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Combination of age-adjusted d-dimer, platelet distribution width and other factors predict preoperative deep venous thrombosis in elderly patients with femoral neck fracture

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Abstract

Purpose This retrospective cohort study aimed to identify factors associated with preoperative deep venous thrombosis (DVT) in elderly patients with femoral neck fractures, and to investigate whether combining these factors could improve the ability to predict DVT.

Method Medical records and laboratory test results were reviewed patients presenting with a femoral neck fracture and receiving routine chemoprophylaxis for DVT between January 2020 and December 2023 in a tertiary referral, university-affiliated hospital. Preoperative DVT was confirmed by Doppler ultrasound or CT venography. Demographic, injury, comorbidity, and laboratory variables were analyzed using univariate and multivariate approaches. The performance of combined predictive factors was evaluated using receiver operating characteristic (ROC) curve analysis.

Results Among the 499 patients included, 47 (9.4%) were diagnosed with a preoperative DVT. In the univariate analysis, five variables were found to be statistically significant, including alcohol consumption ($P=0.017$), history of renal disease ($P<0.001$), elevated D-dimer level (both traditional and age-adjusted cut-off used) ($P=0.007$ or <0.003), increased platelet distribution width (PDW) ($P<0.001$) and reduced albumin in continuous or categorical variable ($P=0.027$, $P=0.002$). Multivariate analysis confirmed all except alcohol consumption as independent predictors (all $P<0.05$). ROC curve analysis showed that combining these four significant variables with age improved the ability to predict preoperative DVT, with an area under the curve of 0.749 (95% CI: 0.676–0.822, $P<0.001$), sensitivity of 0.617, and specificity of 0.757.

Conclusion This study identified several factors associated with preoperative DVT, and combining them demonstrated improved performance in predicting DVT, which can facilitate risk assessment, stratification and improved management in clinical practice.

Keywords Deep venous thrombosis, Femoral neck fracture, Risk assessment and stratification, Age-adjusted D-dimer

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Introduction

Deep venous thrombosis (DVT) is highly prevalent in elderly patients with hip fractures, who face multiple risk factors such as advanced age, organ dysfunction, comorbidities, and major trauma [1]. Despite routine prophylaxis, the incidence of DVT following hip fracture remains high, up to 40% [2–6], and is especially higher in femoral neck fracture compared to intertrochanteric fracture (postoperative incidence, 17% vs. 4%) [7]. DVT is a major cause for pulmonary embolism (PE), which can occur acutely and is a leading cause of in-hospital death [8]. Currently, undifferentiated thromboprophylaxis and targeted surveillance of high-risk populations are the most cost-effective approaches.

D-dimer, a fibrin degradation product, demonstrates a sensitivity exceeding 90% for detection of DVT, and effectively in ruling out the condition; however, it should not be regarded as a diagnostic tool [9]. Recently, researchers have attempted to use age-adjust D-dimer threshold to improve the efficiency (i.e., specificity) in improving the exclusion of DVT/PE, suggesting age x 0.01 mg/L as new cut-off in a general older population [10–13]. However, that cut-off was not applicable to elderly hip fracture patients, as the hip fracture itself was a major DVT/PE risk factor. More recently, a study focused on elderly hip fracture patients proposed an optimal cutoff of age x 0.02 mg/L, which significantly improved specificity, from 37% when using the traditional 0.5 mg/L threshold to 61% [14]. Additionally, given the pathophysiology of DVT (hypercoagulability, endothelial injury and venous stasis) and thrombus composition [15], related factors, e.g. platelet indices (platelet count, mean platelet volume, platelet distribution), inflammatory/immune indices (white blood cell, lymphocyte, neutrophils et al.), clotting indices (prothrombin time, thrombin time, prothrombin activity et al.) may also be potentially predictive of DVT, but relevant literature is scarce.

Given this context, the present study aimed to: 1, identify the factors (from demographics, comorbidities, injuries, laboratory biomarkers) associated with preoperative DVT in elderly femoral neck fracture patients, and 2, investigate whether combining these factors could improve the performance in predicting DVT.

Materials and methods

Inclusion and exclusion criteria

This was a retrospective single-center study, and the study protocol was approved by the ethics committee of the Hebei Medical University Third Hospital, which waived the requirement for informed consent due to de-identity nature of the data used.

By reviewing medical records, the study enrolled patients aged 60 years or older who had a discharge diagnosis of femoral neck fracture and had undergone operative treatment in the Hebei Medical University Third Hospital between January 2020 and December 2023. The inclusion criteria were: an acute femoral neck fracture caused by low-energy injury (i.e., fall from a standing height or lower), independent mobility prior to fracture, surgery within 7 days of injury, and a definitive preoperative record of DVT status (yes or no) in the bilateral lower extremities. Patients were excluded if they had a pathological or metastatic fracture, open fracture, concurrent fracture, bilateral hip fractures, a preoperative wait exceeding 7 days, comorbid thrombophilia or hematological disorders, active malignancy, recent use of anticoagulants or glucocorticoids (within 3 months of injury), or incomplete medical records.

Diagnosis and prophylaxis for DVT

DVT status was confirmed by reviewing the color Doppler ultrasonography (DUS) or spiral CT venography reports, using the diagnosis criteria proposed by Guidelines for Prevention of Venous Thromboembolism in Major Orthopedic Surgery in China (2016 edition) issued by Chinese Orthopaedics Association [16].

As per the departmental standard protocol, patients diagnosed with an acute hip fracture are routinely administered with pharmacological prophylaxis (i.e. subcutaneous injection of standard-dose low-molecular-weight heparin (LMWH), 5000 IU of dalteparin or 40 mg of enoxaparin, once daily) and physical prophylaxis (i.e. elevation of injured extremity, quadriceps strength exercise and ankle pump practices), immediately upon admission.

The examined veins included the common femoral, superficial femoral, deep femoral, popliteal, posterior tibial, anterior tibial and peroneal veins. Thrombus in the intermuscular venous plexus of the calf was not included in this study, as it is considered less clinically significant. The criteria for DVT diagnosis included lumen obstruction or filling defect (on DUS and spiral CT venography), loss of or non-compressibility of the scanned vein with compression maneuvers, absence of spontaneous venous flow, and absence of Doppler signal or increase in vein diameter on DUS.

For patients who undergone serial DVT examinations for surveillance of progress of DVT, the data (date, location, involvement side) from the initial diagnosis were used for analysis.

Data collection

The data were extracted from the patients' medical records and the laboratory test reports. From the medical records, the following variables were collected: demographics (sex, age), lifestyle factors (smoking, alcohol consumption), comorbidities (body mass index (BMI),

hypertension, diabetes, pulmonary disease, cerebrovascular disease, liver disease, renal disease, and American Society of Anesthesiologists (ASA) score), and the time between injury and DVT screening or diagnosis. The laboratory data extracted included plasma albumin, fasting blood glucose (FBG), creatinine, white blood cell (WBC), neutrophil, lymphocyte, platelet, neutrophil/lymphocyte ratio (NLR), platelet /lymphocyte ratio (PLR), red blood cell (RBC), hemoglobin, hematocrit, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit, prothrombin time (PT), prothrombin activity (PTA), thrombin time (TT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen, and D-dimer.

To minimize the potential time-dependent confounding effects, the biomarker values closest to the index DVT diagnosis or the final screening were selected for analysis.

Statistical analysis

Patients were dichotomized into DVT or non-DVT group based on their DVT status. Continuous data were presented as mean ± standard deviation (SD), and their normality was assessed using the Shapiro-Wilk test. For normally distributed data, between-group comparisons were performed using the *Student's t-test*; otherwise, the *Mann-Whitney U test* was used. Categorical data were presented as counts and percentages, and comparisons were made using the *Chi-square or Fisher's exact test*, as appropriate.

To explore the role of various biomarkers in predicting DVT and identify their optimal cut-off values, receiver operating characteristic (ROC) curves were constructed for each variable. The Youden index (sensitivity + 1-specificity) was maximized to determine the optimal cut-off. The area under the curve (AUC), ranging from 0 to 100%, was used to evaluate the predictive ability, with higher values indicating better discriminability.

Variables, including demographics, injury-related factors, and biomarkers with significantly improved prediction ability ($P<0.05$) in the ROC analysis, were then compared between the DVT and non-DVT groups using univariate analyses. Those with substantial significance ($P<0.10$) in the univariate analyses were further entered into a multivariate logistic regression analysis to detect their independent effects on DVT, using the "enter" approach (i.e., the fully adjusted model). The odds ratio (OR) with a 95% confidence interval (95% CI) was estimated to represent the association magnitude. The Hosmer-Lemeshow (H-L) test was used to evaluate the goodness of fit of the model, with $P>0.05$ indicating an acceptable result.

Additionally, a further ROC curve was constructed with DVT as the outcome variable and the predicted probability of DVT, based on the variables with $P<0.10$ in the multivariate model, as the independent variable. The AUC, sensitivity, and specificity were estimated and compared to the ROC results for individual biomarkers.

The statistical significance was set as $P<0.05$ and all analyses were performed using SPSS 23.0 (IBM, Armonk, New York, USA).

Results

Initially, 749 patients were screened, and 174 were exclude due to pathological or metastatic fracture ($n=36$), open fracture ($n=13$), concurrent fracture ($n=42$), bilateral hip fractures ($n=6$), preoperative wait exceeding 7 days ($n=52$), comorbid thrombophilia or hematological disorders ($n=17$), active malignancy ($n=11$), recent use of anticoagulants or glucocorticoids (within 3 months of injury) ($n=49$), or incomplete medical records ($n=24$), leaving 499 for data analysis. There were 153 males and 346 females, and the mean age was 72.6 ± 8.2 years (interquartile range, 66 to 79 years).

Table 1 Non-significant variables in predicting DVT analyzed by ROC curve

Variable	AUC	95%CI		*P*
		Lower limit	Upper limit	
BMI	0.535	0.455	0.615	0.436
FBG	0.539	0.458	0.620	0.384
Creatinine	0.541	0.451	0.630	0.362
WBC	0.511	0.424	0.598	0.803
Neutrophil	0.514	0.600	0.427	0.514
Lymphocyte	0.568	0.480	0.655	0.130
NLR	0.556	0.638	0.474	0.556
PLR	0.534	0.618	0.449	0.534
RBC	0.561	0.478	0.644	0.173
Hemoglobin	0.569	0.484	0.654	0.124
Hematocrit	0.558	0.471	0.644	0.196
Platelet count	0.568	0.484	0.652	0.128
MPV	0.564	0.650	0.478	0.151
Plateletcrit	0.518	0.432	0.604	0.687
PT	0.548	0.633	0.463	0.283
PTA	0.538	0.460	0.616	0.392
INR	0.534	0.617	0.452	0.444
APTT	0.565	0.652	0.478	0.147
TT	0.576	0.666	0.486	0.089
Fibrinogen	0.502	0.412	0.592	0.958

Abbreviation: *ROC* Receiver operating characteristic, *FBG* Fasting blood glucose, *WBC* White blood cell, *NLR* Neutrophil/lymphocyte ratio, *PLR* Platelet/lymphocyte ratio, *RBC* Red blood cell, *MPV* Mean platelet volume, *PDW* Platelet distribution width, *PT* Prothrombin time, *PTA* Prothrombin activity, *TT* Thrombin time, *APTT* Activated partial thromboplastin time, *INR* International normalized ratio

Forty-seven (9.4%) patients were diagnosed with preoperative DVT, and 6 of these patients underwent inferior vena cava (IVC) filter placement to prevent pulmonary embolism. The time to DVT diagnosis was 3.7 ± 1.3 days, with over 2/3 (32/47) occurring after 3 days. There were 85 clots detected, averaging 1.8 (1 to 3) per DVT case. The most commonly involved veins were the fibular vein (59.6%, 28/47), followed by the posterior tibial vein (29.8%, 14/47) and the popliteal vein (23.4%, 11/47). The incidence of proximal DVT (popliteal vein or proximal) was 38.3% (18/47).

The ROC analysis of 20 continuous variables, including body mass index and 20 laboratory indices, did not show any statistically significant predictors of DVT occurrence (Table 1; Fig. 1). However, plasma albumin, platelet distribution width (PDW), and D-dimer (using traditional or age-adjusted cut-offs) were found to be significant predictors of DVT, with favorable area under the curve (AUC) values ranging from 0.596 to 0.611, and sensitivities and specificities ranging from 0.509 to 0.872 and 0.319 to 0.723, respectively (Table 2; Fig. 2).

The univariate analysis comparing the DVT and non-DVT groups (Table 3) showed that patients with DVT were more likely to be alcohol drinkers (53.2% vs. 29.9%, $p=0.017$), have a higher prevalence of renal disease (21.3% vs. 6.6%, $p<0.001$), lower albumin levels (72.3% vs. 49.1%, $p=0.002$), and a higher prevalence of elevated D-dimer using traditional (87.2% vs. 68.1%, $p=0.007$) or age-adjusted cut-offs (55.3% vs. 33.2%, $p=0.003$). Additionally, the DVT group had a lower prevalence of PDW ≥ 16.4% (31.9% vs. 61.5%, $p<0.001$). The DVT group also appeared to be older (74.3 vs. 72.5 years) and had a trend towards a longer interval to DVT screening or diagnosis (68.1% vs. 54.2%), but these differences were not statistically significant ($p=0.078$, $p=0.068$).

In the multivariate analysis, age, renal disease, D-dimer with age-adjusted cut-off, albumin and PDW were retained, with $p<0.10$) (Table 4), which were combined for calculation the probability of DVT. The Hosmer-Lemeshow test showed an acceptable goodness-of-fit for the final model ($\chi 2=10.261$, $p=0.114$; Nagelkerke $R^2=0.139$). The ROC analysis combining these 5 variables (Fig. 3) yielded an AUC of 0.749 (95% CI, 0.676 to 0.822, $p<0.001$), with a sensitivity of 0.617 and a specificity of 0.757.

Discussion

The present study identified four independent risk factors for deep vein thrombosis (DVT): renal disease, elevated D-dimer, lower albumin, and platelet distribution width (PDW) < 16.4%. Moreover, the combination of these factors, along with age, demonstrated improved predictive ability for DVT, with an area under the curve (AUC) of 0.749, confirming the study hypothesis. The Nagelkerke

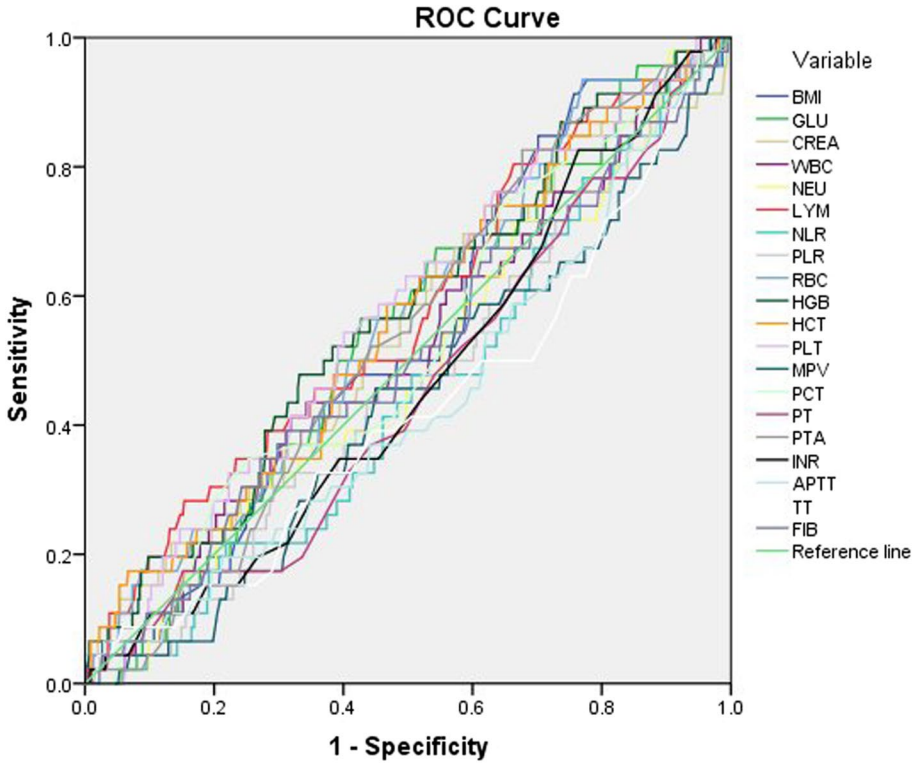

Fig. 1 The ROC curves for 20 blood parameters that are not statistically significant

Table 2 ROC curves showing blood parameter with a significantly improved ability in predicting DVT

Variable	Cut-off	Sensitivity	Specificity	AUC	95%CI		*P*
					Lower limit	Upper limit	
D-Dimer (age adjusted)	Age*0.02 mg/L	0.553	0.668	0.611	0.524	0.697	0.012
D-dimer (traditional)	0.5 mg/L	0.872	0.319	0.595	0.518	0.673	0.031
PDW	16.4%	0.615	0.681	0.604	0.516	0.691	0.019
Albumin	35 g/L	0.509	0.723	0.607	0.528	0.686	0.016

R^2 was 0.139, indicating that 13.9% of the variability in the outcome variable can be explained by the predictors included in the multivariate regression model.

Interestingly, the reported incidence of preoperative DVT in this study (9.4%) was lower than recently published rates, which have ranged from 20.1 to 37.6% [2, 4, 17]. This discrepancy can be largely attributed to the researchers' efforts to minimize potential confounding factors. First, the study excluded calf muscle venous thrombosis, which is less clinically significant in the context of acute trauma requiring emergency surgery. Previous studies have reported that calf muscle venous thrombosis accounts for 47–79% of DVT cases [18–20]. Second, the researchers excluded several well-established risk factors for DVT, such as pre-injury poor mobility, underlying thrombophilia or hematological disorders, and recent use of anticoagulants or glucocorticoids. Third, the study only included patients who underwent surgery within 7 days of injury, as prolonged waiting is a strong risk factor for DVT [2, 6].

Platelet and coagulation indices are potentially useful predictors of DVT, considering the pathophysiological conditions for DVT (Virchow triad: hypercoagulability, endothelial injury and venous stasis) [21]. In this study, we identified PDW < 16.4% as an independent risk factor (OR, 3.494), which seemed contradict the mainstream view [22], since PDW was a well-known marker of activation of coagulation [23]. Indeed, timing of blood sampling may explain this "paradox". During pre-thrombosis stage, platelet activation with membrane ballooning and pseudopod formation of leaded to an increased platelet volume and the secondary PDW increase [24]. However, at late-stage massive platelet-derived microparticles were released from larger volume platelets, leading to a decreased platelet volume, with homogeneous platelets left, leading to a reduced PDW [25]. Therefore, it was very possible that a substantial proportion of blood samples were taken at the late stage of thrombosis or after the thrombus had already formed, given the dynamic changes of coagulation state or inflammatory/immune

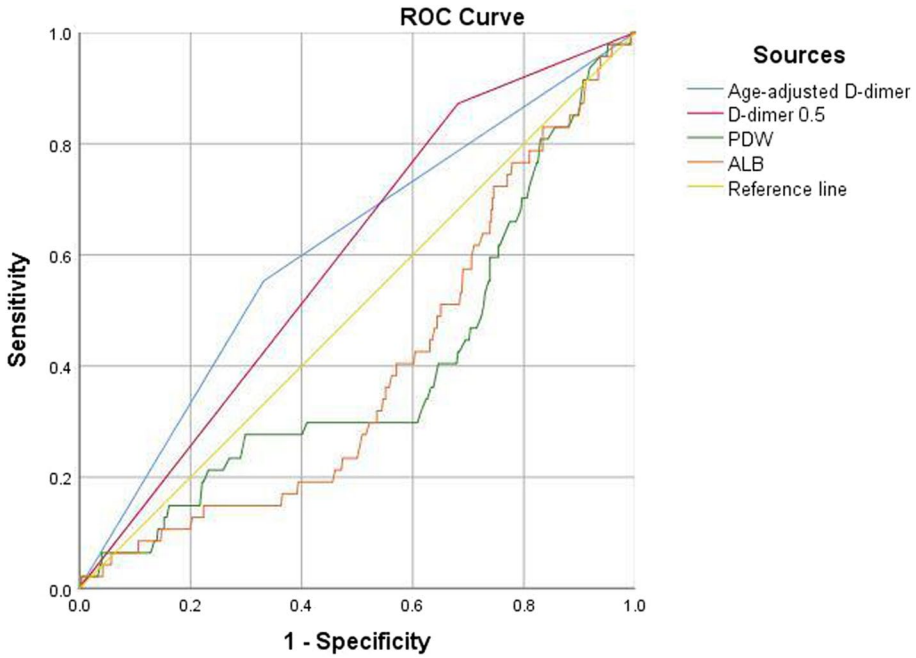

Fig. 2 The ROC curve for plasma age-adjusted D-dimer cutoff, traditional cut-off value (0.5mg/L), PDW and albumin concentration

Table 3 Univariate analysis of potential factors associated with DVT

Variables	Number (%) of patients with non-DVT($n=452$)	Number (%) of patients with DVT ($n=47$)	*P*
Gender (males)	138 (30.5)	15 (31.9)	0.845
Age (years)	72.5 ± 8.3	74.3 ± 7.2	0.078
Body mass index (BMI)	23.5 ± 3.7	23.9 ± 3.8	0.529
< 24.0	248 (54.9)	25 (53.2)	0.728
24.0–27.9	152 (33.6)	18 (38.3)	
≥ 28	52 (11.5)	4 (8.5)	
Smoking	84 (18.6)	12 (25.5)	0.250
Alcohol drinking	135 (29.9)	22 (53.2)	0.017
Hypertension	211 (46.7)	21 (44.7)	0.794
Diabetes mellitus	86 (19.0)	6 (12.8)	0.292
Pulmonary disease	12 (2.7)	1 (2.1)	0.829
Cerebrovascular disease	117 (25.9)	13 (27.7)	0.792
Liver disease	15 (3.3)	1 (2.1)	0.659
Renal disease	30 (6.6)	10 (21.3)	< 0.001
Interval between injury and DVT examination or diagnosis (days)	3.7 ± 1.3	3.9 ± 1.4	0.361
≤ 3	207 (45.8)	15 (31.9)	0.068
> 3	245 (54.2)	32 (68.1)	
ASA score			0.818
I	23 (5.1)	1 (2.1)	
II	275 (60.8)	30 (63.8)	
III and IV	154 (34.1)	16 (34.1)	
D-dimer > age*0.02 mg/L	150 (33.2)	26 (55.3)	0.003
D-dimer > 0.5 mg/L	308 (68.1)	41 (87.2)	0.007
PDW (%)	16.1 ± 1.7	15.9 ± 1.7	0.296
≥ 16.4	278 (61.5)	15 (31.9)	< 0.001
< 16.4	174 (38.5)	32 (68.1)	
Albumin	35.0 ± 5.8	32.9 ± 5.3	0.027
< 35 g/L	222 (49.1)	34 (72.3)	0.002
≥ 35 g/L	230 (50.9)	13 (27.7)	

Abbreviation: *DVT* Deep venous thrombosis, *BMI* Body mass index, *ASA* American Society of Anesthesiologists, *PDW* Platelet distribution width

conditions reported in literature on trauma [26]. On the other hand, a PDW < 16.4% may signify diminished platelet responsiveness or substantial platelet depletion over a short period of time in the context of hip fractures, reflecting the post-fracture vascular injury status, potentially predisposing these patients to thrombotic events. Our finding was consistent with a recent report that increase of 1% of PDW was associated with reduced risk of DVT by 47.4% [27].

The traditional cut-off value of 0.5 mg/L for plasma D-dimer showed very low- or non-specificity for diagnosis of VTE in elderly patients, with reported specificity ranging from 0 to 18% in those aged 80 years or older [28–31]. In the present study, we used the age-adjusted cut-off value (age*0.02 mg/L) proposed by Zhang et al. [14] for elderly hip fracture patients. This approach demonstrated improved predictive ability (increase in AUC from 0.595 to 0.611) and specificity (increase from 0.319 to 0.668), compared to using the traditional 0.5 mg/L cut-off. The age-adjusted D-dimer policy, alone or combined with other indices, could potentially increase the utility of a D-dimer testing for the exclusion of preoperative DVT. However, However, the study did not find associations between platelet-to-lymphocyte ratio (PLR) or neutrophil-to-lymphocyte ratio (NLR) (novel inflammatory/immune-derived markers from platelets, neutrophils, and lymphocytes) and VTE, despite reports of their association with VTE in different clinical conditions [32–34].

The combination of the five variables generated an improved predictive ability for DVT compared to any individual factor, and could therefore be considered as a useful auxiliary tool. On one hand, these results assist in predicting the occurrence of DVT, evaluating individual DVT risk, and facilitating patient risk stratification. For

Table 4 Multivariate analysis results showing factors associated with increased risk of DVT

Variable	OR	95%CI	*P*
Age	1.036	0.994 to 1.079	0.095
Renal disease	2.395	1.005 to 5.706	0.047
D-Dimer (> age-adjusted cut-off)	2.718	1.437 to 5.141	0.002
Albumin < 35 g/L	2.499	1.248 to 5.002	0.010
PDW < 16.4%	3.494	1.733 to 7.043	< 0.001

high-risk patients, targeted and enhanced preventive or intervention measures can be promptly implemented. On the other hand, we acknowledge that the relatively lower sensitivity (0.617) may be of less clinical importance, implying the risk of false-negative test results would still be present in a certain proportion of patients. It is important to note that the predictive power of the combination model is moderate, with an AUC of 0.749, falling short of the optimal threshold typically established at 0.90 or higher for clinical utility. Nonetheless, this model still holds significant potential for improving risk assessment and stratification. Given the intricate nature of this specific patient population and the necessity for prompt surgical interventions, this finding facilitates the identification of high-risk individuals, thereby enabling the prioritization of screening efforts and ensuring surgical safety.

The strengths of this study included the identification of novel biomarkers from a comprehensive set of laboratory test indices ($n=23$) after adjustment for a variety of confounding factors in a high-risk population. However, several limitations should be noted. First, the retrospective design may have introduced biases that could compromise the accuracy of data collection. Specifically, the reliance on historical records can lead to incomplete or inconsistent data. Thereby affecting the overall reliability of the findings. Second, as an observational study, the relationships identified in our analysis are inherently associative rather than causative; thus, caution is warranted in interpreting the results. Additionally, the Nagelkerke R^2 value was relatively modest at 0.139. Given the complexity of injuries like hip fracture in frail populations, this is anticipated and suggested significant confounding effects from unmeasured variables. Third, the relatively small sample size raises concerns about the statistical power, increasing the likelihood of type II errors and limiting the capacity for more nuanced analyses. Lastly, the single-center design, particularly within a level I trauma center, may restrict the generalizability of our findings to other setting and populations. Therefore, future prospective, multicenter studies are warranted to

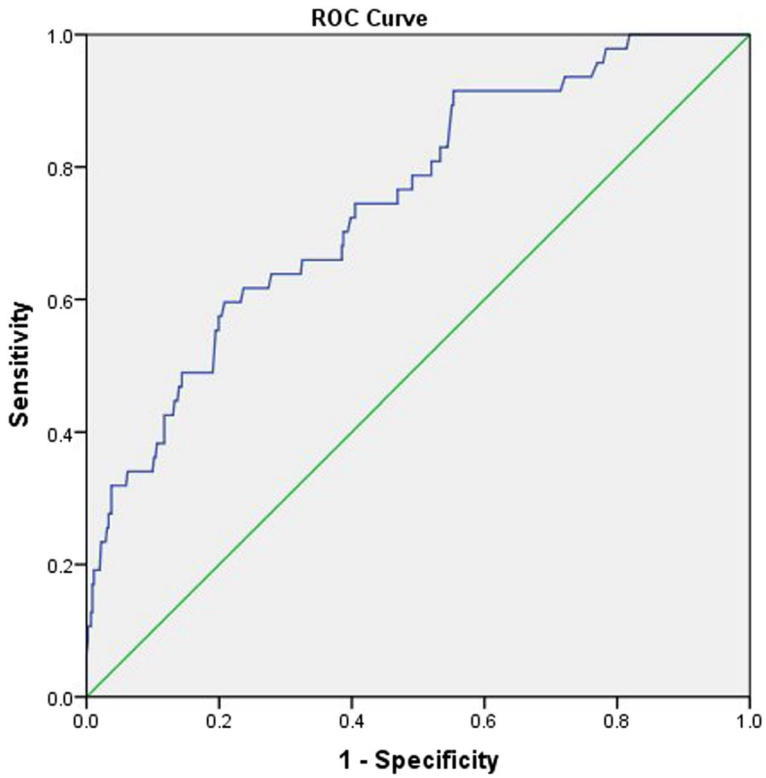

Fig. 3 The ROC curve for generated combination index (age, renal disease history, PDW, albumin and D-dimer with age-adjusted cut-off, combined), with an AUC of 0.749 (95%CI, 0.676 to 0.822,*P*<0.001), with a sensitivity of 0.617 and a specificity of 0.757

further elucidate the role of dynamic changes in PDW and other biomarkers in development of DVT.

In conclusion, we reported a relatively low rate of preoperative DVT in a high-risk elderly hip fracture patient population receiving routine thromboprophylaxis after admission. Four routinely measured biomarkers were identified as increasing the risk of DVT, and their combination with age demonstrated improved performance in predicting DVT, thereby facilitating risk assessment, stratification and management.

Abbreviations

DVT	Deep venous thrombosis
PE	Pulmonary embolism
BMI	Body mass index
ASA	American Society of Anesthesiologists
FBG	fasting blood glucose
WBC	White blood cell
NLR	Neutrophil/lymphocyte ratio
PLR	Platelet /lymphocyte ratio
RBC	Red blood cell
MPV	Mean platelet volume
PDW	Platelet distribution width
PT	Prothrombin time
PTA	Prothrombin activity
TT	Thrombin time
APTT	Activated partial thromboplastin time
INR	International normalized ratio
SD	Standard deviation
ROC	Receiver operating characteristic
AUC	Area under the curve
DUS	Doppler ultrasound
LMWH	Low-molecular-weight heparin
OR	Odd ratio
CI	Confidence interval
VTE	Venous thromboembolism

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Authors' contributions
Y.Z. and P.C. conceived the idea for the study. W.Q., F.W., L.L, and X.L. collected the relevant data. T.Z. prepared the figures and tables. Y.L. and T.Z. performed the statistical analyses. Y.Z. interpreted the data. P.C. and T.Z. drafted this manuscript, and Y.L. and Y.Z. revised and approved the final version.

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Data availability
All the data will be available upon motivated request to the corresponding author of the present paper.

Declarations

Ethics approval and consent to participate
The authors confirmed that all experiments were performed in accordance with relevant guidelines and regulations. The study protocol was approved by the ethics committee of the local hospital, which waived the need for informed consent from participants due to the deidentified data used herein.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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