

# World Journal of *Clinical Cases*

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## Retrospective Cohort Study

## Establishment of a risk assessment score for deep vein thrombosis after artificial liver support system treatment

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## Abstract

## BACKGROUND

The artificial liver support system (ALSS) is an effective treatment method for liver failure, but it requires deep venous intubation and long-term indwelling catheterization. However, the coagulation mechanism disorder of basic liver failure diseases, and deep venous thrombosis (DVT) often occur.

## AIM

To evaluate the risk factors for DVT following use of an ALSS and establish a risk assessment score.

## METHODS

This study was divided into three stages. In the first stage, the risk factors for DVT were screened and the patient data were collected, including ALSS treatment information; biochemical indices; coagulation and hematology indices; complications; procoagulant use therapy status; and a total of 24 indicators. In the second stage, a risk assessment score for DVT after ALSS treatment was developed. In the third stage, the DVT risk assessment score was validated.

## RESULTS

A total of 232 patients with liver failure treated with ALSS were enrolled in the first stage, including 12 with lower limb DVT. Logistic regression analysis showed that age [odds ratio (OR), 1.734;  $P = 0.01$ ], successful catheterization time (OR, 1.667;  $P = 0.005$ ), activity status (strict bed rest) (OR, 3.049;  $P = 0.005$ ), and D-dimer level ( $\geq 500$  ng/mL) (OR, 5.532;  $P < 0.001$ ) were independent risk factors for DVT. We then established a scoring system for risk factors. In the validation group, a total of 213 patients with liver failure were treated with ALSS, including 14 with lower limb DVT. When the cutoff value of risk assessment was 3, the specificity and sensitivity of the risk assessment score were 88.9% and 85.7%, respectively.

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## CONCLUSION

A simple risk assessment scoring system was established for DVT patients with liver failure treated with ALSS and was verified to have good sensitivity and specificity.

**Key Words:** Artificial liver support system; Deep vein thrombosis; Liver failure; Risk factors; Thrombosis

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**Core Tip:** The risk factors for deep vein thrombosis (DVT) after the use of an artificial liver support system (ALSS) and a risk assessment score were established. A total of 232 patients with liver failure treated with ALSS were enrolled in the first stage, including 12 with lower limb DVT. Logistic regression analysis showed that age, successful catheterization time, activity status (strict bed rest), and D-dimer level ( $\geq 500$  ng/mL) were independent risk factors for DVT. In the risk assessment scoring system validation group, when the cutoff value of risk assessment was 3, the specificity and sensitivity of the risk assessment score were 88.9% and 85.7%, respectively.

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## INTRODUCTION

Liver failure is a common but serious liver disease with high mortality rates[1,2]. The artificial liver support system (ALSS) is an effective treatment method for liver failure [3,4], but it requires deep venous intubation and long-term indwelling catheterization. However, the coagulation mechanism disorder of basic liver failure diseases, and complications such as bleeding, infection, and deep venous thrombosis (DVT) often occur[5,6]. The risk of DVT is significantly increased in cases of severe liver disease[7], mainly lower limb DVT and pulmonary embolism[8,9].

The commonly used DVT risk assessment systems are the Wells scoring system[10], Autar DVT risk assessment scale[11], and Caprini risk assessment model[12]. However, these evaluation systems are not suitable for the treatment of liver failure using ALSS. The development of new risk assessment indices for DVT is beneficial for patients with liver failure treated using ALSS therapy.

## MATERIALS AND METHODS

### Study design

This study was divided into three stages. In the first stage, the risk factors for DVT were screened. A retrospective survey was conducted of consecutive hospitalized patients with liver failure who had received ALSS treatment in our hospital between January 2014 and December 2017. Patient data were collected, including demographic information (sex, age, weight, height, body mass index, blood pressure, smoking, past diseases, family history); ALSS treatment information (catheterization method, successful catheterization time, whether heparin was used in catheterization, ALSS treatment duration, etc.); biochemical indices (blood glucose, serum total bilirubin, and alanine aminotransferase levels); blood coagulation and hematological indices (platelet count, international normalized ratio, D-dimer level); complications (ascites, hepatic encephalopathy, hemorrhage, comorbid serious diseases); whether procoagulant therapy was used; and 24 other indicators. A total of 232 patients with liver failure treated with ALSS were evaluated, including 14 with lower limb DVT and 218 without DVT. The incidence of DVT was 6.03%, and the median occurrence duration was 14 d



(range, 7-21 d) after deep venous indwelling. The second stage involved the establishment of a risk assessment for DVT after ALSS treatment. The variable parameters screened out in the first stage were thrombosis and non-thrombosis as dichotomous variables for logistic analysis. The independent risk factors were scored, and a risk assessment score was established. The third stage involved verification of the DVT risk assessment score. Patients were hospitalized in the Liver Disease Department of our hospital between January 1, 2018 and October 31, 2020. A total of 213 patients with liver failure were included and treated with ALSS, including 14 cases with DVT (6.57%) in the lower extremities and 199 cases without DVT. The median time to occurrence was 16 d (range, 7-28 d) after deep vein indwelling.

### **Diagnosis and treatment**

The liver failure diagnosis and ALSS treatment of all patients were delivered according to China's 2012 Guidelines for the Diagnosis and Treatment of Liver Failure [13]. Lower extremity DVT was diagnosed using B-ultrasound (JE Philips L9 model) for venous examination of the bilateral lower extremities. The diagnostic criteria included the following [14]: (1) After the probe was pressurized, the lumen was not compressed; (2) A strong echo or low echo was detected in the lumen, the distal lumen of the obstruction was dilated, the pathological vein wall was thickened, the wall structure was unclear, and lumen stenosis or obstruction was noted; and (3) When the vein was completely obstructed, the proximal color Doppler ultrasound could not detect the blood flow signal.

### **ALSS therapy and deep vein indwelling**

Plasma exchange (PE) or continuous hemofiltration therapy was administered to patients treated with ALSS. Jugular or femoral vein catheterization was performed with a single-needle and a double-lumen catheter (B. Braun GmbH, Model 12F, Germany). The PE involved a plasma volume of 100 mL/min, plasma separation rate of 30%, and plasma exchange volume of 1-1.3 times the patient's plasma volume. Patient plasma volume = patient weight (kg) × 70 mL × [(1.0 hematocrit) × 0.91] × 1.15. In hemofiltration, filtration after PE lasted for 24-72 h. The catheter remained indwelling until the end of the ALSS treatment or complications occurred.

### **Statistical methods**

Measurement data are expressed as mean ± SD, and all data were processed using SPSS22.0 (IBM, Chicago, IL, United States). Measurement data were tested by independent sample t test, count data by the  $\chi^2$  test, and logistic regression by binary classification and the full entry method. The risk assessment form was validated by the area under the receiver operating characteristic curve (AUC) using MedCalc software (version 10.4.7.0; Medcalc, Mariakerke, Belgium). Values of  $P < 0.05$  were considered statistically significant. The AUC was used to evaluate the diagnostic value of the DVT risk assessment score after ALSS treatment.

## **RESULTS**

The demographic and clinical characteristics of patients treated with ALSS in Stage I were compared. Age ( $\chi^2 = 7.17$ ,  $P = 0.027$ ), catheterization method ( $\chi^2 = 4.99$ ,  $P = 0.025$ ), successful catheterization time ( $\chi^2 = 10.856$ ,  $P = 0.004$ ), last ALSS ( $\chi^2 = 67.481$ ,  $P < 0.001$ ), activity status ( $\chi^2 = 9.607$ ,  $P = 0.02$ ), D-dimer level ( $\chi^2 = 12.318$ ,  $P = 0.002$ ), and infection status ( $\chi^2 = 17.231$ ,  $P = 0.001$ ) were significantly different between the thrombus and no-thrombus groups (Table 1).

### **Logistic regression analysis of factors influencing DVT after ALSS treatment**

Taking DVT and non-DVT as dichotomous variables, all entry methods were adopted and conditional parameter variables were included ( $P < 0.1$ ). The dichotomous logistic regression analysis showed that age [odds ratio (OR), 1.734;  $P = 0.01$ ], successful catheterization time (OR, 1.667;  $P = 0.005$ ), activity status (strict bed rest) (OR, 3.049;  $P = 0.005$ ), D-dimer level ( $\geq 500$  ng/mL) (OR, 5.532;  $P < 0.001$ ), and infection status (OR, 2.426;  $P = 0.008$ ) were independent risk factors for DVT (Table 2).

### **Establishment of risk assessment score for DVT after ALSS treatment**

According to the results of the multivariate logistic regression analysis, the proposed scores are listed in Table 3.

**Table 1 Comparison of demographic and clinical characteristics for deep venous thrombosis after artificial liver support system in Stage I**

Parameters	DVT ( <i>n</i> = 12)	No-DVT ( <i>n</i> = 220)	Statistics	<i>P</i> value
Gender, <i>n</i> (%)				
Man	7 (58.3)	165 (75)	1.649	0.306
Woman	5 (41.7)	55 (25)		
Age (yrs), <i>n</i> (%)				
< 40	2 (18.2)	51 (28.7)	7.17	<b>0.027</b>
< 60, ≥ 40	4 (36.4)	101 (56.7)		
≥ 60	5 (45.5)	26 (14.6)		
Mean arterial pressure (mmHg), mean ± SD	83.45 ± 14.47	84.11 ± 13.26	0.768	0.707
Fasting plasma glucose (mmol/L), mean ± SD	5.43 ± 1.51	5.41 ± 1.65	0.332	0.542
Smoke, <i>n</i> (%)				
No	7 (58.3)	142 (64.5)	0.197	0.759
Yes	5 (41.7)	78 (35.5)		
Catheterization mode, <i>n</i> (%)				
Jugular vein	0 (0)	72 (30)	5.09	<b>0.022</b>
Femoral vein	12 (100)	168 (70)		
Times of successful catheterization, <i>n</i> (%)				
One	3 (25)	151 (71.9)	16.669	<b>0</b>
Two	4 (33.3)	41 (19.5)		
Three and more	5 (21.7)	18 (8.6)		
Heparin therapy, <i>n</i> (%)				
No	3 (25)	56 (25.5)	0.01	0.971
Yes	9 (75)	164 (74.5)		
Procoagulant therapy, <i>n</i> (%)				
No	8 (67.7)	164 (74.5)	0.368	0.513
Yes	4 (33.3)	56 (25.5)		
Etiology, <i>n</i> (%)				
Virus hepatitis	9 (75)	133 (60.5)	1.028	0.795
Drug injury	1 (8.3)	29 (13.2)		
Autoimmune liver disease	1 (8.3)	24 (11.8)		
Others	1 (8.3)	32 (14.5)		
ALSS times, <i>n</i> (%)				
< 3	3 (25)	61 (27.7)	7.344	<b>0.025</b>
≥ 3, < 5	5 (21.7)	139 (63.2)		
≥ 5	4 (33.3)	20 (9.1)		
Activity status, <i>n</i> (%)				
Free activities	0 (0)	23 (10.5)	10.773	<b>0.013</b>
Less than 4 h/d	2 (16.7)	89 (40.5)		
Less than 1 h/d	4 (33.3)	74 (33.6)		
Strict bed rest	6 (50.0)	32 (15.5)		
Ascites status, <i>n</i> (%)				

No	3 (25)	67 (28.1)	0.923	0.82
Mild	4 (33.3)	79 (37.6)		
Moderate	3 (25)	56 (25.7)		
Severe	2 (16.7)	19 (8.6)		
Bleeding, <i>n</i> (%)				
No	8 (67.7)	153 (69.5)	0.436	0.833
Yes	4 (33.3)	67 (30.5)		
Hepatic encephalopathy, <i>n</i> (%)				
No	6 (54.5)	148 (67.3)	1.933	0.385
I-II	4 (33.3)	55 (25.0)		
III-IV	2 (17.5)	17 (7.7)		
Infection, <i>n</i> (%)				
No	4 (33.3)	144 (65.5)	5.083	<b>0.031</b>
Yes	8 (67.7)	76 (34.5)		
Complicated by other serious diseases, <i>n</i> (%)				
No	8 (67.7)	174 (79.1)	1.039	0.294
Yes	4 (33.3)	46 (20.9)		
Body mass index (kg/m <sup>2</sup> ), <i>n</i> (%)				
< 23	2 (20.0)	77 (35)	2.262	0.332
≥ 23, < 25	4 (40.0)	97 (44.1)		
≥ 25	4 (40.0)	46 (20.9)		
Platelet count (10 <sup>9</sup> /L), <i>n</i> (%)				
< 100	3 (25)	99 (45)	2.258	0.277
≥ 100, < 300	8 (66.7)	95 (43.2)		
≥ 300	1 (8.3)	16 (11.8)		
Total bilirubin (μmol/L), mean ± SD	234.45 ± 155.12	231.65 ± 132.86	1.476	0.583
Alanine aminotransferase (U/L), mean ± SD	256.82 ± 243.455	294.65 ± 341.36	1.20	0.578
D-dimer (ng/mL), <i>n</i> (%)				
< 200	1 (8.3)	88 (40)	12.232	<b>0.002</b>
≥ 200, < 500	3 (25.9)	82 (37.3)		
≥ 500	8 (66.7)	50 (22.7)		
Fibrinogen (g/L), mean ± SD	1.25 ± 0.43	1.33 ± 1.12	2.554	0.212
International normalized ratio, <i>n</i> (%)				
< 1.5	0 (0)	0 (0)	0.215	0.767
≥ 1.5, < 2	6 (54.5)	125 (56.8)		
≥ 2	6 (45.5)	85 (43.2)		

DVT: Deep venous thrombosis; ALSS: Artificial liver support system.

### Diagnostic value of the risk assessment score of DVT after ALSS treatment

Analysis of the validation group data revealed significant differences in age, successful catheterization time, activity status, D-dimer level, and infection between patients with and without DVT as well as differences in the ALSS treatment duration (Table 4). AUC was used to evaluate the diagnostic value of the DVT risk assessment score after ALSS treatment. The DVT and no DVT after ALSS groups were considered classification variables, while the DVT risk assessment score was considered a variable. When the

**Table 2 Logistic regression analysis of influencing factors of deep venous thrombosis after artificial liver support system**

Parameters	$\beta$	Wald $\chi^2$	OR	95%CI	P value
Age (yrs)	0.454	5.776	1.734	1.034-2.543	<b>0.01</b>
< 40	1				
< 60, $\geq$ 40	0.034	2.765	1.114	0.324-3.654	0.95
$\geq$ 60	3.354	8.234	1.886	1.154-4.853	<b>0.005</b>
Catheterization mode					
Jugular vein	1				
Femoral vein	0.068	0.976	0.645	0.550-1.655	0.121
ALSS times	1.63	1.424		0.257-1.667	0.223
< 3	1				
$\geq$ 3, < 5	0.354	0.564	0.454	0.416-2.534	0.531
$\geq$ 5	0.243	0.486	1.321	1.013-6.534	0.615
Times of successful catheterization					
One	1				
Two	0.672	1.534	0.674	0.056-1.132	0.242
Three and more	1.246	6.435	1.667	1.005-3.235	<b>0.005</b>
Activity status					
Free activities	1				
Less than 4 h/d	0.54	1.004	1.028	0.062-1.002	0.972
Less than 1 h/d	0.764	0.172	1.565	0.999-1.504	0.128
Strict bed rest	1.547	11.074	3.049	1.744-8.414	<b>&lt; 0.001</b>
D-dimer (ng/mL)					
< 200	1				
$\geq$ 200, < 500	1.322	1.653	1.674	1.056-2.232	0.064
$\geq$ 500	2.115	12.231	5.532	1.404-12.133	<b>&lt; 0.001</b>
Infection					
No	1				
Yes	2.431	16.236	2.426	1.003-89.342	<b>0.008</b>

OR: Odds ratio; CI: Confidence interval; ALSS: Artificial liver support system.

cutoff value of the risk assessment score was 3, the specificity and sensitivity of the risk assessment score for DVT were 88.9% and 85.7%, respectively (Figure 1).

## DISCUSSION

The mechanism of ALSS is based on the strong regenerative ability of liver cells through mechanical, physical, chemical, and biological equipment *in vitro*, removing all types of harmful substances, supplying necessary materials, improving the internal environment, temporarily replacing the partial failure of liver function, creating a good condition for liver cell regeneration and liver function recovery, or waiting for an opportunity for liver transplantation[15,16].

Virchow proposed three causes of DVT[17]: Vascular endothelial injury, hemodynamic changes (especially slow and stagnant blood flow), and abnormal blood coagulation. Deep vein catheterization in patients treated with ALSS undoubtedly causes vascular endothelial injury[18]. At the same time, studies have shown that, after vascular endothelial injury[19,20], the subendothelial tissue is exposed[21]; the original

**Table 3 Establishment of risk assessment score for deep venous thrombosis after artificial liver support system**

Indicators	Score
D-dimer	3
Infection	2
Strict bed rest	2
Age ( $\geq 60$ yrs)	2
Times of successful catheterization ( $\geq 3$ )	1

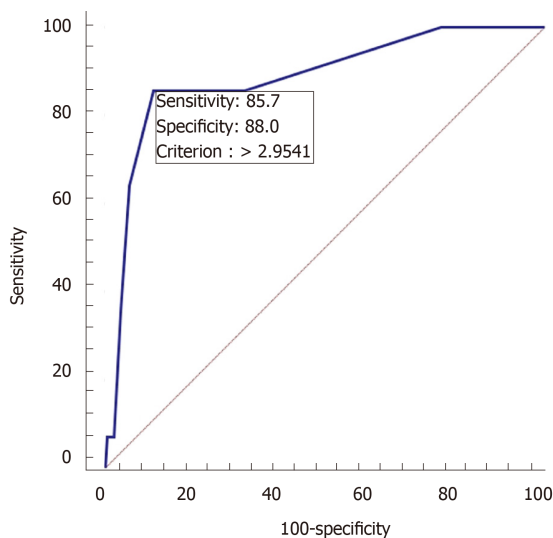
Total points: 10 points,  $\geq 5$  points for high risk,  $\geq 3$ , and  $< 5$  points for moderate risk,  $< 3$  points for low risk.

**Table 4 Comparison of demographic and clinical characteristics for deep venous thrombosis after artificial liver support system stage II, *n* (%)**

Parameters	DVT ( <i>n</i> = 14)	No-DVT ( <i>n</i> = 199)	Statistics	<i>P</i> value
Gender				
Man	9 (64.3)	165 (82.9)	3.035	0.082
Woman	5 (35.7)	34 (17.1)		
Age (yrs)				
$< 40$	2 (16.7)	51 (25.6)	11.004	0.004
$< 60, \geq 40$	2 (16.7)	101 (50.8)		
$\geq 60$	8 (66.7)	47 (23.6)		
Catheterization mode				
Jugular vein	2 (14.3)	51 (25.6)	0.903	0.343
Femoral vein	12 (85.7)	148 (74.4)		
Times of successful catheterization				
One	3 (21.4)	120 (60.3)	13.742	0.001
Two	4 (28.6)	51 (25.6)		
Three and more	7 (50.0)	28 (14.1)		
ALSS times				
$< 3$	4 (28.6)	61 (30.7)	9.207	0.01
$\geq 3, < 5$	5 (35.7)	119 (50.8)		
$\geq 5$	5 (35.7)	19 (9.5)		
Activity status				
Free activities	0 (0)	23 (11.6)	11.761	0.008
Less than 4 h/d	4 (28.6)	69 (34.7)		
Less than 1 h/d	4 (28.6)	84 (42.6)		
Strict bed rest	6 (42.9)	23 (11.6)		
Infection				
No	4 (28.6)	114 (57.6)	4.365	0.037
Yes	10 (71.4)	85 (42.4)		
D-dimer (ng/mL)				
$< 200$	1 (7.1)	65 (32.7)	14.84	0.001
$\geq 200, < 500$	4 (28.6)	94 (47.2)		
$\geq 500$	9 (64.3)	40 (20.1)		



DVT: Deep venous thrombosis; ALSS: Artificial liver support system.



**Figure 1** Diagnostic value of the risk assessment score for deep venous thrombosis after artificial liver support system treatment.

hemostatic anticoagulant balance of the vascular endothelial layer is broken; endothelial cells release tissue factor, von Willebrand factor, fibronectin, and other coagulation factors; and vascular permeability is increased[22-24]. At the same time, leukocytes adhere to the wound and release inflammatory factors, and the wound reaches a pre-coagulation state[25,26].

Liver failure leads to a decrease in hepatic synthetic coagulation factors, hyperfibrinolysis, and thrombocytopenia caused by hypersplenism[27,28]. Therefore, patients with liver failure have always been considered to be in a low coagulation state [29,30]. However, in severe liver disease, the risk of DVT is also significantly increased and mainly manifests as lower extremity DVT and pulmonary embolism[7,31]. During the catheter indwelling period, to prevent bleeding at the puncture site and keep the catheter unobstructed, the patient requires absolute bed rest and limb bracing at the puncture side. Indwelling central venous catheter, intraoperative heparin anticoagulation, postoperative bed rest, and other related factors increased the incidence of DVT in patients with liver failure treated with ALSS.

In this study, older age, more catheterization time, absolute bed rest, increased D-dimer level, and infection were all high-risk factors for DVT. Older age has always been a risk factor in various DVT risk assessment forms, such as the Autoar Thrombosis Risk Assessment Scale, the Caprini risk assessment model, and the JFK Medical Center Thrombosis Assessment Scale[32]. ALSS requires more treatment times. To avoid repeated puncture, puncture and indwelling are adopted, and the jugular vein, subclavian vein, and femoral vein are most commonly used. Deep vein puncture and catheterization itself will inevitably damage the blood vessels, and the literature shows that the proficiency of the puncture technique is negatively correlated with the incidence of DVT[33]. DVT caused by deep vein catheterization occurs primarily in the lower extremities, and use of the femoral vein indwelling method in all of our centers was also a risk factor for DVT formation. Liver failure is often complicated by infection, commonly in the abdominal cavity or lungs[34], and is a risk factor for the development of DVT. DVT and inflammatory responses are closely related from the beginning to the end[35]. Infection promotes the release of inflammatory factors, leading to an increase in immunoglobulin levels that can lead to an increase in blood viscosity and the formation of thrombosis[36,37].

The tool currently used for the risk assessment of DVT is the Autoar Thrombosis Risk Assessment Scale, which includes seven submodules: age, body size, activity, special risk category, trauma, surgery, and high-risk disease. Studies using the Autoar scale showed that it was the most effective at warning the risk of perioperative DVT in patients with bone trauma and could reduce the incidence of VTE in patients with perioperative trauma[38]. The Caprini risk assessment model[39], originally released in 1991 for use in all inpatients as a weighted risk stratification tool, contains 39

indicators and is subject to constant updating. The Wells scoring system is a prediction system based on D-dimer level that can be better used for the early diagnosis of DVT [40] rather than the risk assessment of DVT. However, the setting of these indicators does not fully consider the risk of thrombus formation in this special group of patients with liver failure after treatment using ALSS.

## CONCLUSION

In this study, through the risk assessment of DVT in patients with liver failure, the advantages of other DVT risk assessment systems were fully used and combined with the special clotting state of liver failure to establish a simple scoring system that has good sensitivity and specificity. The shortcoming of this study is that it was a single-center retrospective study. Multi-center, prospective, and large-sample validation is still needed.

## ARTICLE HIGHLIGHTS

### **Research background**

The artificial liver support system (ALSS) is an effective treatment method for liver failure, but it requires deep venous intubation and long-term indwelling catheterization. However, the coagulation mechanism disorder of basic liver failure diseases, and deep venous thrombosis (DVT) often occur.

### **Research motivation**

The commonly used DVT risk assessment systems are not suitable for the treatment of liver failure using ALSS. The development of new risk assessment indices for DVT is beneficial for patients with liver failure treated using ALSS therapy.

### **Research objectives**

To evaluate the risk factors for DVT following the use of an ALSS and establish a risk assessment score.

### **Research methods**

This study was divided into three stages. In the first stage, the risk factors for DVT were screened and the patient data were collected, including ALSS treatment information; biochemical indices; coagulation and hematology indices; complications; procoagulant use therapy status; and a total of 24 other indicators. In the second stage, a risk assessment score for DVT after ALSS treatment was developed. In the third stage, the DVT risk assessment score was validated.

### **Research results**

A total of 232 patients with liver failure treated with ALSS were enrolled in the first stage, including 12 with lower limb DVT. We then established a scoring system for risk factors. In the validation group, a total of 213 patients with liver failure were treated with ALSS, including 14 with lower limb DVT. When the cutoff value of risk assessment was 3, the specificity and sensitivity of the risk assessment score were 88.9% and 85.7%, respectively.

### **Research conclusions**

A simple risk assessment scoring system was established for DVT patients with liver failure treated with ALSS and was verified to have good sensitivity and specificity.

### **Research perspectives**

In this study, through the risk assessment of DVT in patients with liver failure, the advantages of other DVT risk assessment systems were fully used and combined with the special clotting state of liver failure to establish a simple scoring system that has good sensitivity and specificity.

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