



Retrospective Study

# Predictive model for non-malignant portal vein thrombosis associated with cirrhosis based on inflammatory biomarkers

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## Abstract

### BACKGROUND

Portal vein thrombosis (PVT), a complication of liver cirrhosis, is a major public health concern. PVT prediction is the most effective method for PVT diagnosis and treatment.

### AIM

To develop and validate a nomogram and network calculator based on clinical indicators to predict PVT in patients with cirrhosis.

### METHODS

Patients with cirrhosis hospitalized between January 2016 and December 2021 at the First Hospital of Lanzhou University were screened and 643 patients with cirrhosis who met the eligibility criteria were retrieved. Following a 1:1 propensity score matching 572 patients with cirrhosis were screened, and relevant clinical data were collected. PVT risk factors were identified using the least absolute shrinkage and selection operator (LASSO) and multivariate logistic regression analysis. Variance inflation factors and correlation matrix plots were used to analyze multicollinearity among the variables. A nomogram was constructed to predict the probability of PVT based on independent risk factors for PVT, and its predictive performance was verified using a receiver operating characteristic curve (ROC), calibration curves, and decision curve analysis (DCA). Finally, a network calculator was constructed based on the nomograms.

### RESULTS

This study enrolled 286 cirrhosis patients with PVT and 286 without PVT. LASSO analysis revealed 13 variables as strongly associated with PVT occurrence. Multivariate logistic regression analysis revealed nine indicators as independent

PVT risk factors, including etiology, ascites, gastroesophageal varices, platelet count, D-dimer, portal vein diameter, portal vein velocity, aspartate transaminase to neutrophil ratio index, and platelet-to-lymphocyte ratio. LASSO and correlation matrix plot results revealed no significant multicollinearity or correlation among the variables. A nomogram was constructed based on the screened independent risk factors. The nomogram had excellent predictive performance, with an area under the ROC curve of 0.821 and 0.829 in the training and testing groups, respectively. Calibration curves and DCA revealed its good clinical performance. Finally, the optimal cutoff value for the total nomogram score was 0.513. The sensitivity and specificity of the optimal cutoff values were 0.822 and 0.706, respectively.

## CONCLUSION

A nomogram for predicting PVT occurrence was successfully developed and validated, and a network calculator was constructed. This can enable clinicians to rapidly and easily identify high PVT risk groups.

**Key Words:** Portal vein thrombosis; Liver cirrhosis; Nomogram; Inflammatory markers; Aspartate aminotransferase to neutrophil ratio index; Platelet-to-lymphocyte ratio

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**Core Tip:** A nomogram to predict the probability of portal vein thrombosis (PVT) occurrence was successfully developed and validated and further constructed a network calculator. This can help clinicians to quickly and easily identify people at high risk for PVT in cirrhosis and early prevention.

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## INTRODUCTION

The incidence of non-malignant portal vein thrombosis (PVT) in patients with liver cirrhosis is approximately 5%-20% [1] which is more than seven times higher than that in the general population [2]. With the development of liver disease, the incidence of PVT increased gradually. The incidence of PVT in patients with compensated liver cirrhosis is 0.6%-16%, and that in patients with chronic end-stage liver disease is 8%-25% [3,4]. PVT in cirrhosis is gradually being recognized as a complication of cirrhosis and is receiving increasing attention.

PVT is usually asymptomatic in patients with cirrhosis and detected only during incidental imaging studies. In contrast, PVT formation can be complicated by elevated portal vein pressure and increased risk of rupture of esophago-gastric fundic varices, ascites, and mesenteric and intestinal stasis [5,6]. Therefore, there is an urgent need for an early diagnosis of PVT development for early detection and treatment, thereby improving the prognosis of patients with cirrhosis.

In previous studies, inflammatory markers such as the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been reported to correlate with thrombus formation [7-9]. In addition, the gamma-glutamyl transpeptidase to lymphocyte count ratio (GLR) [10,11], prognostic nutritional index (PNI) [12], aspartate transaminase (AST) to neutrophil ratio index (ANRI) [13], albumin-bilirubin grading (ALBI) [14] and AST to lymphocyte ratio index (ALRI) [15] are receiving increasing attention in the diagnosis and prognosis of the disease.

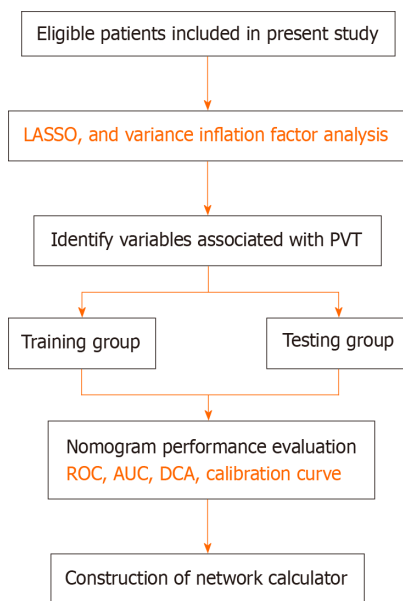
Nomograms are graphical tools that visualize complex clinical metrics to aid clinicians in making medical decisions [16]. Currently nomogram are widely used in the diagnosis and prognosis of various diseases [17,18]. The aim of this study was to investigate the risk factors associated with the development of PVT in the natural course of cirrhosis, rather than in cirrhotic patients with invasive manipulation. To construct and validate a practical nomogram and network calculator for predicting the occurrence of PVT based on screened inflammatory markers and related indicators to help clinicians identify patients at risk of PVT at an early stage, thereby enabling early intervention and improving the prognosis of patients with PVT in cirrhosis.

## MATERIALS AND METHODS

### Study population

Patients with cirrhosis were hospitalized between January 2016 and December 2021 at the First Hospital of Lanzhou University. A total of 572 patients with liver cirrhosis were included in this study. The specific screening process is shown

in Figure 1. The diagnosis of liver cirrhosis is based on pathological biopsy (not applicable to those with intractable ascites and coagulation dysfunction), imaging, clinical symptoms and signs, laboratory tests, medical history, and relevant complications (and consultation with relevant experts; indeterminate cases will be excluded). Diagnosis of PVT depends on the consensus regarding PVT in liver cirrhosis[1]. The following criteria were used to determine inclusion: (1) Age  $\geq 18$  and  $\leq 80$  years; (2) Patients with cirrhosis with complete clinical information confirmed by a combination of medical history, physical signs, laboratory tests, or liver pathology; (3) PVT was diagnostically confirmed based on one abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). Patients with hepatic and extrahepatic malignancies, liver transplantation, splenectomy and periesophagogastric devascularization, transjugular intrahepatic portosystem stent-shunt, Budd-Chiari syndrome, noncirrhotic PVT, those requiring anticoagulation, and other severe diseases. All relevant clinical and laboratory data were collected at our hospital, and all serum indicators were collected at the time of the first diagnosis of PVT.



**Figure 1 The flowchart of present study.** LASSO: Least absolute shrinkage and selection operator; PVT: Portal vein thrombosis; ROC: Receiver operating characteristic curve; DCA: Decision curve analysis.

### Clinical data collection

Data included demographic data, clinical laboratory test results, and ultrasonographic characteristics. Demographic data, including age, sex, and body mass index (BMI). Clinical laboratory tests included D-dimer (D-D), activated partial thromboplastin time (APTT), prothrombin activity (PTA), prothrombin time (PT), international normalized ratio (INR), prothrombin time (TT), AST, albumin (ALB), bilirubin, platelet count (PLT), white blood cell count, neutrophil count, lymphocyte count, monocyte count, ALBI, and Child-Turcotte-Pugh score. The ultrasonographic characteristics included portal vein diameter (PVD), splenic vein diameter (SVD), and portal vein velocity (PVV). The clinical characteristics included etiologies of liver disease, ascites, and gastroesophageal varices (GOV). Moreover, etiologies of cirrhosis include, autoimmune hepatitis, viral hepatitis and other. This study was approved by the Ethics Committee of the First Hospital of Lanzhou University (LDYYLL2021-286) and was conducted in accordance with the principles of the Declaration of Helsinki.

### Definitions

Inflammatory markers and associated scores were calculated as follows: SII, platelet count  $\times$  neutrophil count/lymphocyte count ( $\times 10^9/L$ ). The NLR was calculated as the neutrophil count/lymphocyte count. The GLR was calculated as the gamma-glutamyl transpeptidase/lymphocyte count ratio. The PLR was calculated by dividing the platelet count by the lymphocyte count. The PNI was calculated as follows: serum albumin (g/L)  $+ 5 \times$  total peripheral blood lymphocytes ( $\times 10^9/L$ ). The ANRI was calculated as the AST to neutrophil count ratio. ALRI was calculated as the AST-to-lymphocyte count. ALBI was calculated as  $(\log_{10} \text{bilirubin} \times 0.66) + (-0.085 \times \text{ALB})$ , and ALBI scores were classified into the following three levels:  $\leq -2.60$  (level 1),  $> -2.60$  and  $\leq -1.39$  (level 2),  $> -1.39$  (level 3).

### Predictor selection

All variables were included in least absolute shrinkage and selection operator (LASSO) regression analyses. As the penalty increased, the estimates of the weaker variables converged to zero. Eventually, screening yielded 13 variables. Further, multivariate logistic regression analysis was used to screen for nine independent risk factors associated with PVT. Variance inflation factors (VIF) and correlation matrix plots were used to examine multicollinearity and correlation

between variables.

### Statistical analysis

R software (version 4.1.2) was used for the statistical analysis. Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Quantitative variables are expressed as mean  $\pm$  SD, and significance was determined using Student's *t*-test. Sex, age, and BMI were matched between the groups using propensity score matching (PSM). The total population was divided into training and testing groups in a ratio of 7:3. The training and testing groups were used for model construction and validation, respectively. Multivariate logistic regression analysis was used to determine the independent risk factors of PVT, and the discriminatory ability of the nomogram was measured by calculating the area under the receiver operating characteristic (AUROC). Calibration curves[19], decision curves, and ROC curves were used to assess the clinical value of the nomogram. Statistical significance was defined as a *P*-value < 0.05 (both sides).

Statistical analysis was performed using the CreateTableOne function in the R software TableOne package. The Regplot package constructs a nomogram based on independent risk factors and the DynNom package constructs a network calculator. The pROC package was used to plot ROC curves, and AUROC was used to evaluate nomogram discrimination and compare the AUROC with the nomogram for different variables. Calibration curves were plotted using the rms package decision curve analysis (DCA) and the rmda package. The mctest package was used for VIF analysis, and the corrplot package was used for correlation row matrix plotting.

## RESULTS

### Demographic and clinical characteristics

After PSM (age, sex, and BMI), 286 patients with PVT and 286 without PVT were included in this study. The baseline characteristics of the enrolled patients are shown in Table 1. The laboratory test results, systemic inflammatory markers, and related indices of patients in the two groups are detailed in Table 2.

**Table 1** Baseline of demographics and clinical characteristics of the patients

| Characteristics          | non-PVT ( <i>n</i> = 286) | PVT ( <i>n</i> = 286) | <i>P</i> value |
|--------------------------|---------------------------|-----------------------|----------------|
| Age [mean (SD)]          | 52.60 (11.61)             | 52.87 (12.02)         | 0.783          |
| Sex, <i>n</i> (%)        |                           |                       |                |
| Male                     | 161 (56.30)               | 163 (57.00)           | 0.933          |
| Female                   | 125 (43.70)               | 123 (43.00)           |                |
| BMI [mean (SD)]          | 22.71 (3.28)              | 22.70 (3.02)          | 0.952          |
| Etiology, <i>n</i> (%)   |                           |                       |                |
| AIH                      | 40 (14.00)                | 20 (7.00)             | 0.001          |
| Hepatitis                | 200 (69.90)               | 189 (66.10)           |                |
| Others                   | 46 (16.10)                | 77 (26.90)            |                |
| Ascites, <i>n</i> (%)    |                           |                       |                |
| No                       | 154 (53.80)               | 60 (21.00)            | < 0.001        |
| Yes                      | 132 (46.20)               | 226 (79.00)           |                |
| GOV, <i>n</i> (%)        |                           |                       |                |
| No                       | 73 (25.50)                | 7 (2.40)              | < 0.001        |
| Yes                      | 213 (74.50)               | 279 (97.60)           |                |
| ALBI grade, <i>n</i> (%) |                           |                       |                |
| 1                        | 95 (33.20)                | 53 (18.50)            | < 0.001        |
| 2                        | 163 (57.00)               | 192 (67.10)           |                |
| 3                        | 28 (9.80)                 | 41 (14.30)            |                |
| CTP, <i>n</i> (%)        |                           |                       |                |
| A                        | 106 (37.10)               | 58 (20.30)            | < 0.001        |
| B                        | 136 (47.60)               | 145 (50.70)           |                |

|   |            |            |
|---|------------|------------|
| C | 44 (15.40) | 83 (29.00) |
|---|------------|------------|

PVT: Portal vein thrombosis; AIH: Autoimmune hepatitis; GOV: Gastroesophageal varices; ALBI: Albumin-bilirubin grading; CTP: Child-Turcotte-Pugh score.

**Table 2** Baseline information on laboratory tests and inflammatory markers

| Characteristics [mean (SD)] | non-PVT (n = 286) | PVT (n = 286)   | P value |
|-----------------------------|-------------------|-----------------|---------|
| PLT                         | 78.93 (48.65)     | 70.31 (60.19)   | 0.06    |
| ALB                         | 38.50 (6.87)      | 35.87 (6.21)    | < 0.001 |
| PT                          | 14.80 (3.52)      | 16.41 (6.53)    | < 0.001 |
| PTA                         | 71.29 (20.97)     | 63.24 (15.56)   | < 0.001 |
| INR                         | 1.30 (0.32)       | 1.42 (0.45)     | < 0.001 |
| D-D                         | 1.84 (2.75)       | 3.75 (5.42)     | < 0.001 |
| PVD                         | 12.86 (2.34)      | 14.89 (3.34)    | < 0.001 |
| SVD                         | 8.64 (2.90)       | 10.43 (3.50)    | < 0.001 |
| PVV                         | 21.08 (5.34)      | 19.86 (6.19)    | 0.012   |
| GLR                         | 102.36 (189.29)   | 78.97 (97.41)   | 0.064   |
| SII                         | 258.89 (285.64)   | 298.02 (473.51) | 0.232   |
| ANRI                        | 40.18 (70.91)     | 27.31 (46.83)   | 0.011   |
| PNI                         | 43.51 (7.67)      | 39.47 (6.60)    | < 0.001 |
| NLR                         | 3.42 (3.23)       | 4.04 (3.21)     | 0.022   |
| PLR                         | 92.75 (74.60)     | 110.43 (77.54)  | 0.006   |
| ALRI                        | 107.63 (256.37)   | 77.70 (66.09)   | 0.056   |

PLT: Platelet count; ALB: Albumin; PT: Prothrombin time; PTA: Prothrombin activity; INR: International normalized ratio; D-D: D-dimer; PVD: Portal vein diameter; SVD: Splenic vein diameter; PVV: Portal vein velocity; GLR: Gamma-glutamyl transpeptidase to lymphocyte count ratio; SII: Systemic immune-inflammation index; ANRI: Aspartate transaminase to neutrophil ratio index; PNI: Prognostic nutritional index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; ALRI: Aspartate transaminase to lymphocyte ratio index; PVT: Portal vein thrombosis.

### Predictor selection

All patients formed a cohort to explore the PVT-related risk factors. LASSO regression analysis was used to penalize the absolute values of the coefficients (Figure 2). The LASSO results showed that 13 variables were strongly associated with the occurrence of PVT (Supplementary Table 1). Based on the results of the multivariate logistic analysis, 9 variables were identified, including etiology, ascites, GOV, PLT, D-D, PVD, PVV, ANRI, and PLR. We also performed univariate logistic regression analyses of the 13 variables of interest for further comparison (Table 3). Furthermore, VIF and correlation matrix plots (Figure 3) revealed no significant multicollinearity between the variables. Subsequently, nine independent risk factors for PVT were included in the multivariate logistic regression model.

**Table 3** The results of univariate and multivariate analysis

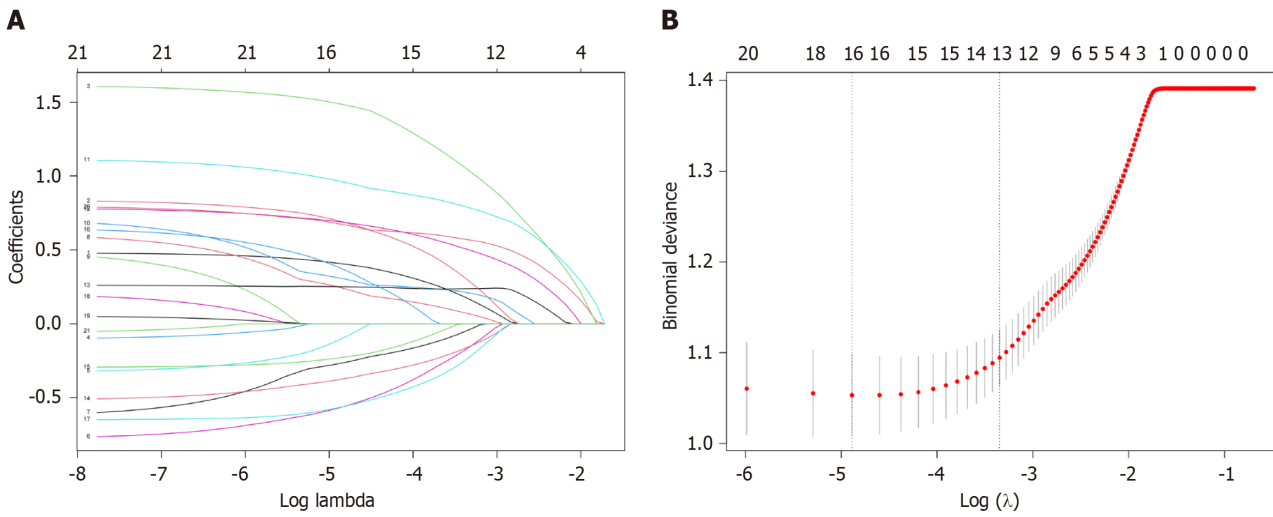
| Characteristics | Univariate analysis |             |         | Multivariate analysis |             |         |
|-----------------|---------------------|-------------|---------|-----------------------|-------------|---------|
|                 | OR                  | CI          | P value | OR                    | CI          | P value |
| Etiology        |                     |             |         |                       |             |         |
| AIH             | Reference           |             |         | Reference             |             |         |
| Hepatitis       | 1.890               | 1.066-3.350 | 0.029   | 1.772                 | 0.869-3.613 | 0.115   |
| Others          | 3.348               | 1.749-6.408 | 0.000   | 2.893                 | 1.309-6.395 | 0.009   |
| Ascites         |                     |             |         |                       |             |         |

|                           |           |              |       |           |              |       |
|---------------------------|-----------|--------------|-------|-----------|--------------|-------|
| No                        | Reference |              |       | Reference |              |       |
| Yes                       | 4.394     | 3.043-6.346  | 0.000 | 2.007     | 1.27-3.174   | 0.003 |
| GOV                       |           |              |       |           |              |       |
| No                        | Reference |              |       | Reference |              |       |
| Yes                       | 13.660    | 6.165-30.266 | 0.000 | 5.844     | 2.385-14.321 | 0.000 |
| ANRI                      |           |              |       |           |              |       |
| < 48                      | Reference |              |       | Reference |              |       |
| ≥ 48                      | 0.418     | 0.257-0.677  | 0.000 | 0.457     | 0.249-0.839  | 0.011 |
| INR                       |           |              |       |           |              |       |
| < 1.27                    | Reference |              |       | Reference |              |       |
| ≥ 1.27                    | 2.646     | 1.887-3.710  | 0.000 | 1.389     | 0.722-2.672  | 0.326 |
| PLR                       |           |              |       |           |              |       |
| ≤ 68.06                   | Reference |              |       | Reference |              |       |
| > 68.06                   | 1.846     | 1.305-2.610  | 0.001 | 2.308     | 1.474-3.615  | 0.000 |
| ALB, g/L                  |           |              |       |           |              |       |
| < 43                      | Reference |              |       | Reference |              |       |
| ≥ 43                      | 0.292     | 0.185-0.460  | 0.000 | 0.700     | 0.387-1.269  | 0.240 |
| D-D, µg/mL                |           |              |       |           |              |       |
| ≤ 2.52                    | Reference |              |       | Reference |              |       |
| > 2.52                    | 4.860     | 3.345-7.059  | 0.000 | 2.795     | 1.805-4.33   | 0.000 |
| PLT, × 10 <sup>9</sup> /L |           |              |       |           |              |       |
| < 85                      | Reference |              |       | Reference |              |       |
| ≥ 85                      | 0.420     | 0.286-0.615  | 0.000 | 0.520     | 0.306-0.884  | 0.016 |
| PT, s                     |           |              |       |           |              |       |
| < 14.4                    | Reference |              |       | Reference |              |       |
| ≥ 14.4                    | 2.458     | 1.755-3.442  | 0.000 | 1.279     | 0.67-2.441   | 0.456 |
| PVD, mm                   |           |              |       |           |              |       |
| < 14.5                    | Reference |              |       | Reference |              |       |
| ≥ 14.5                    | 3.613     | 2.509-5.202  | 0.000 | 2.110     | 1.345-3.31   | 0.001 |
| PVV, cm/s                 |           |              |       |           |              |       |
| < 20.05                   | Reference |              |       | Reference |              |       |
| ≥ 20.05                   | 0.515     | 0.369-0.718  | 0.000 | 0.640     | 0.424-0.965  | 0.033 |
| SVD, mm                   |           |              |       |           |              |       |
| < 8                       | Reference |              |       | Reference |              |       |
| ≥ 8                       | 3.680     | 2.511-5.394  | 0.000 | 1.281     | 0.772-2.128  | 0.338 |

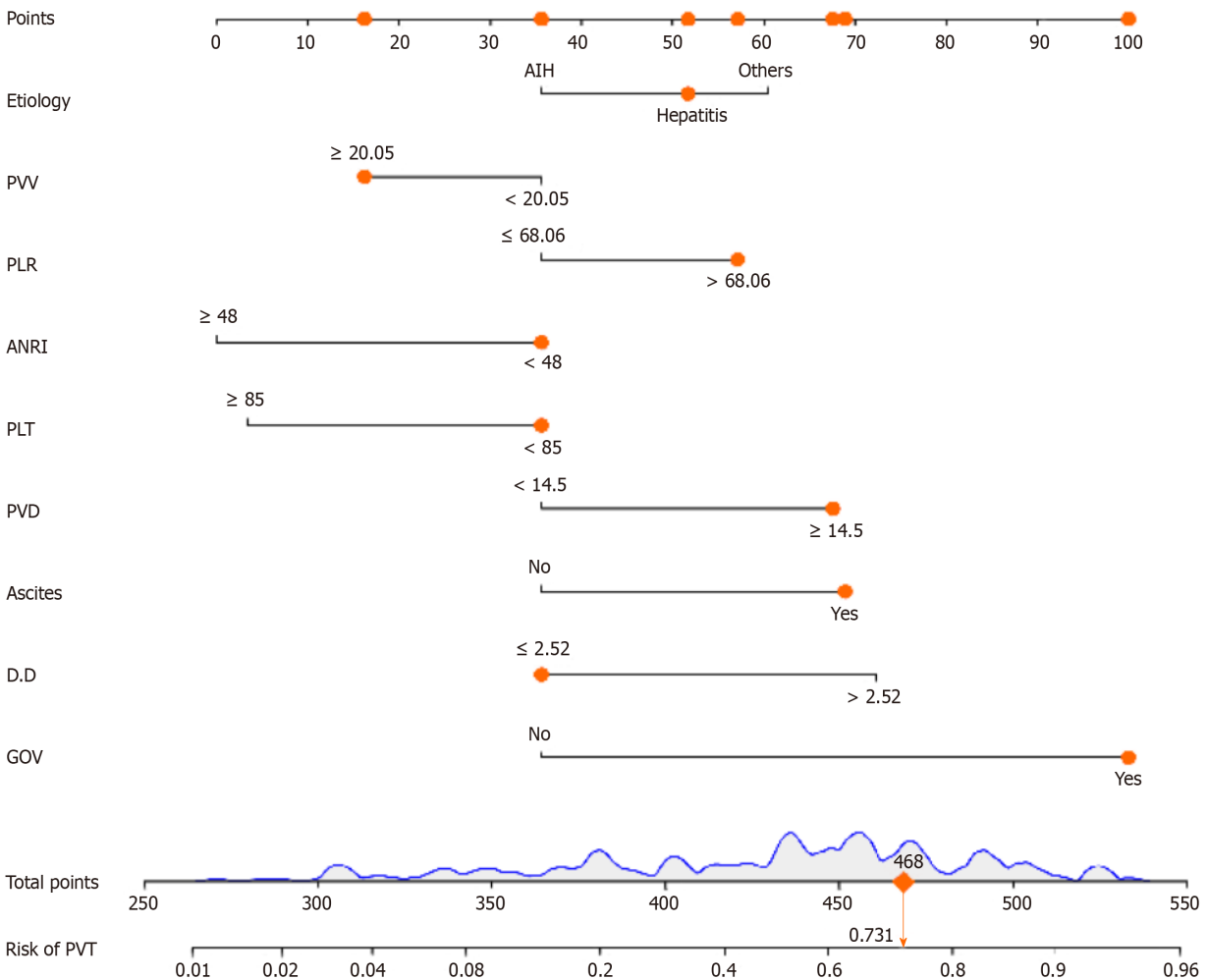
AIH: Autoimmune hepatitis; GOV: Gastroesophageal varices; ANRI: Aspartate transaminase to neutrophil ratio index; INR: International normalized ratio; PLR: Platelet-to-lymphocyte ratio; ALB: Albumin; D-D: D-dimer; PLT: Platelet count; PT: Prothrombin time; PVD: Portal vein diameter; PVV: Portal vein velocity; SVD: Splenic vein diameter.

### Cut-off values for continuous variables

Determine the optimal cut-off value of the continuity variable based on the ROC curve and the actual value of the laboratory test. The optimal cutoff values for PLT, D-D, PVV, PVD, ANRI, and PLR were 85, 2.52, 14.5, 20.05, 48, and 68.06, respectively.



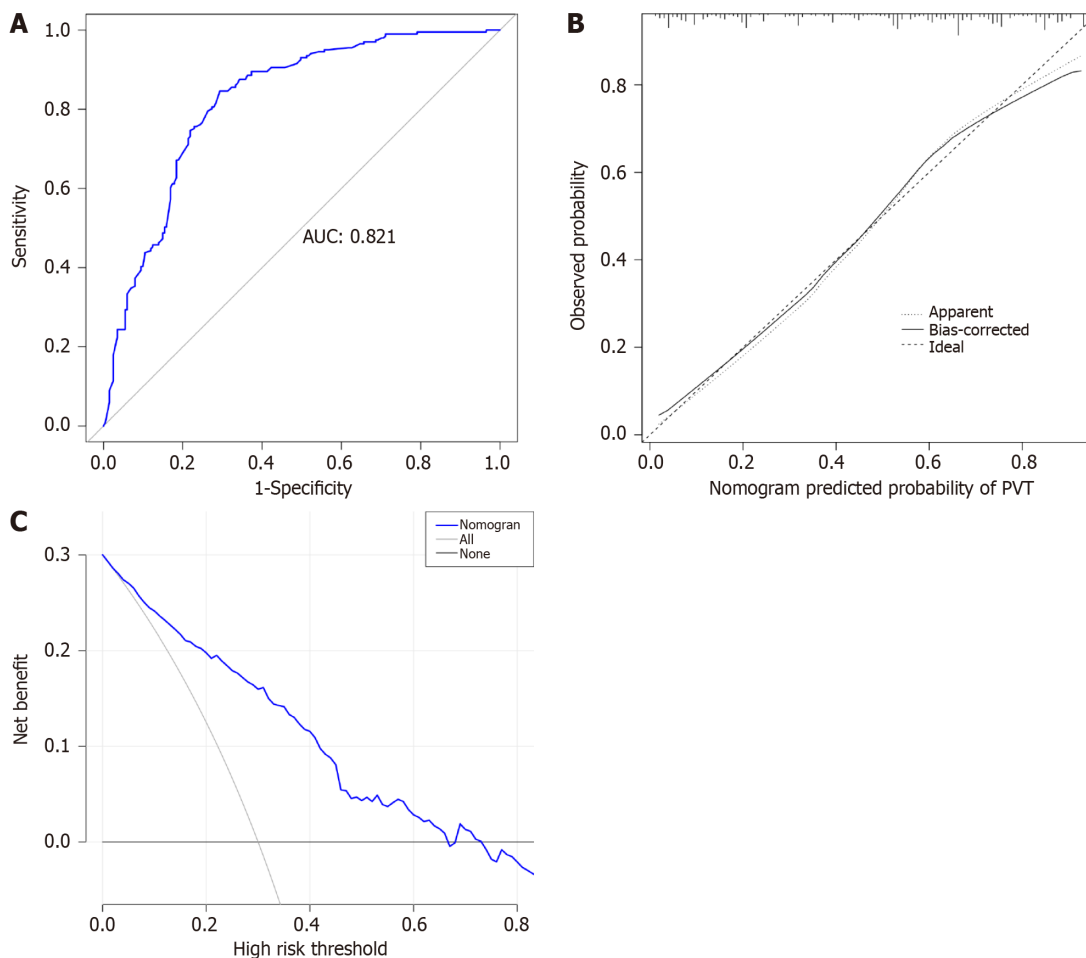
**Figure 2 Predictor selection for least absolute shrinkage and selection operator regression analysis.** A: Least absolute shrinkage and selection operator coefficient profiles of the 21 variables; B: The mean-squared error was plotted vs log lambda. The left vertical dotted line shows the optimal values with the fewest criteria, whereas the right vertical dotted line reflects the single standard error criterion.



**Figure 3 The predictive nomogram for portal vein thrombosis in patients with cirrhosis.** PVV: Portal vein velocity; PLR: Platelet-to-lymphocyte ratio; ANRI: Aspartate transaminase to neutrophil ratio index; PLT: Platelet count; PVD: Portal vein diameter; D-D: D-dimer; GOV: Gastroesophageal varices.

### Construction and validation of the predictive nomogram

The total population was divided into training ( $n = 402$ ) and testing ( $n = 170$ ) groups in a 7:3 ratio, and the baseline characteristics of the two groups are shown in Table 4. A nomogram was constructed based on the independent risk factors in the training group (Figure 4). The ROC curves of the training and testing groups were also plotted, and the AUROC of the nomogram was 0.821 and 0.829 for the training (Figure 5A) and testing groups (Figure 6A), respectively. To verify the calibration performance of the nomogram, calibration curves were plotted for the training (Figure 5B) and testing groups (Figure 6B). The calibration plot showed excellent predictive accuracy between the actual and predicted probabilities. To further evaluate the value of the model for clinical application, the DCA of the nomogram was plotted for the training group (Figure 5C) and testing groups (Figure 6C). The DCA results showed that the nomogram had good clinical application value. To further validate the discrimination of the nomogram, the ROC curve of each independent risk factor and nomogram was plotted for the training and testing groups (Figure 7). Finally, we constructed an online web calculator based on the nomogram ([https://glf1993823.shinyapps.io/PVT\\_DynNomapp/](https://glf1993823.shinyapps.io/PVT_DynNomapp/)). Figure 8 shows the application interface of the web calculator. Finally, the optimal cutoff value for the total nomogram score was 0.513. The sensitivity and specificity of the optimal cutoff values were 0.822 and 0.706, respectively (Supplementary Figure 1).



**Figure 4** The receiver operating characteristic curve (A), calibration curve (B), and decision curve analysis (C) for the training group. PVT: Portal vein thrombosis.

## DISCUSSION

The prevalence of PVT in patients awaiting liver transplantation ranges from 2% to 26% [20]. In contrast, prospective studies have shown that the incidence of PVT ranges from 1.6% to 8.4% [21,22]. Studies have shown that PVT is often associated with nonalcoholic steatohepatitis [23]. Therefore, the different incidences and prevalence of PVT may be associated with cirrhotic etiology. This may also be one reason for the large variation in the incidence of PVT in studies conducted in different countries. Similarly, a cirrhotic etiology was found to be an independent risk factor for PVT in the present study. Regarding clinical signs, patients with cirrhosis with PVT had more common ascites and GOV. On laboratory tests, patients with cirrhosis with PVT had higher D-D and lower ALB and PLT levels, while patients with cirrhosis with PVT had wider PVD and slower PVV. Regarding systemic inflammatory markers, patients with cirrhosis and PVT had higher NLR and PLR and lower ANRI levels.



Table 4 The baseline of training and testing groups, *n* (%)

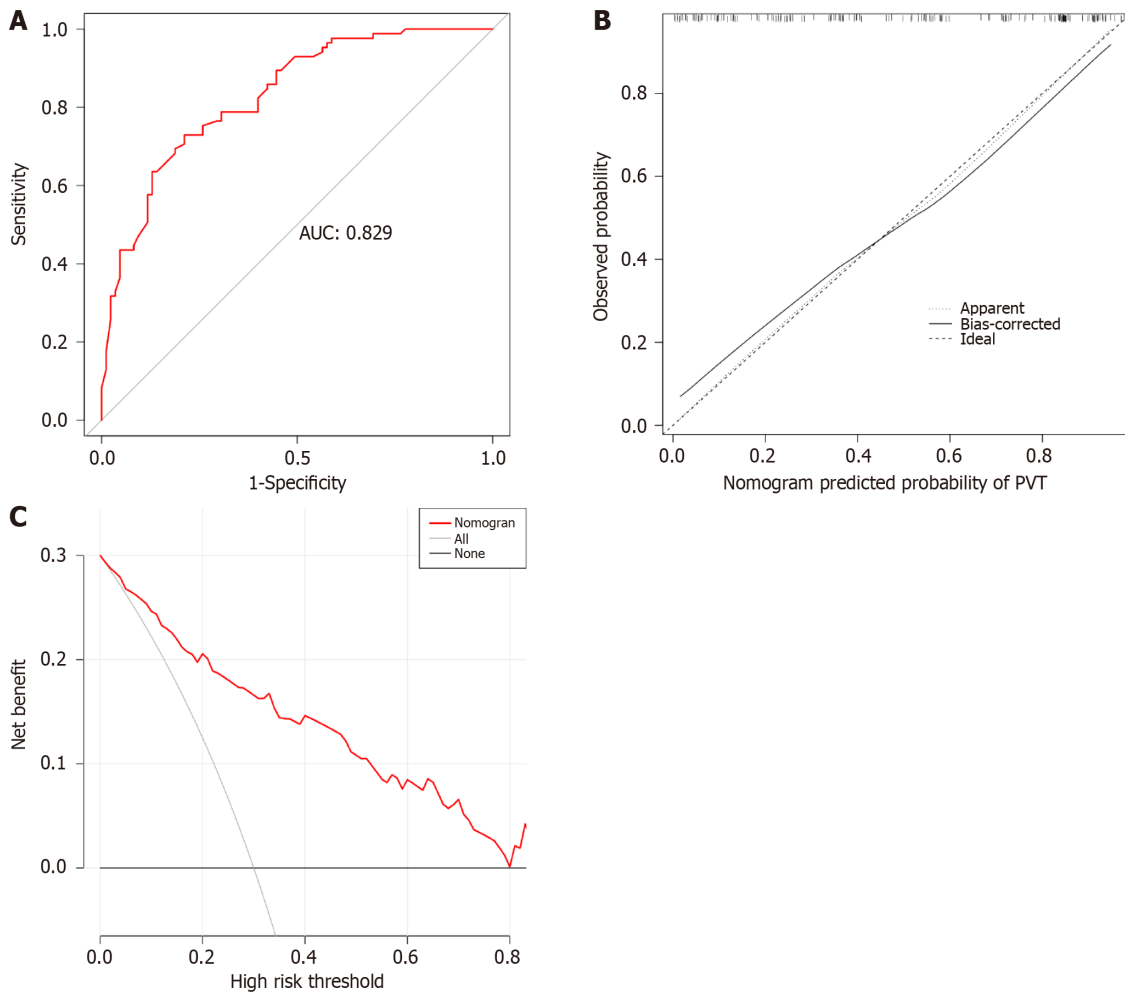
| Characteristics | Training group ( <i>n</i> = 402) | Testing group ( <i>n</i> = 170) | <i>P</i> value |
|-----------------|----------------------------------|---------------------------------|----------------|
| Etiology        |                                  |                                 |                |
| AIH             | 44 (10.90)                       | 16 (9.40)                       | 0.572          |
| Hepatitis       | 268 (66.70)                      | 121 (71.20)                     |                |
| Others          | 90 (22.40)                       | 33 (19.40)                      |                |
| Ascites         |                                  |                                 |                |
| No              | 138 (34.30)                      | 76 (44.70)                      | 0.024          |
| Yes             | 264 (65.70)                      | 94 (55.30)                      |                |
| GOV             |                                  |                                 |                |
| No              | 56 (13.90)                       | 24 (14.10)                      | 1.000          |
| Yes             | 346 (86.1)                       | 146 (85.90)                     |                |
| PLT             |                                  |                                 |                |
| < 85            | 287 (71.40)                      | 129 (75.90)                     | 0.318          |
| ≥ 85            | 115 (28.60)                      | 41 (24.10)                      |                |
| D-D             |                                  |                                 |                |
| ≤ 2.52          | 262 (65.20)                      | 99 (58.20)                      | 0.140          |
| >2.52           | 140 (34.80)                      | 71 (41.80)                      |                |
| PVD             |                                  |                                 |                |
| < 14.5          | 253 (62.90)                      | 114 (67.10)                     | 0.398          |
| ≥ 14.5          | 149 (37.10)                      | 56 (32.90)                      |                |
| PVV             |                                  |                                 |                |
| < 20.05         | 196 (48.80)                      | 89 (52.40)                      | 0.487          |
| ≥ 20.05         | 206 (51.20)                      | 81 (47.60)                      |                |
| ANRI            |                                  |                                 |                |
| < 48            | 344 (85.60)                      | 141 (82.90)                     | 0.501          |
| ≥ 48            | 58 (14.40)                       | 29 (17.10)                      |                |
| PLR             |                                  |                                 |                |
| ≤ 68.06         | 148 (36.80)                      | 58 (34.10)                      | 0.604          |
| > 68.06         | 254 (63.20)                      | 112 (65.90)                     |                |

AIH: Autoimmune hepatitis; GOV: Gastroesophageal varices; PLT: Platelet count; D-D: D-dimer; PVD: Portal vein diameter; PVV: Portal vein velocity; ANRI: Aspartate transaminase to neutrophil ratio index; PLR: Platelet-to-lymphocyte ratio.

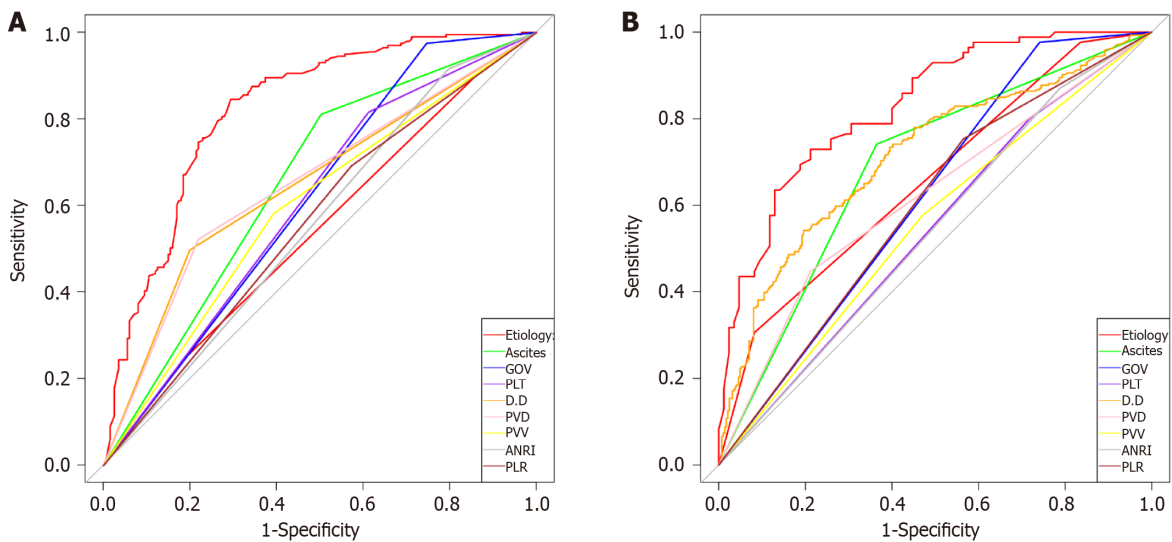
The mechanisms underlying the development of PVT are still being investigated and may be related to a hypercoagulable state, platelet activation, endothelial cell injury, or hemodynamic changes[24,25]. SVD, PVD, PLT, PVV, GOV, D-D, ALB, and ascites have all been reported as independent risk factors of PVT[26-29]. In the present study, PVV, PVD, GOV, D-D, PLT, and ascites were found to be independent risk predictors of PVT.

The diagnosis of portal vein thrombosis associated are still facing great challenges in the process of liver cirrhosis. Early diagnosis and intervention of portal vein thrombosis are of great significance to patient prognosis. Systemic inflammatory markers and clinical indices are closely associated with disease diagnosis and prognosis. In this study, we explored the correlation between systemic inflammatory markers, clinical indices, and PVT. Compared to other PVT prognostic models[30,31], PLR was also found to be an independent risk factor for PVT in present study. The model in this study used clinical indicators and indices as predictors; the indicators were easy to calculate, and the nomogram was more convenient for clinicians to apply.

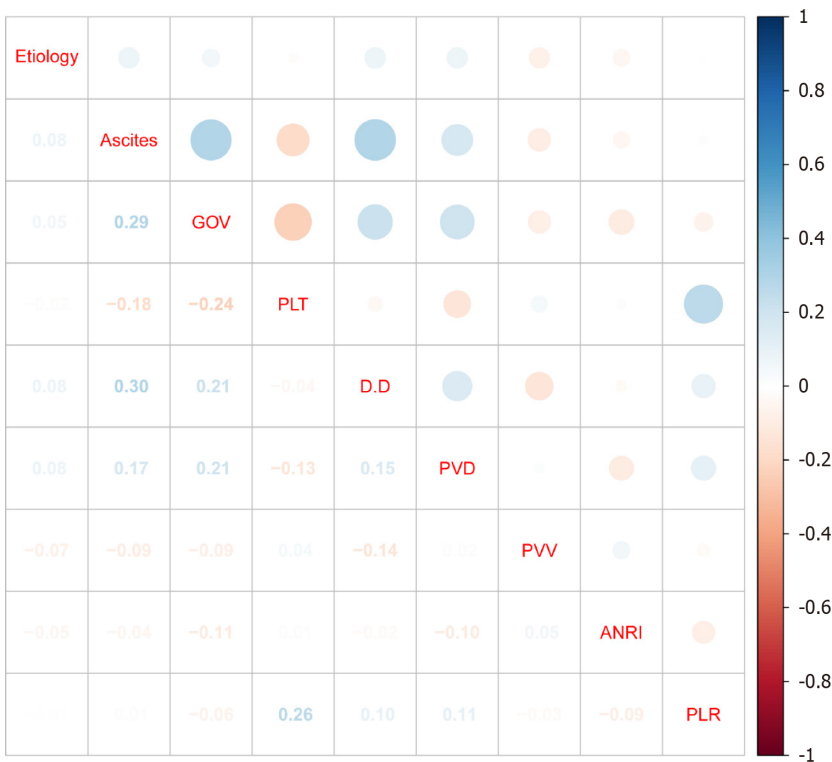
The AST is a routine test for patients with cirrhosis. It is commonly used to assess the severity of liver diseases[32]. Recently, studies have reported that prognostic indices based on inflammatory cells such as neutrophils and lymphocytes can reflect the survival of various malignancies, and ANRI is a commonly used index[33,34]. Interestingly, ANRI was found to be an independent risk factor for PVT in this study.



**Figure 5** The receiver operating characteristic curve (A), calibration curve (B), and decision curve analysis (C) for the testing group. PVT: Portal vein thrombosis.

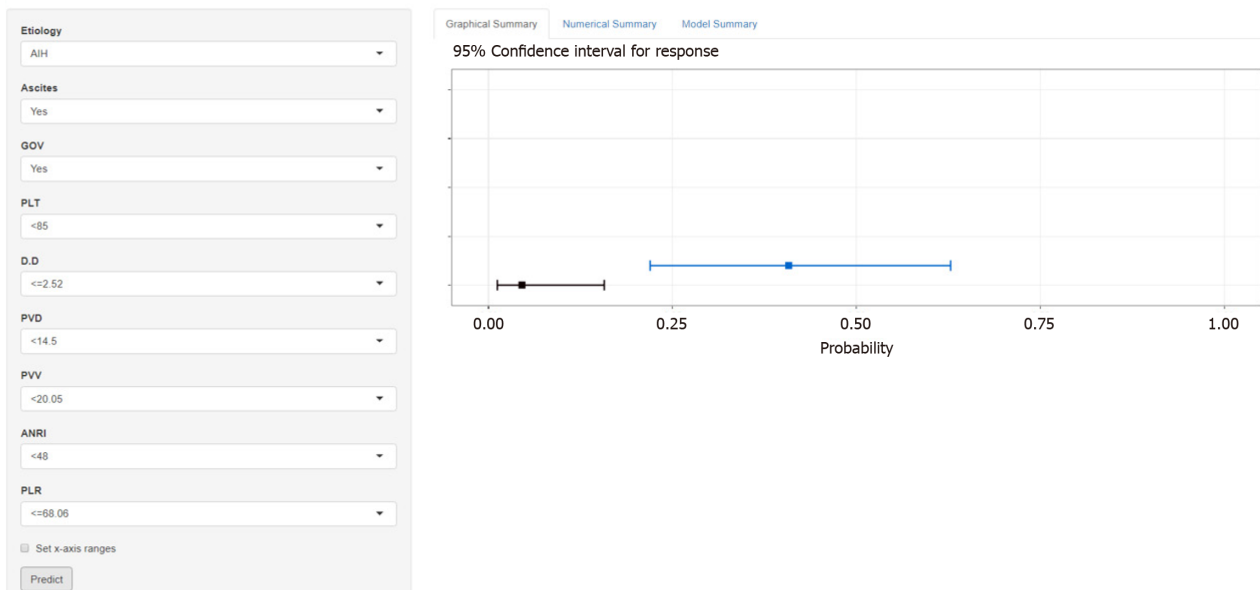


**Figure 6** Comparison of area under the receiver operating characteristic between the nomogram and all independent risk factors in the training group (A) and testing group (B). PVV: Portal vein velocity; PLR: Platelet-to-lymphocyte ratio; ANRI: Aspartate transaminase to neutrophil ratio index; PLT: Platelet count; PVD: Portal vein diameter; D-D: D-dimer; GOV: Gastroesophageal varices.



**Figure 7 Correlation matrix plot for independent risk factors.** PVV: Portal vein velocity; PLR: Platelet-to-lymphocyte ratio; ANRI: Aspartate transaminase to neutrophil ratio index; PLT: Platelet count; PVD: Portal vein diameter; D-D: D-dimer; GOV: Gastroesophageal varices.

Dynamic nomogram



**Figure 8 The interface for network calculator.** PVV: Portal vein velocity; PLR: Platelet-to-lymphocyte ratio; ANRI: Aspartate transaminase to neutrophil ratio index; PLT: Platelet count; PVD: Portal vein diameter; D-D: D-dimer; GOV: Gastroesophageal varices.

Relevant studies on the novel markers of PVT have also been reported. A disintegrin and metalloprotease with thrombospondin 1 repeats Nr.13 (ADAMTS-13), is expected to be the most promising marker of PVT. ADAMTS-13 activity is inversely correlated with PVT, and is independently associated with PVT in patients with cirrhosis[35]. A recent prospective study showed that an ADAMTS-13/VWF ratio < 0.4 in patients with compensated cirrhosis could be a reliable biomarker for predicting the development of PVT[36]. The intestinal flora is also closely related to the formation of thrombosis[37]. And the portal vein is a bridge between the intestines and liver. The intestinal flora and related metabolites may also be essential for portal vein formation. However, further research is needed on the value of these indicators in PVT. With continuous research and the application of new biotechnologies, an increasing number of novel markers will be discovered, which will be helpful in diagnosing PVT.

The present study had several strengths and limitations. The sample size included in this study is one of the strengths of this study. However, this was a retrospective, single-center study, and only patients with cirrhosis who developed PVT during the natural course of cirrhosis were included. Therefore, a large multicenter study is needed to obtain a more representative sample and a higher statistical efficacy of the results.

## CONCLUSION

A nomogram for predicting PVT in a cirrhotic population was successfully constructed and validated based on etiology, PLT, ANRI, ascites, GOV, D-D, PVD, PLR, and PVV. Meanwhile, a more intuitive and easy-to-use web calculator for clinical decision-makers was constructed based on the nomogram. The model will help identify people at a high risk of PVT in cirrhosis, which is expected to enable early intervention and improve patient prognosis.

## ARTICLE HIGHLIGHTS

### Research background

Portal vein thrombosis (PVT) is one of the complications of cirrhosis and one of the major public health concerns. PVT is found incidentally during the natural course of cirrhotic patients, and the formation of PVT is closely related to patient prognosis.

### Research motivation

The identification of people at high risk for PVT is crucial for the prevention and treatment of PVT, therefore, it is necessary to develop an early prediction model of the probability of developing PVT in cirrhotic patients to guide clinical decision-making.

### Research objectives

Development and validation of a nomogram and network calculator based on clinical blood inflammation markers for early identification of people at high risk of PVT.

### Research methods

By 1:1 propensity score matching, 572 eligible patients with cirrhosis were screened and their relevant clinical data were collected. Risk factors associated with the development of PVT were identified using the least absolute shrinkage and selection operator and multivariate logistic regression analysis. Variance inflation factor and correlation matrix plots tested for multicollinearity between variables. Finally, nomograms and network calculators predicting the risk of PVT occurrence were constructed and validated based on the independent risk factors for PVT.

### Research results

A total of 572 patients with cirrhosis were included in this study. The final nine parameters identified as independent risk factors for PVT in cirrhosis were etiology, ascites, gastroesophageal varices (GOV), platelet count (PLT), D-dimer (D-D), portal vein diameter (PVD), portal vein velocity (PVV), aspartate aminotransferase-to-neutrophil ratio index (ANRI), and platelet-to-lymphocyte ratio (PLR). The area under the receiver operating characteristic of the constructed nomogram was 0.821 and 0.829 in the training and test groups, respectively. The calibration curves and DCA showed good clinical performance. Finally, the best threshold for the total score of the nomogram was 0.513. The sensitivity and specificity of the best threshold were 0.822 and 0.706, respectively.

### Research conclusions

Etiology, ascites, GOV, PLT, D-D, PVD, PVV, ANRI, and PLR were the independent risk factors for PVT in cirrhosis. The constructed nomogram had its excellent clinical performance.

### Research perspectives

In this article, we constructed a prediction model about the risk of developing PVT in the natural course of cirrhosis, and also confirmed that inflammatory markers have a good application value in the diagnosis of PVT. A convenient web-based calculator was also constructed to enable the assessment of the risk of developing PVT in patients with cirrhosis.

## FOOTNOTES

**Author contributions:** Nie GL and Zhang HL wrote the first draft of the manuscript; Li Y and Yan J established inclusion and exclusion criteria; Xie DN and Zhu XW conducted literature searches; GL N and Zhang HL performed the data analysis and drew tables and pictures; Li Y, Yan J, and Li X reviewed and provided feedback on various drafts of the manuscript and approved the final manuscript.

**Institutional review board statement:** This study was approved by the Ethics Committee of the First Hospital of Lanzhou University

(LDYYLL2021-286) and was conducted in accordance with the principles of the Declaration of Helsinki.

**Informed consent statement:** As the study was a retrospective study, the extracted clinical data and laboratory tests were from the electronic case retrieval system of the First Hospital of Lanzhou University. The study was approved by the Ethics Committee of the First Hospital of Lanzhou University (LDYYLL2021-286). The data are a non-anonymous, and the requirement for informed consent was therefore waived.

**Conflict-of-interest statement:** The authors reported no financial interests or potential conflicts of interest.

**Data sharing statement:** Data supporting the findings of this study are available from the author upon request.

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