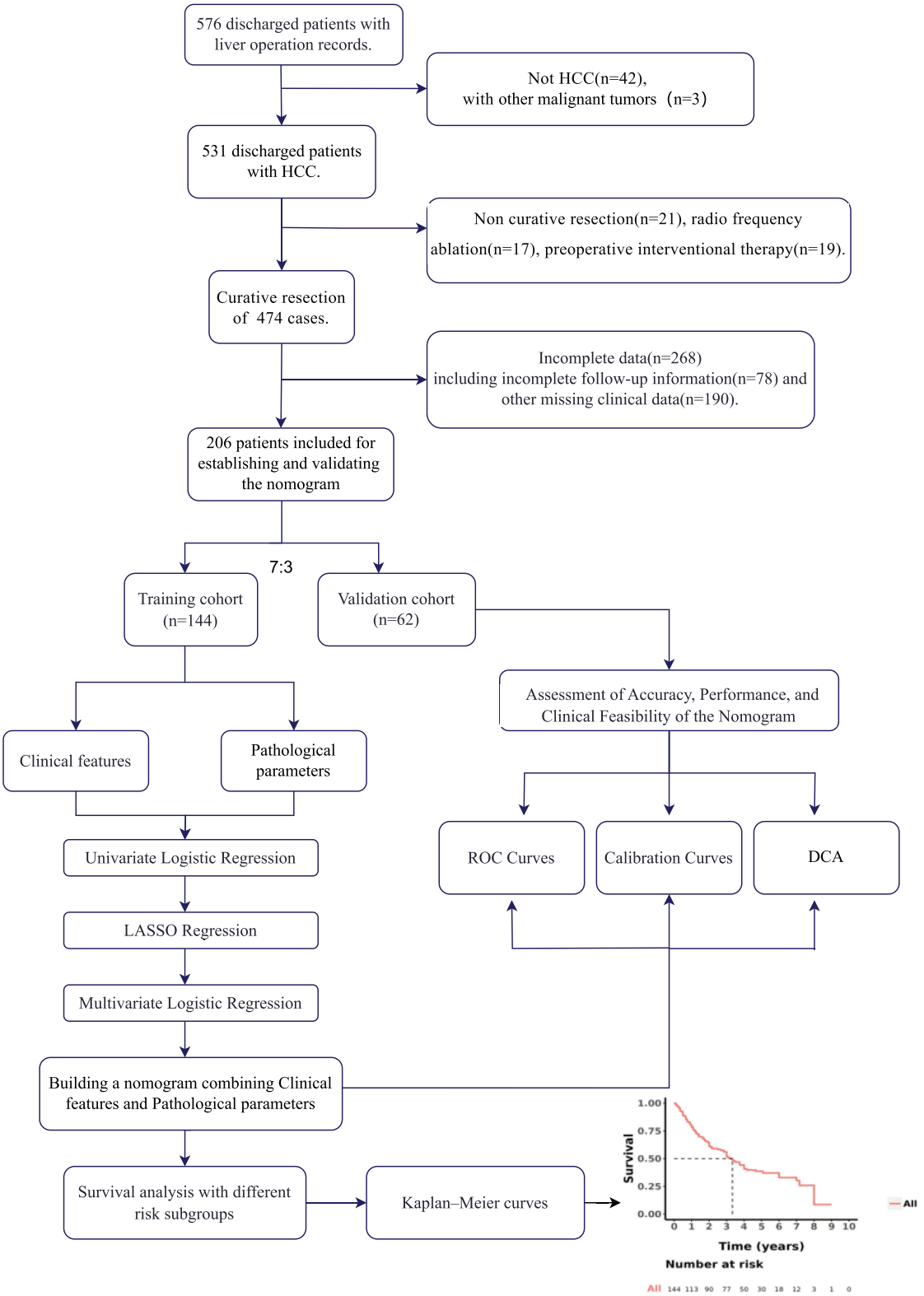

Figure 1 Flowchart of the selection and processing of patients with hepatocellular carcinoma.

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Statistical Analysis

The dataset from Taizhou Hospital was randomly divided into training and validation cohorts at a 7:3 ratio. Optimal cutoff points for continuous variables were determined using X-Tile 3.6.1 software, after which these variables were categorized into binary groups. Normally or approximately normally distributed data were presented as mean ± standard deviation (SD), and inter-group comparisons were performed using Student's *t*-test. Categorical variables were analyzed using the chi-square or Fisher's exact test. The Kaplan-Meier method was used to estimate early recurrence rates and RFS. In the training cohort, Lasso Cox regression was applied for multivariate analysis to identify independent risk factors while minimizing overfitting. A nomogram was then developed to predict recurrence. The performance of the nomogram was evaluated using receiver operating characteristic (ROC) curves and calibration plots, with the area under the curve (AUC) ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Decision curve analysis (DCA) was performed to assess the net clinical benefit of the predictive model.

Results

Patient Characteristics

A total of 206 patients with HCC who underwent curative surgery were included in this study, with no perioperative deaths reported. Table 1 presents the baseline characteristics of the training cohort (n = 144) and the validation cohort (n = 62). No significant differences were observed between the two cohorts in terms of sex distribution, age, cirrhosis prevalence, Child-Pugh classification, or BCLC stage (all $p > 0.05$). Additionally, lesion numbers, mean tumor diameter, and MVI rates were comparable between the two groups ($p = 0.147$, $p = 0.384$, and $p = 0.097$, respectively), indicating similar clinical characteristics. Ki67 expression levels and tumor differentiation also showed no significant differences ($p = 0.716$ and $p = 0.237$, respectively).

The median follow-up period was 36 months (range: 1–108 months). The 1-year, 2-year, and 5-year RFS rates were 78.0%, 63.0%, and 35.0%, respectively (Figure 2A). Patients with positive MVI had significantly poorer

Table 1 Demographics and Baseline Characteristics of the Patients

Characteristics	Training Cohort N = 144	Internal Test Cohort N = 62	*p*-value*
Sex, n (%)			0.791
Female	23 (16.0)	9 (14.5)	
Male	121 (84.0)	53 (85.5)	
Age, n (%)			0.540
<48 years	25 (17.4)	13 (21.0)	
≥48 years	119 (82.6)	49 (79.0)	
ALT, n (%)			0.568
<37 U/L	101 (70.1)	41 (66.1)	
≥37 U/L	43 (29.9)	21 (33.9)	
ALB, n (%)			0.320
<34.1 g/L	16 (11.1)	10 (16.1)	
≥34.1 g/L	128 (88.9)	52 (83.9)	
TBIL, n (%)			>0.999
<26.5 μmol/L	133 (92.4)	58 (93.5)	
≥26.5 μmol/L	11 (7.6)	4 (6.5)	
NEUTLYMPH, n (%)			0.682
<2.6	56 (38.9)	26 (41.9)	
≥2.6	88 (61.1)	36 (58.1)	
PT, n (%)			0.245
<16.4 s	140 (97.2)	58 (93.5)	
≥16.4 s	4 (2.8)	4 (6.5)	

(*Continued*)

Table 1 (Continued).

Characteristics	Training Cohort N = 144	Internal Test Cohort N = 62	*p*-value*
Child-Pugh grade, n (%)			>0.999
A	140 (97.2)	60 (96.8)	
B	4 (2.8)	2 (3.2)	
Cirrhosis, n (%)			0.515
No	29 (20.1)	15 (24.2)	
Yes	115 (79.9)	47 (75.8)	
Number of tumors, n (%)			0.147
1	129 (89.6)	50 (80.6)	
2	13 (9.0)	11 (17.7)	
3	2 (1.4)	1 (1.6)	
Diameter, cm, Mean ± SD	3.85 ± 2.48	3.57 ± 1.98	0.384
CNLC staging, n (%)			0.111
Ia or Ib	135 (93.8)	54 (87.1)	
IIa or Ib	9 (6.3)	8 (12.9)	
BCLC staging, n (%)			0.760
0 or A	128 (88.9)	56 (90.3)	
B	16 (11.1)	6 (9.7)	
AFP, n (%)			0.713
<531 ng/mL	128 (88.9)	54 (87.1)	
≥531 ng/mL	16 (11.1)	8 (12.9)	
Differentiation grade, n (%)			0.237
Moderately or highly differentiated	12 (8.3)	2 (3.2)	
Poorly differentiated	132 (91.7)	60 (96.8)	
MVI, n (%)			0.097
No	105 (72.9)	38 (61.3)	
Yes	39 (27.1)	24 (38.7)	
Ki67, n (%)			0.716
<0.3	75 (52.1)	34 (54.8)	
≥0.3	69 (47.9)	28 (45.2)	

Note: *Pearson's Chi-squared test; Fisher's exact test; Welch Two Sample *t*-test.
Abbreviations: ALT, alanine aminotransferase; ALB, albumin; TBIL, total bilirubin; NEUTLYMPH, neutrophil-to-lymphocyte ratio, PT, prothrombin time, CNLC, China Liver Cancer classification; CNLC Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; MVI, microvascular invasion.

prognoses, with 2-year and 5-year RFS rates of 57.0% and 31.0%, respectively, compared to 86.4% and 75.0% in the MVI-negative group ($p < 0.001$) (Figure 2B). Patients aged <48 years had worse prognoses than those aged ≥48 years, with 2-year RFS rates of 43.3% vs 65.0% and 5-year RFS rates of 15.2% vs 41.6% ($p = 0.007$) (Figure 2C). The presence of cirrhosis was associated with a poorer prognosis, with 2-year RFS rates of 57.1% vs 75.0% and 5-year RFS rates of 31.2% vs 55.8% ($p = 0.049$) (Figure 2D). Additionally, patients with serum ALT levels ≥37 U/L had significantly worse prognoses than those with ALT <37 U/L, with 2-year RFS rates of 48.4% vs 66.7% and 5-year RFS rates of 21.3% vs 43.6% ($p = 0.009$) (Figure 2E). These findings suggest that positive MVI, age <48 years, cirrhosis, and elevated serum ALT levels (≥37 U/L) are key factors associated with poorer RFS and prognosis in HCC patients.

Predictive Model

A total of 17 candidate predictors, including demographic, clinical, and tumor-related factors, were initially considered. Lasso regression analysis performed on the training cohort reduced the number of predictors to five key variables. Table 2 presents the corresponding coefficients, while Figure 3 illustrates the coefficient profile. The cross-validated error plot for the Lasso regression model is shown in Figure 4. The final model was selected

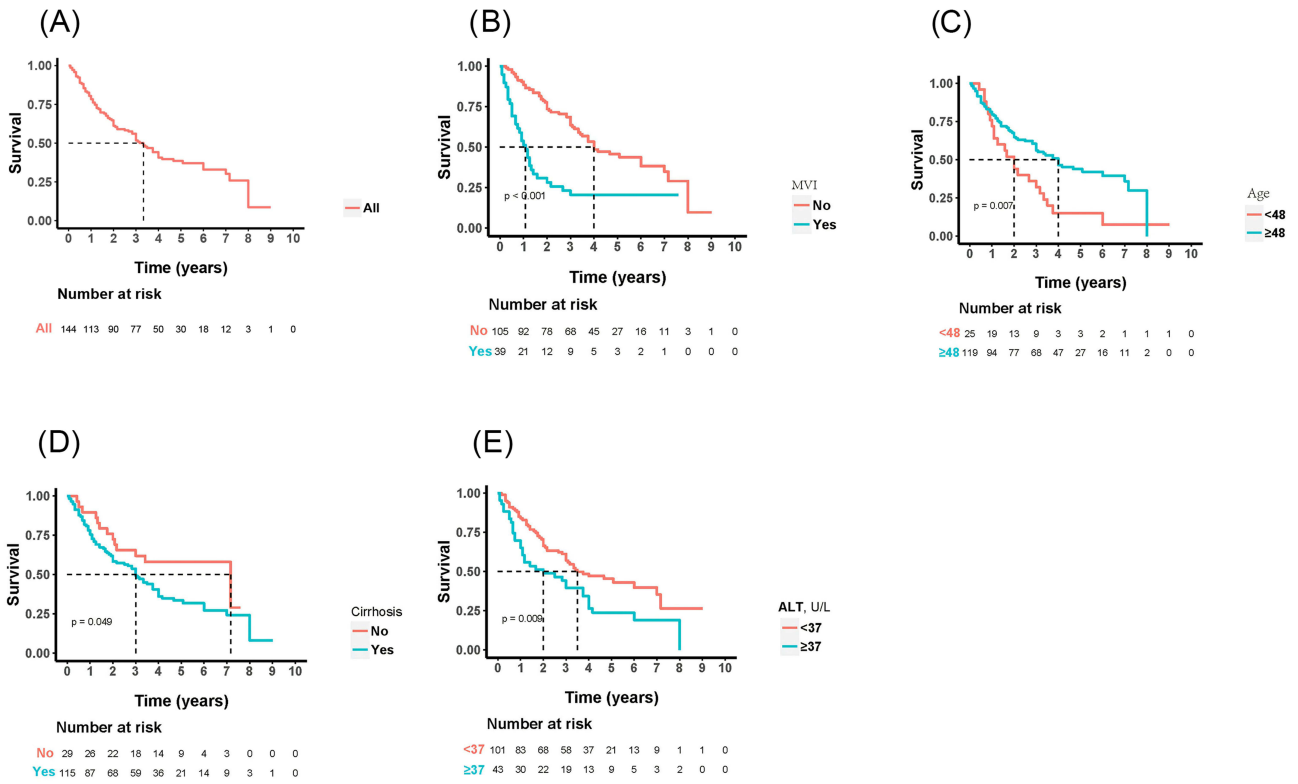

Figure 2 Kaplan-Meier curve survival analysis: (**A**) Overall survival for the entire cohort. (**B**) Survival outcomes stratified by microvascular invasion status ($p = 0.001$). (**C**) Survival comparison between patients aged <48 years and ≥48 years ($p < 0.001$). (**D**) Survival differences between patients with and without cirrhosis ($p = 0.046$). (**E**) Survival comparison based on serum alanine aminotransferase levels (<37 U/L vs ≥37 U/L, $p = 0.004$).

based on the minimum cross-validated error within one standard deviation, ensuring an optimal balance between complexity and predictive performance.

Multivariate Cox regression analyses were performed on the training cohorts analysis, and the results are summarized in Table 3. The final Cox model identified five independent predictors: age, serum ALT levels, cirrhosis, tumor size, and MVI. Figure 5 illustrates the hazard ratios (HRs) and 95% confidence intervals (CIs) for these variables, with the red dashed line indicating HR = 1. The model was then translated into an easy-to-use nomogram for clinical application (Figure 6).

Table 2 The Coefficients of Lasso Regression Analysis

Coefficient	Variable
0.00000000	Sex_level_1
−0.11868366	Age_level_1
0.20129318	ALT_level_1
0.00000000	ALB_level_1
0.00000000	TBIL_level_1
0.00000000	NEUTLYMPH_level_1
0.00000000	PT_level_1
0.00000000	ChildPugh_level_2
0.02826677	Cirrhosis_level_1
0.00000000	Number_level_2
0.00000000	Number_level_3

(*Continued*)

Table 2 (Continued).

Coefficient	Variable
0.04499798	Diameter_level_
0.00000000	BCLC_level_I
0.00000000	CNLC_level_I
0.00000000	AFP_level_I
0.00000000	Differentiation_level_I
0.66221476	MVI_level_I
0.00000000	Ki67_level_I

The AUCs for the model in the training and validation cohorts are shown in (Figure 7A and B). The AUC for the validation cohort was 82.3% (95% CI: 68.6–96.0) at 1 year, 80.4% (95% CI: 68.6–92.2) at 2 years, and 85.7% (95% CI: 72.2–99.2) at 5 years. These results indicate that the prediction model demonstrates strong discriminative ability.

The nomogram model developed in this study demonstrated strong predictive performance for postoperative HCC recurrence, with AUC values of 0.828, 0.799, and 0.742 for 1-, 2-, and 5-year RFS, respectively. Figure 8A and B display the 1-, 3-, and 5-year calibration plots for the nomogram in both cohorts, demonstrating a high agreement between observed and predicted RFS probabilities.

DCA

Figure 9A and B present the DCA for the developed nomogram in the training and validation cohorts, respectively. The high-risk threshold probability indicates potential discrepancies in model predictions, particularly when clinicians face challenges in applying the nomogram for diagnosis and decision-making. The DCA curves demonstrated that the nomogram provided substantial net benefits, outperforming both "treat-all" and "treat-none" strategies across most

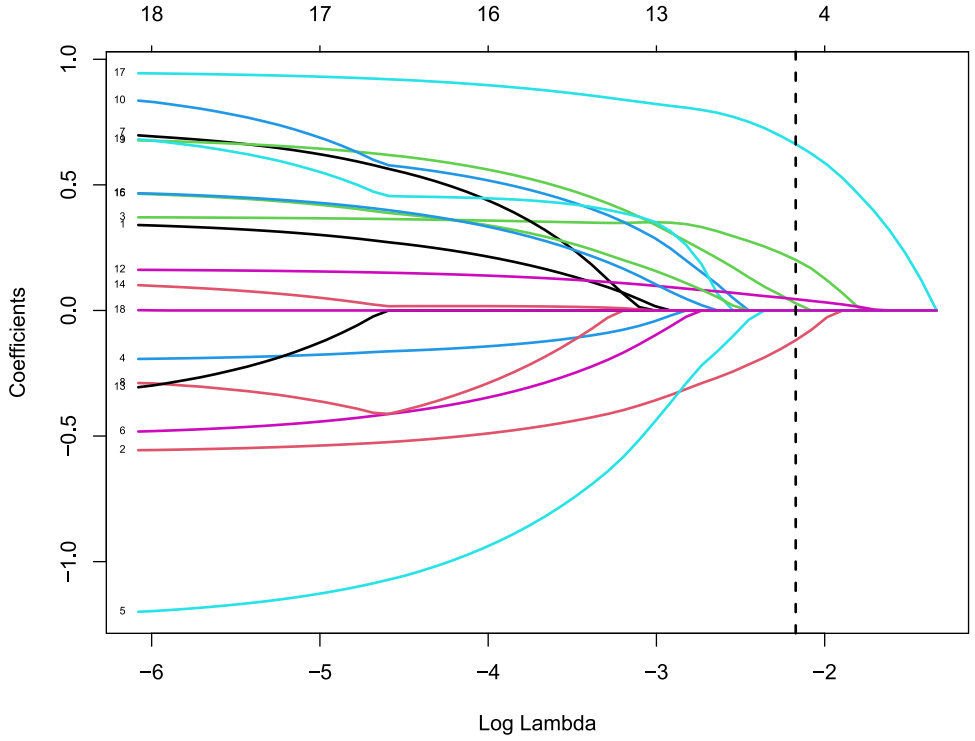

Figure 3 Lasso regression coefficient path plot.

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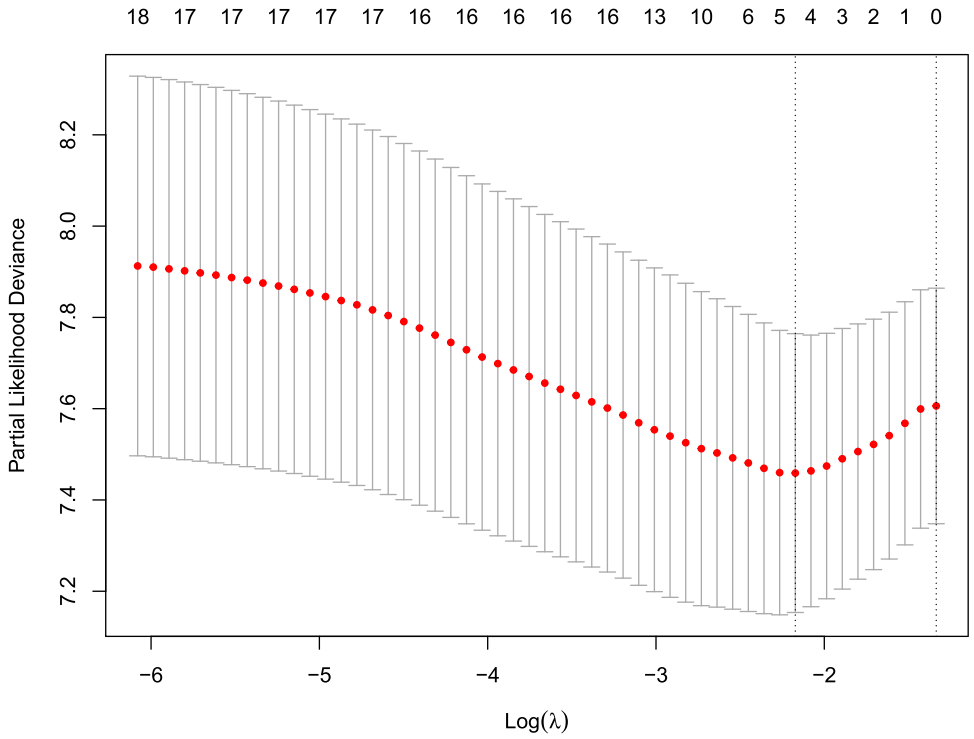

Figure 4 Lasso regression cross-validation plot.

threshold probabilities, particularly excelling within the 25–75% risk threshold range, thereby supporting its clinical application.

Discussion

HCC, the most common type of primary liver cancer, is responsible for over 800,000 deaths worldwide each year.[21] HCC has a high five-year recurrence rate of up to 60%, even after curative liver resection.[22,23] Approximately 50% of patients with HCC experience recurrence within two years post-resection.[24] Recurrence within this two-year period is classified as "early recurrence",[15,25,26] a critical distinction for understanding the mechanisms driving tumor recurrence. Early

Table 3 Results of Multivariate Cox Regression for Training Cohort

Characteristic	N	Event N	HR	95% CI	*p*-value
Age, years					
<48	25	22	—	—	
≥48	119	68	0.61	0.37, 1.01	0.054
ALT, U/L					
<37	101	55	—	—	
≥37	43	35	1.64	1.04, 2.60	0.034
Cirrhosis					
No	29	13	—	—	
Yes	115	77	1.64	0.87, 3.09	0.125
Diameter	144	90	1.12	1.04, 1.20	0.002
MVI					
No	105	59	—	—	
Yes	39	31	2.82	1.78, 4.46	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; MVI, microvascular invasion.

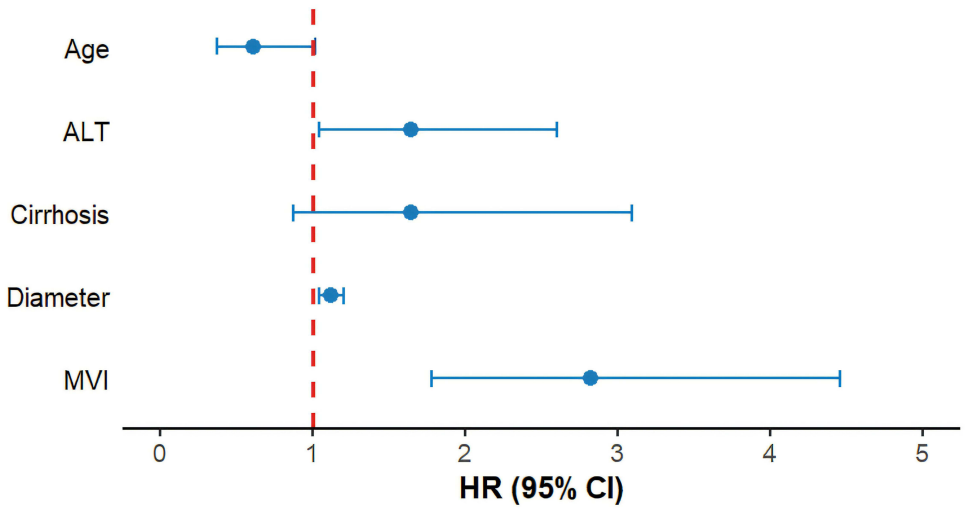

Figure 5 Cox proportional hazards regression incorporating Lasso regularization for recurrence prediction.

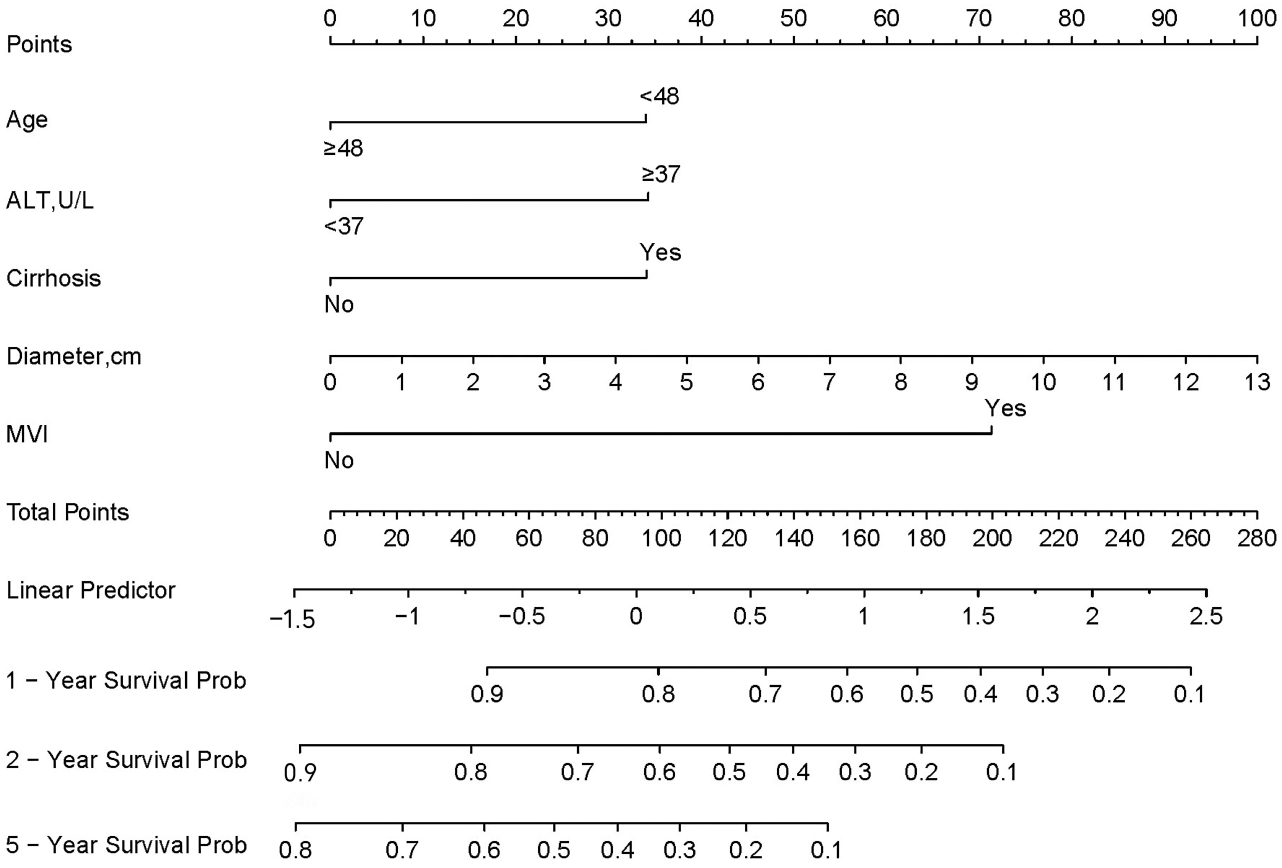

Figure 6 Nomogram prediction model for early recurrence in HCC.

recurrence is typically attributed to occult intrahepatic metastasis, whereas late recurrence (occurring after two years) often results from de novo tumors arising in a cirrhotic liver.[15] This classification significantly impacts patient management and prognosis. Previous studies have identified tumor size, multiplicity, and vascular invasion as key factors associated with post-resection recurrence of HCC.[27–29] Limited research has focused on prognostic predictors of early HCC recurrence within two years post-surgery. In this study, the final model contains five clinical indicators for the

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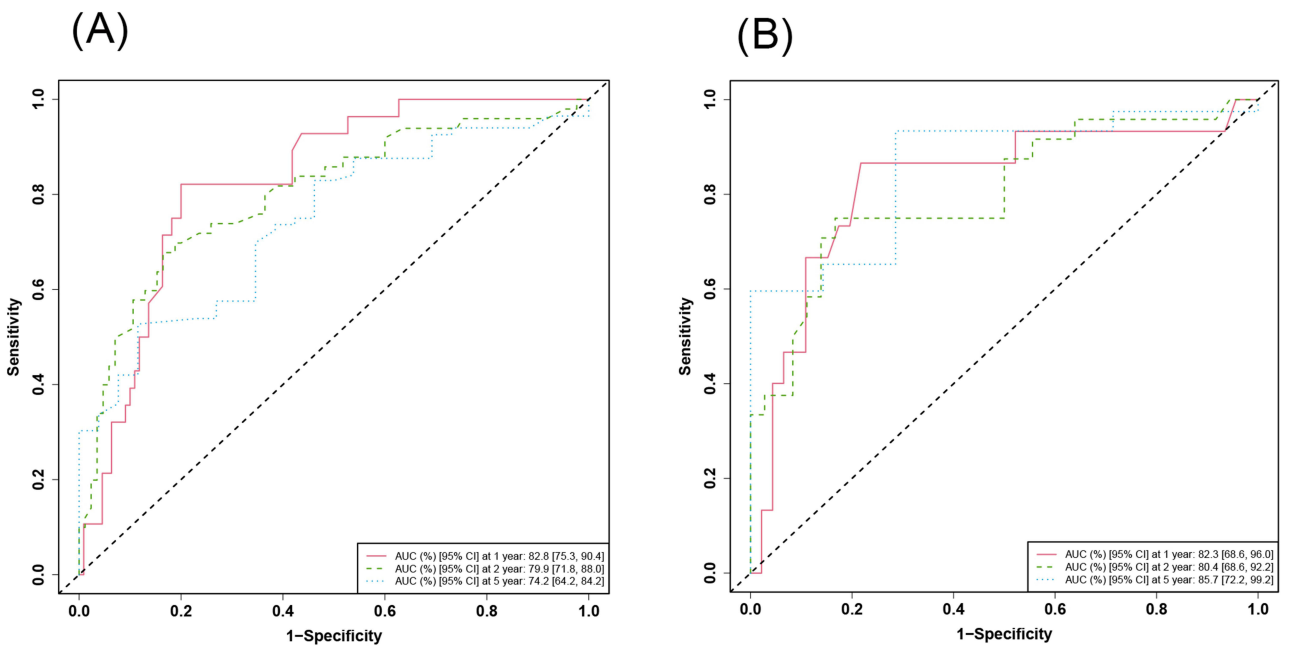

Figure 7 Receiver operating characteristic curves for the nomogram prediction model: (**A**) the training cohort and (**B**) the internal test cohort.

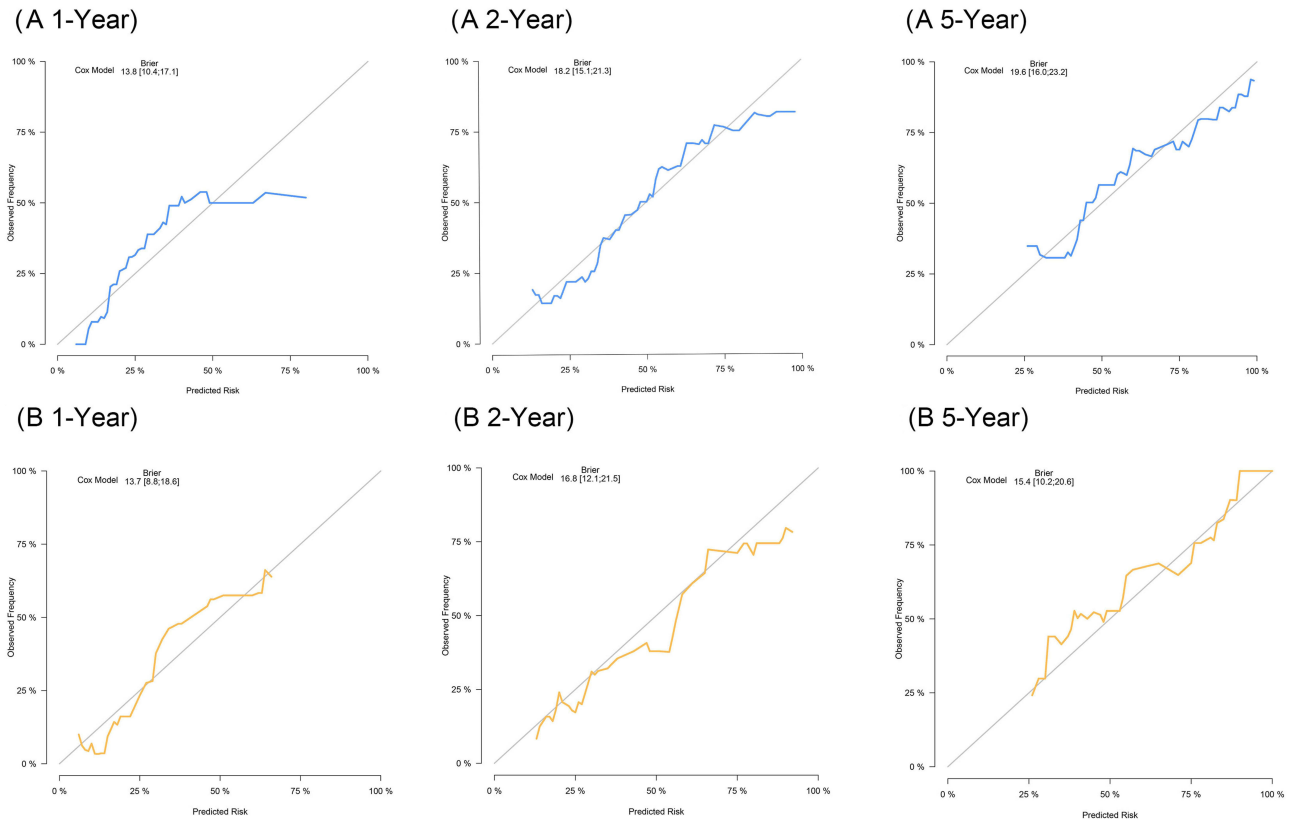

Figure 8 Calibration plots assessing the predictive accuracy of the Cox regression model for 1-, 2-, and 5-year recurrence-free survival in: (**A**) the training set and (**B**) the validation set.

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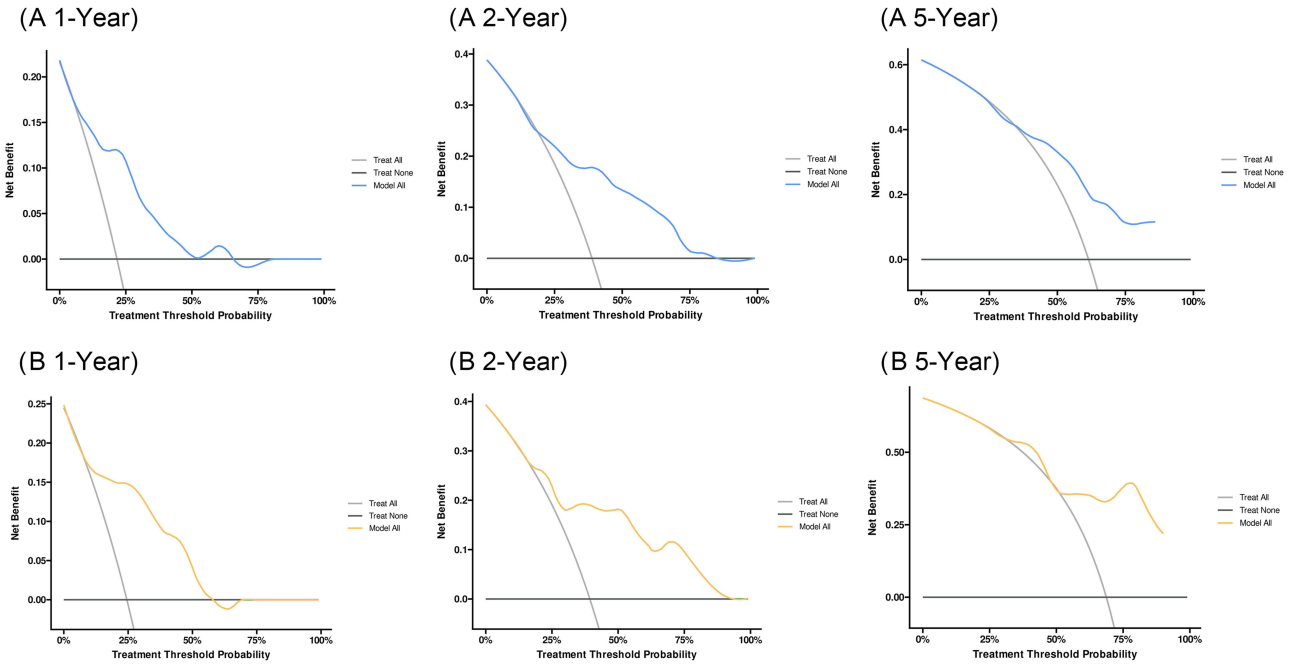

Figure 9 Decision curve analysis evaluating the clinical utility of the nomogram for predicting 1-, 2-, and 5-year recurrence-free survival of HCC patients in the (**A**) training and (**B**) validation sets.

prediction, including tumor burden (MVI and tumor diameter), hepatic function (serum ALT levels and cirrhosis status), and patient demographics (age).

The impact of age on early recurrence after curative resection of HCC remains controversial. In our study, patients aged ≥48 years exhibited a non-significant trend toward a protective effect against early recurrence. The linear prediction model identified age as a significant predictor, with advanced age correlating with lower predicted scores, suggesting an improved prognosis.[30] Previous studies have reported that younger patients are more likely to experience early recurrence after curative HCC surgery, potentially due to tumor biological characteristics such as higher AFP levels, larger tumor size, and a higher incidence of MVI.[31,32] Additionally, a more active immune system in younger individuals may facilitate rapid tumor cell proliferation and recurrence following surgical intervention.[33] Conversely, some studies have reported that older patients face a higher risk of recurrence after HCC surgery. This may be attributed to poorer liver function, more advanced liver fibrosis, and reduced postoperative recovery capacity, all of which increase the likelihood of recurrence.[34,35] Additionally, elderly patients may have more comorbidities, such as chronic liver disease or metabolic disorders, which can further impact postoperative recurrence and survival rates.[36] Thus, the influence of age on early HCC recurrence is complex, acting as both a protective and a risk factor, it needs further study.

Numerous studies have explored the relationship between tumor-related pathological factors and the risk of early recurrence following curative resection of HCC.[6,25,37] Among these factors, tumor size has been identified as a key contributor to intrahepatic recurrence. A meta-analysis by Zhong et al[38] demonstrated that tumors exceeding 5 cm significantly increase the risk of early recurrence within two years post-resection. Similarly, a retrospective study by Sumie et al[39] found that a tumor diameter greater than 5 cm serves as an independent risk factor for early recurrence within one year after curative liver resection. Other studies suggest that tumor size correlates more closely with the risks of vascular invasion and dissemination, with recurrence risk increasing proportionally with tumor diameter rather than being defined by a strict threshold.[26,40] These findings underscore the complex relationship between tumor size and early HCC recurrence following surgery. In our study, tumor diameter was a significant predictor of early recurrence within two years post-resection. Specifically, each 1 cm increase in tumor diameter was associated with a 12% increase in the hazard ratio for early recurrence, supporting previous research findings.

The International Liver Cancer Association identifies cirrhosis as the sole risk factor for recurrence in HCC patients who survive beyond two years post-surgery.[25] The observed hazard ratio in this study suggests a 64% higher recurrence

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risk in cirrhotic patients compared to non-cirrhotic patients. However, the difference was not statistically significant, which may be attributed to factors such as sample size (115 cirrhotic vs 29 non-cirrhotic patients) or follow-up duration. Additionally, elevated serum ALT levels (≥37 U/L) were observed to be significantly associated with a higher recurrence risk. Since elevated serum ALT often indicates ongoing liver damage,[41] this finding may indirectly support the role of cirrhosis and chronic liver inflammation in HCC recurrence. The identical hazard ratios for cirrhosis and elevated serum ALT (both 1.64) suggest a potential combined effect in promoting HCC recurrence. Based on these findings, we recommend intensified postoperative surveillance for patients with elevated preoperative serum ALT levels or liver cirrhosis. We also recommend liver-protective and antiviral treatments after surgery to slow cirrhosis progression.

Our results indicated that MVI was a significant predictor of early recurrence in patients with HCC following hepatic resection. MVI-positive patients had a 2.82-fold increased risk of early postoperative recurrence. This finding confirms previous studies, highlighting MVI as a key factor in early recurrence after liver resection.[6,7,24,29,42] Although MVI can only be definitively diagnosed through postoperative histological examination, its role as a prognostic indicator is well-supported. A multicenter randomized controlled trial by Fan et al[3] demonstrated that combining sorafenib with TACE improved clinical outcomes compared to TACE alone in patients with recurrent intermediate-stage HCC and positive MVI, significantly enhancing survival rates. These findings underscore the necessity of personalized adjuvant treatment strategies, including tailored interventional approaches such as TACE and targeted therapies, for high-risk patients.

An important advantage of our study is combining Lasso regression with a nomogram to create a simple yet powerful prediction tool. The feature selection capability of Lasso enhances model accuracy while simplifying interpretability. However, this study had some limitations. The narrow scope of data collection limits the generalizability of our findings, necessitating validation across different patient groups and medical settings. Given the retrospective nature of our study, future prospective, multi-center, large-scale studies are crucial to further assess the model's predictive accuracy and clinical utility in different populations.

Conclusions

Age, serum ALT levels, cirrhosis, tumor diameter, and MVI were identified as independent risk factors for early HCC recurrence. This study developed a nomogram based on Lasso-Cox regression, providing clinicians with a simple and effective tool for assessing individual risk of post-hepatectomy recurrence. It may help identify high-risk patients who need close monitoring.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

This study was approved by the Ethics Committee of Taizhou Hospital, Zhejiang Province. As a retrospective study, patient consent was not required. All patient data were anonymized to maintain confidentiality. The study adhered to the principles of 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 declare no conflicts of interest.

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