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Study on risk factors of preoperative deep vein thrombosis in patients with lower limb fractures and construction and validation of risk prediction nomogram model

Fan Zheng[1†], Xiaobin Chen[1*†], Jianqiang Huang[1] and Chen Lin[1*]

Abstract

Background To explore the correlation between the levels of D-dimer (D-D), fibrinogen (FIB), fibrinogen degradation products (FDP) and platelets (PLT) in peripheral blood of patients with lower limb fractures and the formation of deep vein thrombosis in lower limbs, and to establish a new thrombosis prediction model for patients with lower limb fractures.

Methods The patients were divided into DVT group and non DVT group according to whether there was deep vein thrombosis of the lower extremity. The differences in the levels of D-D, FIB, FDP and platelets between the two groups were analyzed and compared. ROC curve was used to evaluate the levels of D-D, FIB, FDP and PLT in the peripheral blood of patients with lower extremity fracture to predict the formation of deep vein thrombosis of the lower extremity. Logistic regression analysis was used to analyze the related risk factors of deep vein thrombosis, and the corresponding nomogram risk prediction model of lower limb deep vein thrombosis in patients with lower limb fractures was drawn according to the regression coefficient, which was verified by calibration curve, receiver operating characteristic curve (ROC) and consistency index (C-index).

Results The levels of D-D, FIB, FDP, and PLT in the DVT group were higher than those in the non DVT group, with statistical significance ($P < 0.05$); Moreover, FIB is superior to D-D, FDP, and PLT in predicting the risk of fractures and thrombosis, while PLT has the weakest predictive power. Multivariate logistic analysis showed that platelet, D-D, FIB and FDP were independent risk factors for deep vein thrombosis in patients with lower limb fractures ($P < 0.05$); Based on the independent risk factors mentioned above, the complex logistic regression formula was transformed into a visual column chart, and the consistency index (C-index) was 0.962 and 0.936, and the external verification C-index was 0.841. The calibration curve showed that the nomogram is in high agreement with the actual results. The AUC value of ROC curve indicated that the nomogram has high prediction value.

[†]Fan Zheng and Xiaobin Chen contributed equally to this work.

*Correspondence:
Xiaobin Chen
cxb104189@126.com
Chen Lin
chenlin.med@hotmail.com
Full list of author information is available at the end of the article

Conclusions The levels of D-D, FIB, FDP and PLT in peripheral blood of patients with lower limb fracture and DVT were significantly increased. Early monitoring of D-D, FIB, FDP and PLT levels in patients with lower limb fracture can effectively screen for lower limb deep vein thrombosis.

Keywords Lower limb fracture, Deep vein thrombosis of lower extremity, Risk factors, Nomogram, Fibrinogen

Introduction

Deep vein thrombosis (DVT) of lower limbs is caused by a variety of reasons, which lead to changes in the coagulation mechanism of the body to promote thrombosis, and then lead to stenosis or occlusion of the vascular lumen, which is more likely to occur in lower limb blood vessels (including femoral vein and deep leg vein) [1, 2]. It has been reported that deep vein thrombosis is a common complication after traumatic fracture. Among hospitalized patients, the risk of deep vein thrombosis in trauma patients is 13 times higher than that in non trauma patients [3]. Considering that fractures can damage the vascular wall to make the blood in a hypercoagulable state, which is easy to lead to thrombosis [4]. If the patient is complicated with deep vein thrombosis, the fracture healing will be greatly affected; In addition, pulmonary embolism (PE) caused by lower limb deep vein thrombosis poses a pathogenic threat to the health of patients [5]. In addition, lower limb fractures, as one of the common types of fractures, account for one-third of fracture patients and are mostly concentrated in the elderly population. With the increasing aging of the population, the proportion of patients with lower limb fractures is showing an increasing trend [6]. Clinically, the early symptoms of lower limb deep vein thrombosis are lack of specificity, and the symptoms are relatively hidden. Only 10–17% of DVT patients have obvious clinical symptoms (such as lower limb swelling, local deep tenderness, back flexion pain), which is easy to cause misdiagnosis and missed diagnosis. Therefore, early diagnosis and intervention for high-risk patients has important clinical significance [7, 8]. At present, the commonly used methods for diagnosis of deep vein thrombosis include imaging detection methods such as vascular color ultrasound and venography. Although these technologies have certain specificity and sensitivity, they cannot be used to predict the occurrence of DVT (the high price and complicated operation limit their application in clinical disease screening). Therefore, it is very important for clinical diagnosis and treatment of lower limb deep vein thrombosis to explore new and effective predictive indicators for early diagnosis.

According to reports, levels of D-dimer (D-D), fibrinogen (FIB), fibrinogen degradation products (FDP), and platelets (PLT) can reflect the hypercoagulable state of the blood to some extent [9, 10]. FIB, as a glycoprotein synthesized and secreted by hepatocytes, can induce secondary fibrinolysis hyperfunction by increasing the activity of plasmin, and then participate in the process of coagulation and hemostasis, which has a certain correlation with the occurrence of DVT; While D-D, as plasmin hydrolyzed cross-linked fibrinogen, can also be used as an indicator of body thrombosis. When there is thrombosis in the vascular lumen, its indicator can significantly rise [11]; FDP have a certain correlation with D-D, which can reflect the coagulation function of the patient's body and are recognized as biochemical indicators of thrombotic diseases in clinical practice; Platelets mainly participate in the body's coagulation process by promoting hemostasis and accelerating coagulation. This study retrospectively analyzed 145 patients with lower limb fractures admitted to the emergency department of our hospital, analyzed the correlation and predictive value of D-D, FIB, FDP and PLT with lower limb deep vein thrombosis, analyzed the risk factors of lower limb fractures complicated with lower limb deep vein thrombosis, and constructed a nomogram of the risk probability of lower limb deep vein thrombosis, in order to effectively guide clinical diagnosis and treatment.

Materials and methods

Data collection

Retrospective analysis of the clinical data of 145 patients with traumatic fractures of the lower limbs who visited the department of General Surgery of our hospital from September 2022 to March 2023, including 70 males and 75 females, aged 26 to 76 years, with an average age of 53.78 ± 11.76 years. Upon admission, the patients were divided into DVT group and non DVT group according to whether there was deep vein thrombosis of lower limbs. Inclusion criteria: (1) All fracture patients were diagnosed in accordance with the clinical diagnostic criteria for limb fractures in the "Chinese Open Fracture Diagnosis and Treatment Guidelines (2019 Edition)" [12]; (2) All patients underwent lower limb venous ultrasound examination, and patients with lower limb thrombosis were diagnosed by completing lower limb angiography (DSA) if necessary; (3) The patient has no previous history of lower limb thrombosis. Exclusion criteria: (1) Previous history of pulmonary embolism; (2) Previous history of atrial fibrillation; (3) Patients who have undergone vascular related surgery in the past; (4) Patients with

other organ tumors; (5) Patients with abnormal coagulation function. This study followed the ethical standards of Helsinki Declaration, and all patients were informed and signed the relevant consent before treatment.

Data collection

General and clinical data of all patients were collected, including gender, age, body mass index (BMI), trauma site, history of diabetes, history of hypertension, cause of injury, platelet, D-D, FIB and FDP levels. Compare the differences in D-D, FIB, FDP, and platelet levels between DVT and non DVT groups.

Diagnostic criteria of DVT

According to the "Guidelines for Diagnosis and Treatment of Deep Venous Thrombosis" [13]: (1) The lower limbs are swollen and painful; (2) The blood coagulation function is in hypercoagulable state; (3) D-D level > 500 μg/L; (4) B-ultrasound examination can directly see that the blood vessels can not be squashed by the probe, and there is uneven echo shadow in the lumen; (5) The blood vessels can't be completely filled or appear defect after filling. During the examination, 1 ~ 4 items were screened first, and those whose first four items met the requirements were screened for the fifth item, and the diagnosis was DVT according to the results.

Therapeutic method

For each fracture patient upon admission, we immediately performed lower limb venous ultrasound to assist in the diagnosis, followed by selective interventions to prevent or treat lower limb deep vein thrombosis (DVT). For patients without thrombus, it is considered that fracture can make blood in hypercoagulable state by damaging blood vessel wall, which will easily lead to thrombosis and increase the risk of thrombosis, so low dose anticoagulation can be selected to prevent it, and the dose is 0.2 ml of low molecular weight heparin (2/ day); According to the "Guidelines for Prevention of Venous Thromboembolism in Orthopedic Surgery in China" [14], for patients with thrombus, they can be treated according to their weight. The routine dose is 0.6 ml of low molecular weight heparin (2/ day). Both patients stopped anticoagulation one day before operation and resumed anticoagulation treatment as soon as possible after operation. In addition, for patients with deep venous thrombosis of lower limbs, pneumatic pump can be used to contract the muscles of the ankle and calf after operation to promote local blood circulation. Improving the venous return of lower limbs can also play a therapeutic role to some extent.

Statistical analysis

SPSS (version 26.0) and R language (version 4.2.1) software was used for statistical analysis of the data. The counting data is represented by n (%), and inter group comparisons are performed using χ^2 tests or Fisher tests ($n < 5$); The measurement data is expressed as mean ± standard deviation (x ± s), and t-test is used for inter group comparison. The predictive value of using receiver operating characteristic curve (ROC curve) to evaluate D-D, FIB, FDP, and PLT levels in DVT patients with lower limb fractures. Logistic regression analysis was used to analyze the related risk factors of deep vein thrombosis. Multifactor Logistic regression was used to establish a prediction model for the risk of deep vein thrombosis of lower limbs. The model was visualized by nomogram, and the prediction accuracy and discrimination ability of the model were determined by calibration curve, ROC curve and consistency index (C index), $\alpha = 0.05$ is the inspection level.

Results

Comparison of D-D, FIB, FDP, PLT levels between two groups

The levels of D-D, FIB, FDP, and PLT in the DVT group were higher than those in the non DVT group, with statistical significance ($P < 0.05$), as shown in Table 1.

Comparison of D-D, FIB, FDP, and PLT in predicting the risk of fracture combined with thrombosis

Draw ROC curves of D-D, FIB, FDP, and PLT to evaluate their ability to predict the risk of lower limb thrombosis. The results showed that the AUC of D-D, FIB, FDP, and PLT were 0.810 (95%CI: 0.725–0.894, $P < 0.001$), 0.861 (95%CI: 0.800–0.923, $P < 0.001$), 0.834 (95%CI: 0.755–0.913, $P < 0.001$), and 0.752 (95%CI: 0.670–0.834, $P < 0.001$), respectively. It can be seen that FIB is superior to D-D, FDP in predicting the risk of fracture complicated thrombosis PLT has the weakest predictive performance, as shown in Fig. 1.

Table 1 Comparison of D-dimer, FIB, FDP levels between two groups (x ± s)

Indicator	DVT group ($n = 66$)	Non-DVT group ($n = 79$)	t	P
D-D (mg/L)	2.06 ± 2.94	0.87 ± 1.43	-3.180	0.002
FIB (g/L)	6.05 ± 2.09	3.55 ± 1.45	-8.482	< 0.001
FDP (mg/L)	6.96 ± 2.03	4.27 ± 2.15	-7.681	< 0.001
PLT ($\times 10^9$/L)	289.83 ± 90.79	203.50 ± 84.96	-5.906	< 0.001

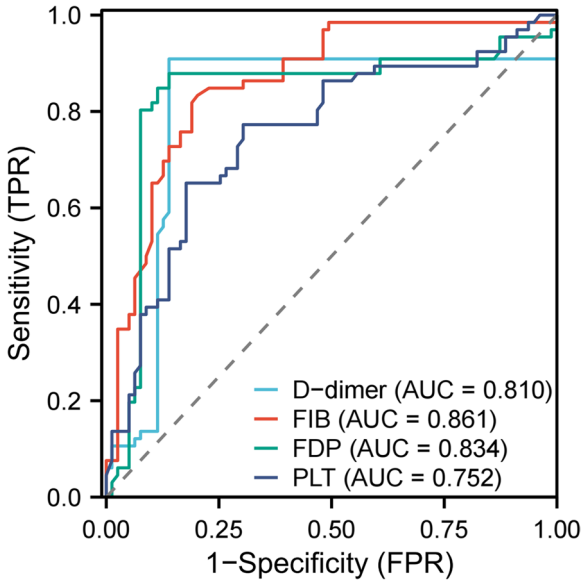

Fig. 1 ROC Curve for Predicting the Risk of Fracture Complication with Thrombosis in D-D、FIB、FDP and PLT

Single factor analysis of deep vein thrombosis in patients with lower limb fractures

This study included 145 patients with lower limb fractures, including 66 patients with lower limb deep vein thrombosis and 79 patients with non deep vein thrombosis. By comparing the differences of general information between the two groups, we found that BMI, trauma site, whether diabetes was combined with history, platelets, D-D, FIB and FDP were related to lower limb deep vein thrombosis ($P<0.05$), while gender, age The history of hypertension and the cause of injury were not related to the occurrence of deep vein thrombosis in the lower limbs ($P>0.05$), as shown in Table 2.

Multifactor analysis of deep vein thrombosis in patients with lower limb fractures

Single factor meaningful indicators were included in the multivariate logistic regression model for analysis. The results showed that platelets (OR = 19.233, 95%CI: 2.890–127.975, $P=0.002$), D-D (OR = 10.457, 95%CI: 1.492–73.270, $P=0.018$), FIB (OR = 5.220, 95%CI: 1.315–20.715, $P=0.019$), FDP (OR = 11.634, 95%CI: 1.710–79.168, $P=0.012$) were independent risk factors for deep vein thrombosis in patients with lower limb fractures ($P<0.05$), as shown in Table 3.

Construction of risk model for deep vein thrombosis in patients with lower limb fractures

We converted the complex logistic regression formula into a visual nomogram based on independent risk factors, with a C index of 0.962 (0.936–0.988), suggesting that the nomogram has good discrimination and consistency, and the calibration curve shows that the risk probability of deep vein thrombosis of the lower extremity predicted by the nomogram model is consistent with the actual observation results in the study cohort ($\chi^2=5.242$, $P=0.731$), the AUC value of the ROC curve is 0.962, indicating that the predicted value of this column chart is high, as shown in Figs. 2, 3, and 4.

Table 2 Comparison of general information between two groups of patients (n)

Indicator	n	DVT group *n* = 66	Non-DVT group *n* = 79	χ^2	P
Gender				0.509	0.476
Male	70	34	36		
Female	75	32	43		
Age (years)				2.166	0.141
≤ 60	94	47	47		
> 60	51	19	32		
BMI (kg/m^2)				4.140	0.042
≤ 24	92	36	56		
> 24	53	30	23		
Fracture site				9.539	0.008
Tibiofibular	27	18	9		
femur	102	38	64		
hip bone	16	10	6		
History of diabetes				17.235	< 0.001
No	100	34	66		
Yes	45	32	13		
History of hypertension				0.541	0.462
No	92	44	48		
Yes	53	22	31		
Energy				0.417	0.518
Low	107	47	60		
High	38	19	19		
PLT (× 10^9/L)				31.979	< 0.001
≤ 300	89	24	65		
> 300	56	42	14		
D-D (mg/L)				85.283	< 0.001
≤ 0.5	74	6	68		
> 0.5	71	60	11		
FIB (g/L)				59.624	< 0.001
≤ 4	75	11	64		
> 4	70	55	15		
FDP (mg/L)				78.851	< 0.001
≤ 5	76	8	68		
> 5	69	58	11		

Table 3 Multivariate logistic regression analysis on the occurrence of DVT in fracture patients

Risk factor	Coef (β)	S.E	Wald	OR	95% CI	P
Intercept	-5.498	1.845	8.882	0.004	-	0.003
BMI	0.944	0.716	1.741	2.571	0.632–10.456	0.187
Fracture site	-0.502	0.629	0.637	0.605	0.176–2.078	0.425
History of diabetes	1.410	0.776	3.300	4.095	0.895–18.743	0.069
PLT	2.957	0.967	9.349	19.233	2.890–127.975	0.002
D-D	2.347	0.993	5.584	10.457	1.492–73.270	0.018
FIB	1.652	0.703	5.521	5.220	1.315–20.715	0.019
FDP	2.454	0.978	6.290	11.634	1.710–79.168	0.012

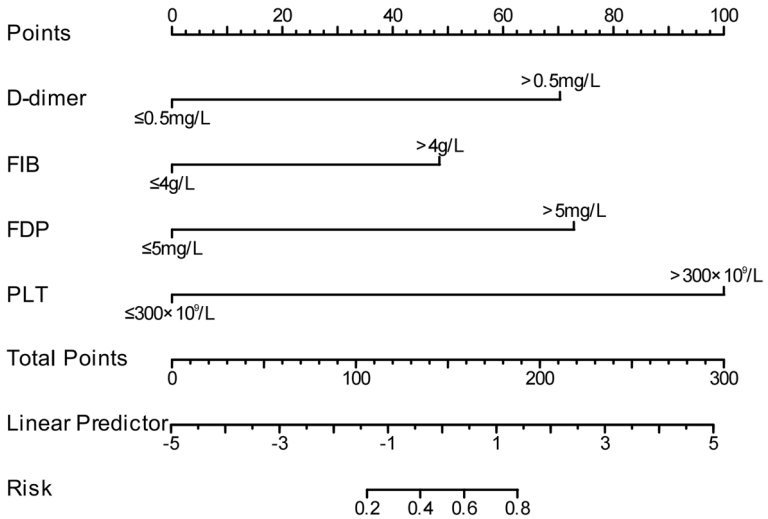

Fig. 2 Nomogram prediction model of risk probability of lower limb deep vein thrombosis in fracture patients

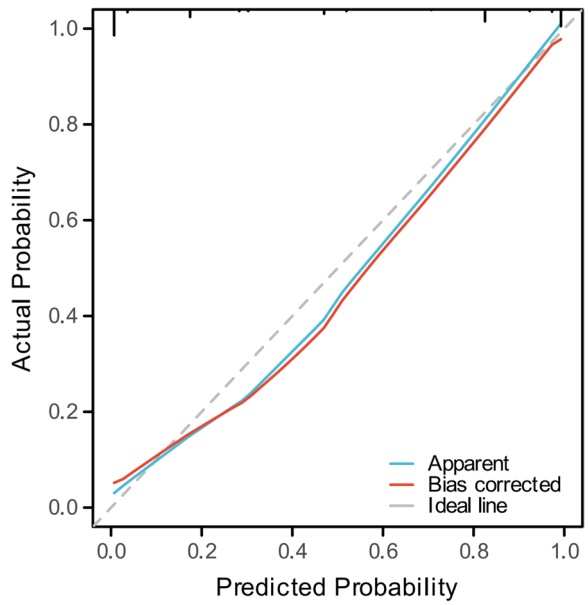

Fig. 3 Calibration curve of column chart prediction model

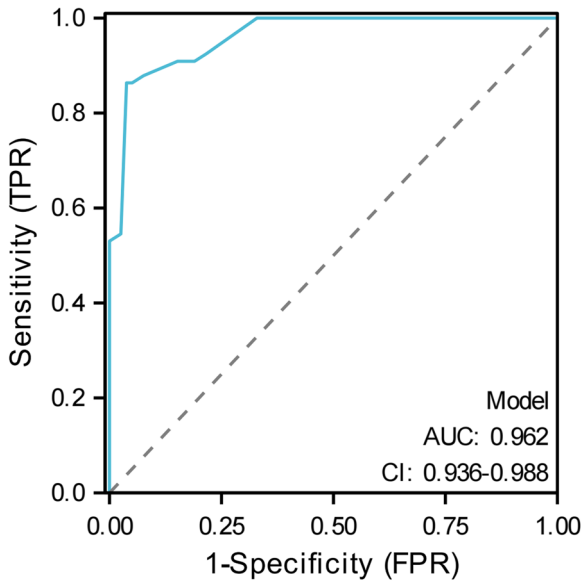

Fig. 4 ROC curve used to verify the predictive ability of the model

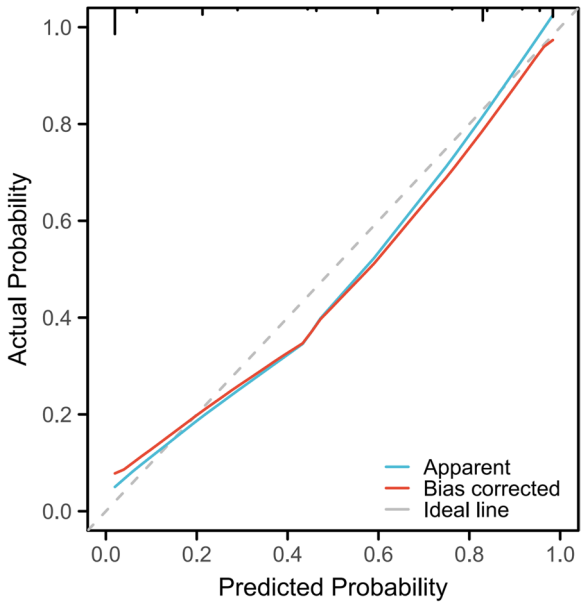

Fig. 5 Calibration curve of column chart prediction model (internal verification)

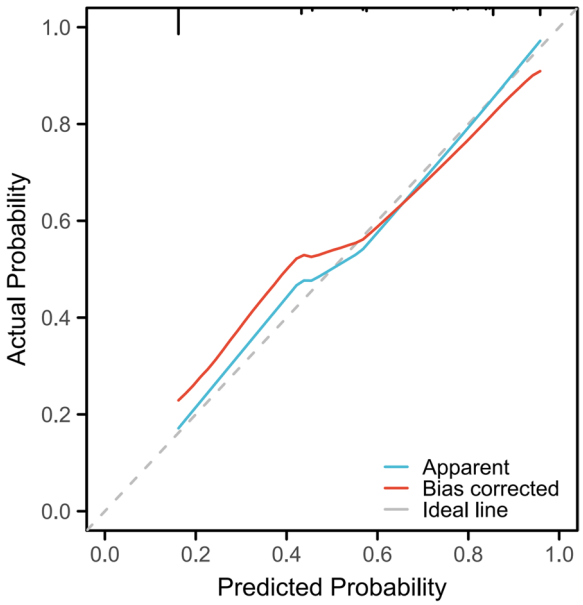

Fig. 7 Calibration curve of column chart prediction model (external verification)

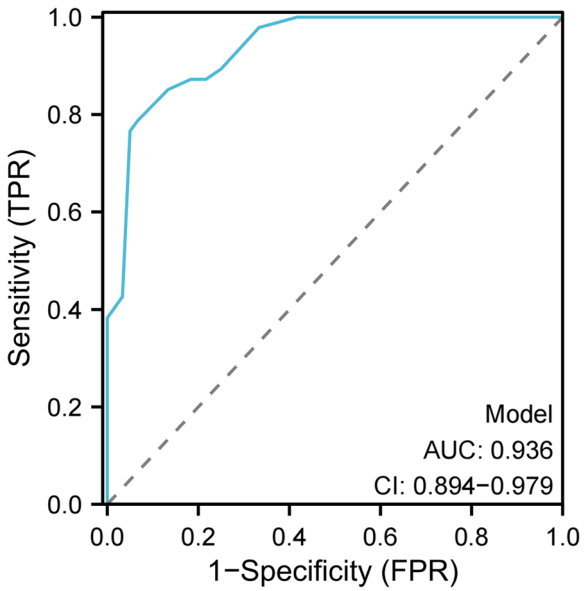

Fig. 6 ROC curve used to verify the predictive ability of the model (internal verification)

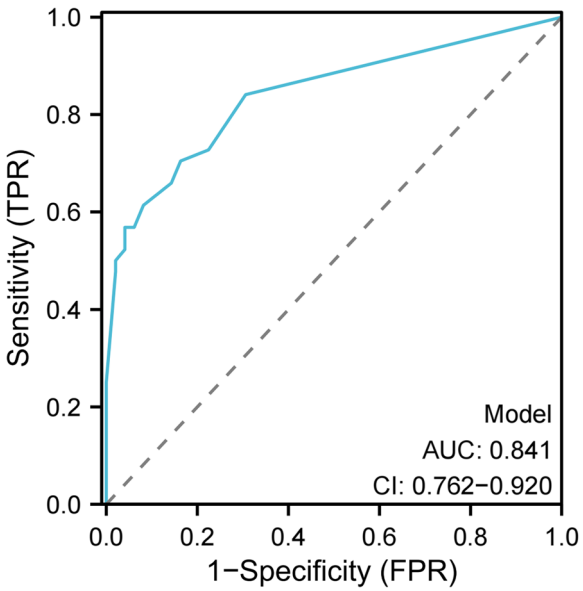

Fig. 8 ROC curve used to verify the predictive ability of the model (external verification)

Verification of nomogram prediction model

In the internal verification queue, the C index is 0.936 (0.894–0.979) by bootstrapping validation analysis, which shows that the model has good discrimination. The calibration curve also performed well in the verification set, as shown in Figs. 5 and 6. Similarly, we conducted external verification by collecting the relevant data of 93 patients with lower extremity fractures (including 44 patients with lower extremity deep vein thrombosis and 49 patients without lower extremity deep vein thrombosis) in the No.900th Hospital Cangshan branch from June 2023 to August 2024. The verification C index is 0.841 (0.761–0.921), and the calibration curve also performed well in the verification set, as shown in Figs. 7 and 8.

Discussion

Lower limb deep vein thrombosis is a kind of abnormal blood coagulation in the deep vein lumen, resulting in vascular stenosis or occlusion, which has been proved to be a common complication of lower limb fractures [1]. Considering that the pain at the fracture site in the early stage of trauma and local edema limit the movement of the patient's limbs, thereby slowing down the blood flow of the affected limb, coupled with the stress response caused by fractures, platelet adhesion may increase [15, 16]. Considering that deep vein thrombosis can bring bad prognosis to fracture patients and prolong the fracture healing time, in order to improve the quality of life of patients, it is clinically necessary to increase the assessment of early diagnosis and treatment of fracture patients with deep vein thrombosis risk [17]. However, in the past, a large number of studies have focused on exploring the prevention and treatment of thrombosis, and there have been relatively few studies related to the prediction of risk factors for lower limb thrombosis. At present, Doppler ultrasound (DUS) is a commonly used non-invasive examination method for deep vein thrombosis. Its positive rate for diagnosis of deep vein thrombosis of lower limbs can reach 95%, while its sensitivity for diagnosis of distal deep vein thrombosis is only 50%-70% [18]. Phlebography has high specificity and sensitivity, and when the clinical diagnosis of thrombosis by DUS is unclear, it can be diagnosed by phlebography [18]. However, due to its high price, complicated operation, invasive operation and other reasons, it is not conducive to the general survey of clinical diseases. At present, some researchers have proposed that the laboratory test results can be applied to the diagnosis of lower limb deep vein thrombosis to some extent, and confirmed that the levels of D-D and fibrinogen are at a high expression level in patients with deep venous thrombosis of lower limbs after fracture [19]. Pang et al. [20] also pointed out that PLT, D-D and FDP can be used as indicators to predict postoperative deep vein thrombosis in breast cancer patients, and the probability of postoperative deep vein thrombosis in breast cancer patients with high levels of PLT, D-D and FDP increased significantly. In this study, we divided the fracture patients into DVT group and non DVT group according to whether they were complicated with lower limb deep vein thrombosis at the time of admission. By comparing the levels of D-D, FIB, FDP and platelets between the two groups, we found that the levels of D-D, FIB, FDP and PLT in DVT group were higher than those in non DVT group, indicating that the levels of D-D, FIB, FDP and platelet were related to the occurrence of deep venous thrombosis in fracture patients. We used ROC curve to evaluate the levels of D-D, FIB, FDP and PLT in the peripheral blood of patients with lower limb fractures to predict lower limb deep vein thrombosis. The results showed that the four levels had a certain predictive value, and FIB was better than D-D, FDP and PLT in predicting the risk of fracture with thrombosis, while PLT had the weakest predictive effect.

In this study, we found that BMI, trauma site, whether diabetes was combined with history, platelets, D-D, FIB and FDP were related to the occurrence of deep venous thrombosis in lower limbs ($P<0.05$). However, the meaningful indicators of single factor were analyzed by multivariate Logistics regression model. The results showed that platelets, D-D, FIB and FDP were independent risk factors for deep venous thrombosis in patients with lower limb fractures ($P<0.05$). The analysis mainly includes the following reasons: (1) Fibrinolysis system is the key anticoagulant mechanism in the body, which can maintain the permeability Blood flow status and involvement in tissue repair [21]; As the degradation product of fibrin after plasmin is activated, D-D has strong antigenic specificity. Relevant research reports that its level increases with the activation of the fibrinolytic system [22], and its level change can be used to evaluate the balance between patients' coagulation and fibrinolytic systems, so it can be used as an important monitoring indicator of thrombotic diseases [23, 24]. (2) FIB, as a protein synthesized in the liver and involved in coagulation, belongs to a class of coagulation factors (coagulation factor I). It increases blood viscosity and peripheral resistance by promoting platelet aggregation, endothelial cell growth, proliferation, and enhancing smooth muscle contraction to accelerate thrombosis formation [25]. (3) FDP can reflect the activation of the fibrinolytic system and thrombosis of the body to a certain extent, and the FDP content is significantly higher than the normal value during primary fibrinolysis and venous thrombosis [26]. (4) PLT, as one of the common blood cells in the human body, are mainly involved in the hemostasis and coagulation processes of the body. People with higher levels of PLT in their peripheral blood are more likely to cause thrombosis than other populations (activated platelets can induce platelet aggregation by producing thromboxanes, leading to thrombosis) [10]. This study constructed a line chart risk prediction model based on independent risk factors (platelet, D-D, FIB, FDP) screened by logistic regression models. The predictive factors used in this model are common and easy to identify in clinical practice. The nomogram model shows strong predictive ability, good discrimination and consistency index (C-index) is 0.962 and 0.936, and the external verification C-index is 0.841, And during the validation process, the calibration curve showed that there was no significant difference ($P>0.05$) between the predicted risk probability of DVT using the column plot model and the actual observation results,

indicating that the predictive model had a good fit. The AUC value of ROC curve indicated that the nomogram has high prediction value. Therefore, the nomogram prediction model is expected to be a useful tool to guide the anticoagulation treatment of patients with lower extremity fractures. Clinicians can effectively predict and screen patients with lower limb fractures complicated with DVT and formulate corresponding individualized prevention and treatment plans based on this model. For low-risk patients with DVT, we can temporarily stop anticoagulation treatment, closely observe the vital signs of patients and reduce unnecessary anticoagulation risks. For high-risk patients with DVT, we can take timely preventive and therapeutic measures (even before DUS results are available), and immediately start preventive anticoagulant therapy (such as low molecular weight heparin) and other supportive interventions (such as early activities, physical therapy, compression socks and the use of pneumatic compression devices, etc.), which may reduce the incidence of DVT and related complications (such as pulmonary embolism), thus improving the quality of life of patients. There are certain limitations to this study. The sample size included in this study is small and the time span is long. Some patients are excluded because of lack of data, so selection bias cannot be ruled out. In the future research, we will further expand the sample size in order to provide more accurate data support for clinic.

In summary, patients with lower limb fractures combined with DVT have significantly increased levels of D-D, FIB, FDP, and PLT in their peripheral blood, which is a good predictive indicator for lower limb fractures combined with DVT. In clinical practice, dynamic detection of peripheral blood D-D, FIB, FDP, and PLT levels can be used for early screening and diagnosis of patients with lower limb fractures to avoid affecting their poor prognosis. In addition, the column chart constructed based on this has high clinical application value, which can help clinical doctors formulate or adjust reasonable diagnosis and treatment plans in a timely manner.

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Clinical trial number
Not applicable.

Authors' contributions
F Z: study design, data collection and manuscript writing. Xb C, Jq H: data collection and manuscript review. Xb C and C L: data collection and analysis

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted according to the ethical principles of medical research involving human subjects in the Declaration of Helsinki and have been approved by the biomedical ethics committee of the 900th Hospital of Joint Logistics Support Force (Number: 2024–093). Patients and their families signed informed consent before operation.
Written consent has been received from the subject.

Consent for publication
Written informed consent for publication was obtained from the participant.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of General Surgery, The 900th Hospital of Joint Logistic Support Force, PLA, Fuzhou, Fujian 350025, P.R. China.

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