

Construction of Risk Prediction Model for Lower Extremity Deep Vein Thrombosis in Patients with Decompensated Cirrhosis

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Abstract: *Objective:* To develop a prediction model for the risk of lower extremity deep venous thrombosis (DVT) in patients with decompensated liver cirrhosis. *Methods:* A retrospective study was conducted on 236 inpatients with decompensated cirrhosis who were admitted to the Department of Infectious Diseases of a tertiary grade A comprehensive hospital in Wenzhou from January 2018 to December 2021. A risk prediction model was established by univariate analysis and binary logistic regression, and the effectiveness of the model was verified by the area under the ROC curve. *Results:* The DVT risk prediction model of patients with decompensated liver cirrhosis included 5 predictors: age (OR= 4.377), BI score (OR= 0.946), bedridden time (OR=5.229), CRP value (OR=1.021) and D-dimer concentration (OR=1.216). Model formula: $Z=1.227+1.476\times \text{age}-0.056\times \text{BI score}+1.654\times \text{bedridden time}+0.020\times \text{CRP}+0.196\times \text{D-dimer}$. The AUC is 0.921, the sensitivity is 0.797, the specificity is 0.949, and the Youden index is 0.746. Validation with 57 cases showed that the AUC is 0.866, the sensitivity is 0.807, the specificity is 0.842, and the accuracy rate is 81.58%, indicating satisfactory prediction effects. *Conclusion:* The risk assessment model constructed in this study shows good predictive performance, which can provide reference for clinical medical staff to assess the risk of DVT in patients with decompensated liver cirrhosis.

Keywords: Liver Cirrhosis, Deep Venous Thrombosis, Risk Factors, Prediction Model

1. Introduction

Liver cirrhosis is traditionally regarded as an acquired bleeding disorder, due to abnormal coagulation function and decreased platelet synthesis [1]. However, in recent years, with the concept [2, 3] of "hemostatic rebalance", added studies [4] have suggested that patients with liver cirrhosis have a high risk of both bleeding and venous thromboembolism (VTE). Studies [3] have shown that VTE occurs in about 1% of hospitalized patients with liver diseases, and the prevalence of DVT is 0.7%. Likewise, a study by Lesmana et al. showed [5] that the prevalence of DVT in patients with cirrhosis was as high as 4.7%. It is not uncommon for patients with cirrhosis to develop DVT and

carry a higher risk. Due to the early clinical symptoms of patients with liver cirrhosis are often lack of specificity, most of them have entered the decompensated period when they visit the hospital [6]. By consulting the relevant literature databases such as CNKI, Wanfang, VIP and NCBI, the current research on VTE in liver cirrhosis in China mainly focuses on portal vein thrombosis (PVT), while less attention is paid to the research reports on the formation of DVT in liver cirrhosis. This study aims to explore the risk factors of decompensated liver cirrhosis complicated with DVT, and to construct a risk prediction model, aiming to provide medical staff with convenient and effective risk assessment tools for DVT.

2. Objects and Methods

2.1. Study Subjects

This study is a retrospective analysis of medical records. From January 2018 to December 2021, patients with decompensated cirrhosis in the Department of Infectious Diseases of a tertiary grade A comprehensive hospital in Wenzhou were selected. The inclusion criteria for this study were as follows: (1) In accordance with the diagnosis of decompensated cirrhosis in the "Guidelines for the diagnosis and Treatment of liver cirrhosis" [7]; (2) The diagnosis of DVT was in accordance with the guidelines for the diagnosis and treatment of deep vein thrombosis by the Branch of Vascular Surgery, Surgery Society of Chinese Medical Association (third edition) [8]; (3) age ≥ 18 years old. Exclusion criteria were: 1) Critically ill patients with unstable vital signs; 2) patients diagnosed with VTE or superficial vein thrombosis on admission; 3) using warfarin, nadroparin, rivaroxaban and other anticoagulant drugs. Excluding 22 patients who did not meet the inclusion and exclusion criteria, 118 patients with decompensated liver cirrhosis complicated with DVT were finally enrolled as the DVT group. At the same time, 118 patients with decompensated liver cirrhosis who were admitted in the same year and had the same main diagnosis without DVT were randomly selected as the non-DVT group.

A total of 57 patients with DVT during hospitalization in the department from January to December 2022 were selected as the external validation sample of the model, and the inclusion and exclusion criteria were the same as above. The control group selected non-DVT patients admitted in the same year and with the same main diagnosis according to the same proportion. This study was approved by the Ethics Committee of our hospital, and the approval number was Clinical Research Ethics (2022) No. R122.

2.2. Survey Tools

2.2.1. General Data Collection Form

The general information questionnaire was designed by the researchers by referring to the relevant literature and combining with the consultation of clinical experts. The form included the following information: (1) Basic information: gender, age, etiology of cirrhosis, length of hospital stay, history of deep vein catheterization, bedridden time, BMI, BI score; (2) Disease-related information: medical history (history of alcohol consumption, smoking, diabetes, hypertension, venous embolism, and malignant tumor); Complications (ascites, lower extremity edema); (3)

Laboratory test results: complete blood count/coagulation, liver function, biochemical and other laboratory indicators; (4) Results of imaging examination: ascites measured by B-ultrasound, DVT diagnosis, etc. Child-Pugh score [9] and MELD score [10] were calculated, and patient stratification was performed based on the scores.

2.2.2. Methods of Data Collection

Five trained personnel in the research group consulted the electronic medical record system, collected the patients' medical records, and reviewed the data. In case of discrepancies, the data were re-checked to ensure the accuracy and objectivity of the data.

2.3. Statistical Methods

SPSS26.0 software was used to analyze the data. $\bar{x} \pm s$ Normal distribution measurement data were described, and t-tests were used for comparison between groups. Non-normal distributed metric data were described using M(P25, P75), and the rank-sum test was used for comparison between groups. Count data were expressed as examples (%), and the chi-square test was used for comparison between groups. Logistic regression analysis was used to determine the independent risk factors and a predictive model was established. Hosmer-Lemeshow chi-square test was used to evaluate the fitting degree of the model. AUC was used to evaluate the predictive ability of the model, and the application efficacy of the model was tested by sensitivity, specificity and accuracy. A significance level of $P < 0.05$ was considered statistically significant for detecting differences.

3. Results

3.1. General Data on the Study Subjects

A total of 236 patients were enrolled, including 174 males (73.73%) and 62 females (26.27%), aged from 37 to 92 years. The median age was 68 (60, 77) years in the DVT group and 58 (51.75, 65.25) years in the non-DVT group. In the DVT group, there were 88 patients with both lower extremities DVT, 14 patients with left lower extremity DVT, 16 patients with right lower extremity DVT and 78 patients with PVT.

3.2. Univariate Analysis of Lower Limb DVT in Patients with Decompensated Liver Cirrhosis

According to the occurrence of DVT, the patients were divided into DVT group and Non DVT group. The related disease data of the two groups are compared in Table 1.

Table 1. Comparison of risk factors between the two groups.

Aspects	DVT group (n=118)	Non DVT group (n=118)	Test statistic	P value
Age [cases (percentage, %)]			30.451 ¹⁾	< 0.001
≥60 years old	88 (74.58)	46 (38.98)		
< 60 years old	30 (25.42)	72 (61.02)		
Gender [example (percentage, %)]			4.288 ¹⁾	0.038
male	80 (74.80)	94 (79.66)		
female	38 (32.20)	24 (20.34)		

Aspects	DVT group (n=118)	Non DVT group (n=118)	Test statistic	P value
Length of stay [d, M([P ₂₅ , P ₇₅)]	14 (10,25.25)	11.5 (8.00, 17.00)	3.276	0.001
BMI [example (percentage, %)]			1.372 ¹⁾	0.241
≥24kg/m ²	28 (23.73)	36 (30.51)		
< 24kg/m	90 (76.27)	82 (69.49)		
BI score [score, M([P ₂₅ , P ₇₅)]	65.00 (45.00,90.00)	100.00 (90.00, 100.00)	9.028	< 0.001
Time in bed [cases (%,%)]			56.5931)	< 0.001
≥3 days	107 (90.68)	53 (44.92)		
< 3 days	11 (9.32)	65 (55.08)		
CRP [mg/L, M([P ₂₅ , P ₇₅)]	27.65 (8.56,48.75)	15.50 (5.00,21.43)	4.835	< 0.001
Hemoglobin (g/L, $\bar{x}\pm s$)	105.37 ±20.86	112.21 ±28.29	2.114	0.036
Platelet [$\times 10^9/L$, M([P ₂₅ , P ₇₅)]	106.00 (69.25,154.00)	98.00 (64.00,154.00)	0.769	0.442
Prothrombin time [s, M([P ₂₅ , P ₇₅)]	16.25 (14.90,19.35)	15.60 (14.40,18.10)	1.599	0.11
Fibrinogen [g/L, M([P ₂₅ , P ₇₅)]	2.26 (1.64,3.33)	2.65 (1.87,3.52)	1.875	0.061
Activated partial thromboplastin time [s, M([P ₂₅ , P ₇₅)]	43.55 (36.98,48.30)	41.70 (38.00,47.03)	0.362	0.717
International normalized ratio [M([P ₂₅ , P ₇₅)]	1.33 (1.17,1.62)	1.28 (1.12,1.54)	1.237	0.216
Total bilirubin [$\mu\text{mol/L}$, M([P ₂₅ , P ₇₅)]	43.00 (19.00,109.25)	27.00 (14.75,69.25)	2.19	0.028
Albumin (g/L, $\bar{x}\pm s$)	29.79 ±5.19	29.99 ±5.64	0.276	0.783
Alanine aminotransferase [U/L, M([P ₂₅ , P ₇₅)]	40.50 (20.00,69.25)	36.00 (20.75,64.00)	0.707	0.480
Aspartate aminotransferase [U/L, M([P ₂₅ , P ₇₅)]	57.00 (32.00,111.00)	66.50 (38.00,110.25)	0.542	0.588
Glucose [mmol/L, M([P ₂₅ , P ₇₅)]	7.20 (5.40,8.70)	6.55 (5.20,9.20)	0.577	0.564
Creatinine [$\mu\text{mol/L}$, M([P ₂₅ , P ₇₅)]	68.50 (55.75,95.25)	69.00 (56.75,88.50)	0.316	0.752
D-dimer concentration [$\mu\text{g/L}$, M([P ₂₅ , P ₇₅)]	5.47 (2.86,8.89)	1.55 (0.61,3.23)	7.585	< 0.001
MELD score [score, M([P ₂₅ , P ₇₅)]	11.50 (7.00,18.00)	9.00 (4.00,14.00)	2.881	0.004
MELD grade [cases (percentage, %)]			3.4591)	0.177
Low grouping	42 (35.59)	56 (47.46)		
Middle group	54 (45.76)	45 (38.14)		
High group	22 (18.64)	17 (14.41)		
CHILD score [score, M([P ₂₅ , P ₇₅)]	9.00 (8.00, 10.00)	8.00 (7.00,10.00)	2.436	0.015
CHILD grading [example (percentage, %)]			7.248 ¹⁾	0.027
Grade A	19 (16.10)	25 (21.19)		
B grade	45 (38.14)	59 (50.00)		
Grade C	54 (45.76)	34 (28.81)		
Lower extremity edema [cases (percentage, %)]			5.371 ¹⁾	0.020
There are	50 (42.37)	33 (27.97)		
There is no	68 (57.63)	85 (72.03)		
Degree of ascites [example (percentage, %)]			6.200 ¹⁾	0.102
Mild	20 (16.95)	23 (19.49)		
Moderate	32 (27.12)	31 (26.27)		
Severe	30 (25.42)	16 (13.56)		
Combined portal hypertension [cases (percentage, %)]			2.066 ¹⁾	0.151
There are	29 (24.58)	39 (33.05)		
There is no	89 (75.42)	79 (66.95)		
Esophageal varices [cases (percentage, %)]			0.664 ¹⁾	0.415
There are	21 (17.80)	26 (22.03)		
There is no	97 (82.20)	92 (77.97)		
History of diabetes [cases (percentage, %)]			6.2041 ¹⁾	0.013
There are	48 (40.68)	30 (25.42)		
There is no	70 (59.32)	88 (74.58)		
History of hypertension [percentage, %]			12.634 ¹⁾	< 0.001
There are	54 (45.76)	28 (23.73)		
There is no	64 (54.24)	90 (76.27)		
Smoking history [cases (percentage, %)]			12.378 ¹⁾	< 0.001
There are	70 (59.32)	43 (36.44)		
There is no	48 (40.68)	75 (63.56)		
Drinking history [example (percentage, %)]			4.561 ¹⁾	0.033
There are	54 (45.76)	38 (32.20)		
There is no	64 (54.24)	80 (67.80)		
History of malignant tumor [cases (percentage, %)]				
There are	40 (33.90)	24 (20.34)	5.488 ¹⁾	0.019
There is no	78 (66.10)	94 (79.66)		
History of venous embolism [cases (percentage, %)]			5.954 ¹⁾	0.015
There are	23 (19.49)	10 (8.47)		
There is no	95 (80.51)	108 (91.53)		
History of deep vein catheterization [percentage, %]			14.791 ¹⁾	< 0.001
There are	28 (23.73)	7 (5.93)		
There is no	90 (76.27)	111 (94.07)		

Notes: 1) χ^2 values; 2) t value; And 3) Z-score.

3.3. Multivariate Analysis of Factors Associated with Lower Extremity DVT in Patients with Decompensated Cirrhosis

Taking the occurrence of DVT as the dependent variable, the statistically significant items in the univariate analysis were included in the Logistic regression analysis as independent variables. The assignment is performed as follows. Child-Pugh grading, A=1, B=2, C=3; Gender: male=1, female=0; The risk factors such as age ≥ 60 years old, history of VTE, deep vein catheterization, lower extremity edema, hepatic encephalopathy, diabetes, hypertension, smoking, drinking, infection, and

malignant tumor were assigned as no = "0" and yes = "1". The remaining continuous variables were entered with original values. The results of the study showed that age ≥ 60 years, high D-dimer concentration, bed time ≥ 3 days, and high CRP level were risk factors for DVT in patients with decompensated cirrhosis (OR > 1 , $P < 0.05$), and high BI score was a protective factor (OR < 1 , $P < 0.05$), as shown in Table 2. The model formula was as follows: $Z = 1.227 + 1.476 \times \text{age} - 0.056 \times \text{BI score} - 1.654 \times \text{bedridden time} + 0.020 \times \text{CRP value} + 0.196 \times \text{D-dimer value}$. Furthermore, the obtained model was tested using the Hosmer-Lemeshow chi-square test with a result of 14.554 and a P-value of 0.068.

Table 2. Results of Logistic regression analysis of patients with lower extremity deep vein thrombosis.

Risk Factors	Partial regression coefficient	Standard error	Wald χ^2 values	P-value	OR value	95%CI
Constant	1.227	1.223	1.007	-	-	-
Age	1.476	0.413	12.778	< 0.001	4.377	1.948-9.834
BI score	0.056	0.012	21.487	< 0.001	0.946	0.924-0.968
Bedridden time	1.654	0.457	13.104	< 0.001	5.229	2.135-12.804
CRP	0.020	0.008	6.639	0.010	1.021	1.005-1.037
D-dimer	0.196	0.051	15.01	< 0.001	1.216	1.102-1.343

3.4. Validation of the Risk Prediction Model for Lower Extremity Deep Venous Thrombosis in Patients with Decompensated Cirrhosis

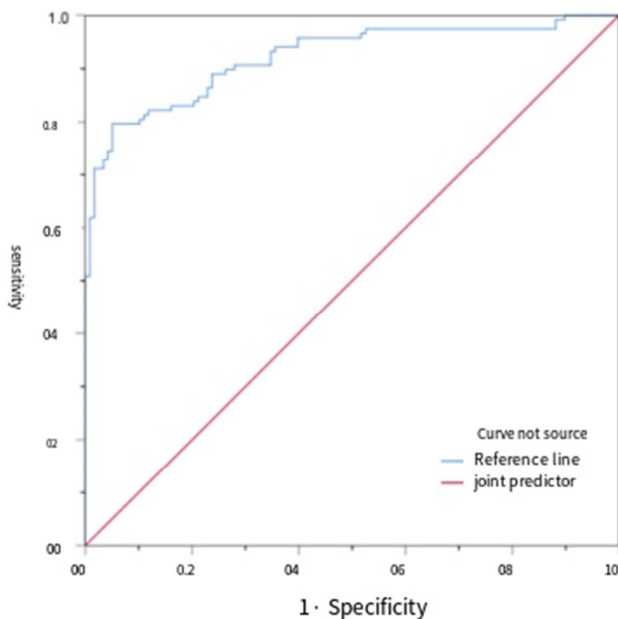


Figure 1. ROC curve of the risk prediction model for lower extremity deep venous thrombosis of patients in modeling group.

According to the risk assessment model, the joint prediction probability of DVT risk in patients with liver cirrhosis was calculated, and the ROC curve was drawn with the groups of modeling group and validation group as the state variables and the prediction probability as the test variable, as shown in Figure 1 and Figure 2. The results showed that the AUC of the modeling group was 0.921 (95%CI: 0.886-0.957), the sensitivity was 0.797, the specificity was 0.950, and the Youden index was 0.746. The best cut-off value of 0.655 was taken as

the risk threshold. It was suggested that the model score < 0.655 was the low risk group of DVT in patients with decompensated liver cirrhosis, and ≥ 0.655 was the high risk group. The AUC of the validation group was 0.866 (95%CI: 0.798-0.935), the discrimination sensitivity was 0.807, the specificity was 0.842, and the accuracy of the model was 81.58%.

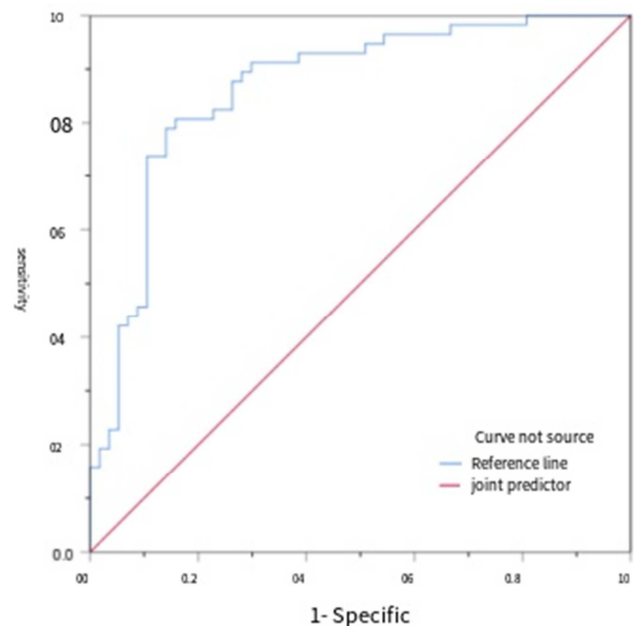


Figure 2. ROC curve of the risk prediction model for lower extremity deep venous thrombosis in the validation group.

4. Discussion

4.1. The Risk Prediction Model Constructed is Scientific and Practical

Clinical practice has proved that early implementation of

nursing and medical intervention measures can benefit patients with high risk of thrombosis. Deep venous thrombosis (DVT) is a kind of disease that can be prevented and easily prevented. Choosing an appropriate risk assessment model is the basis for DVT risk assessment and precision medical services for patients. The risk prediction model constructed in this study has certain scientificity and practicability. Through the establishment of the model, the nursing perspective of taking intervention after the patient's symptoms can be changed to the prevention of DVT after the patient is admitted to the hospital with purpose and focus. At the same time, the model can visually display the relationship between the predictors and DVT, which is helpful for nursing staff to grasp the DVT risk dynamics of patients in a timely and accurate manner, and carry out prospective assessment and prevention.

4.2. Risk Factors Analysis of Lower Extremity Deep Vein Thrombosis in Patients with Decompensated Liver Cirrhosis

4.2.1. Age Affects the Formation of Lower Extremity Deep Venous Thrombosis in Patients

Age is generally considered to be an independent risk factor for hypercoagulable state [11]. In this study, the median age of patients in the DVT group was 68 (60, 77) years old, which was inconsistent with Wu *et al.* [12]'s conclusion that patients under 45 years old with liver cirrhosis were more likely to develop DVT. Patients with liver cirrhosis have a long course of disease, and with the increase of age, they are prone to dyslipidemia, arteriosclerosis, blood concentration, and blood viscosity, which increase the risk of DVT [13]. This study showed that the risk of DVT in patients over 60 years old was 1.476 times that in patients under 60 years old. For the elderly, especially the elderly patients, nurses should strengthen health education, improve the awareness of early warning of elderly patients, and do a good job of discharge follow-up and tracking.

4.2.2. Patients with Impaired Activities of Daily Living (ADL) Are Prone to Lower Extremity Deep Vein Thrombosis

BI is an important index for ADL evaluation and efficacy evaluation [14]. In this study, it was found that patients with bedridden time ≥ 3 days and lower BI scores were more likely to develop DVT. Patients with decompensated liver cirrhosis need to stay in bed for a long time and have limited activity, which leads to the obstruction of venous blood return of the lower limbs and the weakening of the pumping ability of the heart, which increases the risk of thrombosis. Venous thrombosis further prolongs the bedridden time of patients, and increases the occurrence of nosocomial infection and disuse syndrome [15-16]. For bedridden patients with ADL impairment, nurses should encourage patients to take active and passive activities in bed, get out of bed as soon as possible, and reduce the time of resting.

4.2.3. Inflammatory Response Is Closely Related to Deep Venous Thrombosis of Lower Limbs in Patients

C-reactive protein (CRP) is a sensitive and objective

indicator of bacterial infection [17]. Possible factors of bacterial infection in patients with decompensated cirrhosis:

(1) Immune dysfunction caused by decreased number and function of lymphocytes; (2) Biliary tract infection; (3) The richness and diversity of intestinal flora are decreased, and the intestinal mucosal barrier function is weakened. Compared with patients with stable liver disease, patients with decompensated liver cirrhosis are more likely to be complicated with multiple systemic infections such as pneumonia, spontaneous peritonitis, and urinary tract infection [18]. This study shows that CRP is an influencing factor of DVT in patients, suggesting that thrombosis is closely related to infection, which is consistent with several studies [19, 20]. In clinical work, medical staff should abide by aseptic operation, strict diagnosis and treatment operation, pay attention to abnormal infection indicators, and actively prevent and treat nosocomial infection.

4.2.4. D-Dimer Is a Sensitive Indicator for Predicting Deep Venous Thrombosis of Lower Extremities

D-dimer level is one of the molecular markers of hypercoagulable state and hyperfibrinolysis [21]. The level of D-dimer in patients with liver cirrhosis is usually higher than that in the general population, and its level can increase significantly with the deterioration of liver function [17]. In this study, the sensitivity of D-dimer in the diagnosis of DVT was 0.847, the specificity was 0.653, and the best critical value was 2.295ng/ml, which was higher than the normal value of 0.5 ng/ml. D-dimer is not only closely related to the evaluation of thrombosis, but also related to the severity of liver cirrhosis, ascites and gastrointestinal bleeding [22]. Therefore, elevated D-dimer does not necessarily predict thrombosis, and at the same time, other comprehensive factors should be considered. According to the Chinese Guidelines for the prevention and treatment of thrombotic Diseases [23], although D-dimer cannot be used as a basis for the diagnosis or exclusion of deep vein thrombosis alone, it can be used to exclude acute pulmonary thromboembolism in patients with low clinical evaluation probability. It is suggested that attention should be paid to the detection and result evaluation of D-dimer level in clinical nursing, especially for high-risk groups.

4.2.5. Traditional Coagulation Assessment Markers Have a Low Test Efficiency for the Risk of Lower Extremity Deep Venous Thrombosis

The results of this study showed that there was no significant difference in platelet count, prothrombin time, international normalized ratio, activated partial thromboplastin time and fibrinogen between the two groups ($P > 0.05$), which was consistent with the results reported by Wang Yu-liang *et al.* [24]. The coagulation mechanism of patients with decompensated liver cirrhosis is complex, and there may be a variety of processes, at the same time, such as the decrease of fibrinolysis, coagulation, anticoagulant function, the decrease of platelet number, aggregation and anti-aggregation ability, and endothelial exposure [25]. It may not only tilt to hypocoagulation, showing bleeding, but also

tilt to hypercoagulation, showing thrombosis, or thrombosis and bleeding coexist [24]. Some studies have shown that the hypercoagulable and thrombophilic state in patients with liver cirrhosis may be related to the increased concentration of coagulation factor VIII [24], enhanced platelet activity [26], decreased circulating level of high protein C, and anticardiolipin antibodies [27]. The conventional single bleeding and coagulation indicators reflect a single stage of the coagulation process, which cannot truly reflect the whole picture of coagulation. Due to the unique coagulation disorders of liver cirrhosis, clinical nurses should not only closely monitor patients for bleeding symptoms such as skin ecchymosis and petechias, hematuria, gastrointestinal bleeding, but also be alert to the occurrence of DVT and implement individualized treatment and nursing programs.

5. Conclusions

The thrombosis risk prediction model constructed in this study plays a certain auxiliary role in predicting the occurrence of DVT in patients with decompensated cirrhosis during hospitalization. However, there are limitations to this study, including the limited sample size used to validate the model. Further model validation and improvement are needed under multi-center and large-sample conditions.

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