Frequency and Risk Factors of Deep Venous Thrombosis in Aged Patients with Intertrochanteric Fracture on Admission

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ABSTRACT

Objective: To investigate the frequency of deep vein thrombosis (DVT) in patients aged over 80 years on admission after intertrochanteric femur fracture and to explore the risk factors of DVT.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Orthopaedics, China-Japan Friendship Hospital, Beijing, China, from 1st January 2019 to 31st December 2022.

Methodology: A group of patients aged over 80 years with intertrochanteric fracture were included according to the presence or absence of DVT confirmed by ultrasonography on admission. The patients were divided into the non-DVT and DVT groups. Clinical data were retrospectively compared between the two groups and analysed by multivariate logistic regression to screen risk factors of DVT.

Results: A total of 130 patients meeting the inclusion criteria were enrolled, and 37 of them had DVT on admission, with a prevalence of 28.5%, including 25 (67.6%) distal peripheral DVT, 11 (29.7%) proximal central DVT, and 1 (2.7%) mixed DVT. The American Society of Anaesthesiologists (ASA) classification, Charlson comorbidity index, the serum levels of D-dimer, fibrinogen degradation products, albumin, potassium, inorganic phosphorus, and calcium showed significant differences between the two groups ($p < 0.1$). Multivariate analysis identified increased D-dimer (>6.005 mg/L), decreased albumin (<36.45 g/L), and reduced potassium (<3.650 mmol/L) as independent factors for DVT in aged intertrochanteric fracture patients (AIFPs).

Conclusion: A high incidence of DVT was revealed in AIFPs, and elevated D-dimer levels, reduced albumin levels, and reduced potassium concentrations were shown to be correlated to DVT.

Key Words: *Intertrochanteric fracture, Deep vein thrombosis, Aged patients, Risk factor, Multivariate logistic regression.*

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INTRODUCTION

Increased expected age is leading to an increase in the incidence of hip fracture, which will cause more than 6 million cases worldwide by 2050.[1] After orthopaedic trauma, venous thromboembolism as a potentially fatal complication can occur.[2] Deep vein thrombosis (DVT) is often associated with hip fractures and can lead to chronic pain, secondary varicose veins, ulcers or potentially fatal pulmonary embolism.[3] Previous studies have shown that the incidence of preoperative DVT in hip fractures is 8 to 34.9%.[3,4] In addition, aged patients after fracture are often in poor physical condition, so advanced age is reported to be an independent risk factor of DVT.[5-7] It is a crucial and challenging job to identify risk factors for preoperative DVT in aged patients after fracture because of numerous noteworthy risk factors.

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Currently, the available related studies are limited. Moreover, early detection and prevention of thromboembolism in aged patients with intertrochanteric fractures remain controversial. Therefore, it is important for patients' prognosis to understand the risk factors for DVT in aged intertrochanteric fracture patients (AIFPs), which may be beneficial to the timely interventions. The aim of this study was to retrospectively analyse the clinical data of AIFPs over 80 years of age at the time of admission to identify the epidemiologic characteristics and associated risk factors of DVT.

METHODOLOGY

The study got approval from the Ethical Board of the China-Japan Friendship Hospital (ERB No. 2023-KY-145) and was carried out in accordance with the instructions of the Declaration of Helsinki. A total of 130 AIFPs treated at the Department of Orthopaedics in China-Japan Friendship Hospital, Beijing, China, from 1st January 2019 to 31st December 2022 were recruited. The inclusion criteria were patients over 80 years old, low-energy trauma-caused unilateral intertrochanteric fracture, and admission within 7 days of fracture. Participants with high-energy injuries, open or multiple injuries, surgical intolerance, history of venous thromboembolism, pathologic fractures, anticoagulant treatments, cancer treatments, and incomplete imaging or lab examination were excluded.

All patients underwent a Duplex ultrasonography of both legs on admission for the presence of DVT, which was conducted and reviewed by radiologists. DVT was manifested with vein incompressibility, solid echo, and blood flow signal-filling defect in the cavity and patients were grouped into the proximal central (popliteal, femoral, and iliac veins), distal peripheral (calf muscle, fibular, anterior / posterior tibial veins), and mixed thrombosis.[8] According to the presence or absence of DVT on admission, the enrolled AIFPs combined with DVT were identified as the DVT group (n = 37), and patients without DVT were the non-DVT group (n = 93).

The clinical data of all the patients on admission were collected based on the resource management platform of China-Japan Friendship Hospital. These data were age, gender, body mass index (BMI), injury-related characteristics (site, time from injury to admission, and fracture type based on AO / OTA classification), The American Society of Anaesthesiologists (ASA) classification, Charlson comorbidity index, laboratory test results on admission including white blood cell count (WBC), red blood cell count (RBC), haemoglobin (HGB), platelet (PLT), alanine aminotransferase (ALT), albumin (ALB), fasting blood glucose (GLU), serum sodium (Na), serum potassium (K), inorganic phosphorus (IP), serum calcium (Ca), creatinine (CR), estimated glomerular filtration rate (eGFR), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, and fibrinogen degradation products (FDP).

Statistical analysis was carried out using the software SPSS version 20.0. The measurement data were presented as mean ± standard deviation or median and quartile based on normal distribution by Kolmogorov–Smirnov test. Student's t-test or Mann–Whitney U test was performed for the comparison of means or medians between the two groups, respectively. The categorical data were expressed as count and percentage, and compared by Chi-squared test. Univariate analysis was used to investigate risk factors with approximately significant ($p < 0.1$) contributions to the occurrence of DVT. Some DVT-associated continuous variables were converted to categorical variables by the cut-off values, obtained by maximum Youden index (sensitivity + specificity-1) in receiver operating characteristic (ROC) curves to evaluate the relationship of new variables and DVT. Multivariate stepwise logistic regression analysis was further adopted to analyse the factors with significant difference and generate adjusted odds ratios (ORs). A $p < 0.05$ was considered statistically significant.

RESULTS

According to the presence or absence of DVT on admission, 37 patients with a mean age of 86.5 ± 3.9 years and a gender ratio of 10:27 (male:female) were diagnosed with DVT and identified as the DVT group, so the prevalence of DVT in intertrochanteric fracture patients over 80 years old on admission was 28.5% in this study. As for the DVT location, 25 (67.6%) patients had distal peripheral DVT, 11 (29.7%) had proximal central DVT, and 1 (2.7%) had mixed DVT.

There were no significant differences in age, gender, BMI, injury side, time from injury to admission, fracture classification, and the levels of WBC, RBC, HGB, PLT, ALT, GLU, Na, CR, eGFR, PT, and APTT between the non-DVT, and DVT groups ($p > 0.1$). However, ASA classification, Charlson comorbidity index, and the levels of D-dimer, FDP, ALB, K, IP, and Ca showed significant differences between the two groups ($p < 0.1$, Table I).

Table I: Comparison of clinical data between the non-DVT and DVT groups.

Variables	Non-DVT (n = 93)	DVT (n = 37)	p-value
Age (years)	86.7 ± 4.6	86.5 ± 3.9	0.853[1]
Gender (n, %)			0.485[2]
Male	31 (33.3%)	10 (27.0%)	
Female	62 (66.7%)	27 (73.0%)	
BMI (kg/m^2)	22.51 ± 4.29	22.67 ± 4.05	0.854[1]
Injury side (n, %)			0.892[2]
Left	44 (47.3%)	18 (48.6%)	
Right	49 (52.7%)	19 (51.4%)	
Time from injury to admission (days)	1.0 (0.4-2.0)	1.0 (1.0-2.5)	0.412[3]
Fracture classification (n, %)			0.839[2]
Stable	56 (60.2%)	23 (62.2%)	
Non-Stable	37 (39.8%)	14 (37.8%)	
ASA class (n, %)			0.007[2]
2	33 (35.5%)	6 (16.2%)	
3	59 (63.4%)	28 (75.7%)	
4	1 (1.1%)	3 (8.1%)	
Charlson comorbidity index	5 (4-6)	5 (5-6)	0.065[3]
WBC (×10^9/L)	8.86 ± 2.4	8.44 ± 2.6	0.381[1]
RBC (×10^{12}/L)	3.36 ± 0.59	3.42 ± 0.67	0.641[1]
HGB (g/L)	104.5 ± 18.1	104.9 ± 17.2	0.918[1]
PLT (×10^9/L)	191.8 ± 69.4	186.0 ± 56.9	0.650[1]
ALT (g/L)	15 (10.5-19)	14 (11-19.5)	0.871[3]
ALB (g/L)	36.8 ± 3.0	35.7 ± 3.5	0.078[1]
GLU (g/L)	6.87 (5.98-8.25)	7.02 (6.00-8.93)	0.518[3]
K (mmol/L)	4.00 (3.75-4.40)	3.8 (3.45-4.00)	0.004[3]
Na (mmol/L)	138.0 ± 3.4	137.3 ± 5.1	0.326[1]
IP (mmol/L)	1.025 (0.91-1.16)	0.98 (0.89-1.07)	0.066[3]
Ca (mmol/L)	2.16 ± 0.13	2.11 ± 0.13	0.040[1]
CR (μmol/L)	72.6 (61.8-94.2)	64.1 (57.2-85.7)	0.860[3]
eGFR [mL/(min*1.73 m^2)]	70.5 (55.7-79.7)	78.7 (58.9-83.7)	0.145[3]
PT (s)	14.2 ± 0.8	14.4 ± 0.7	0.293[1]
APTT (s)	39.7 ± 6.2	41.2 ± 7.5	0.245[1]
D-dimer (mg/L)	3.89 (2.07-7.02)	6.46 (2.71-13.4)	0.001[3]
FDP (ug/mL)	14.38 (6.97-31.43)	22.58 (11.07-48.73)	0.034[3]

[1]Data are presented as mean ± standard deviation and compared by Student's t-test. [2]Data are presented as count and percentage and compared by Chi-squared test. [3]Data are presented as median and quartile and compared by Mann–Whitney U test.
BMI: Body mass index, ASA: American Society of Anaesthesiologists, WBC: White blood cell count, RBC: Red blood cell count, HGB: Haemoglobin, PLT: Platelet, ALT: Alanine aminotransferase, ALB: Albumin, GLU: Fasting blood glucose, Na: Serum sodium, K: Serum potassium, IP: Inorganic phosphorus, Ca: Serum calcium, CR: Creatinine, eGFR: Estimated glomerular filtration rate, PT: Prothrombin time, APTT: Activated partial thromboplastin time, FDP: Fibrinogen degradation products.

By analysis of the ROC curve as shown in Figure 1 and Youden's index, the cut-off levels of these laboratory indexes were determined to be D-dimer of 6.005 mg/L, FDP of 20.78 μg/ml, ALB of 36.45 g/L, K of 3.650 mmol/L, IP of 1.075 mmol/L, and Ca of 2.045 mmol/L. After converting these six variables into categorical variables, they were still associated with DVT as shown in Table II.

The eight indexes with significant difference in the univariate analysis were used as independent variables, and the presence of DVT in AIFPs was set as the dependent variable in multivariate stepwise logistic regression analysis. The results showed that high D-dimer level (>6.005 mg/L, OR 3.586, 95% CI 1.501-8.570, p = 0.004), low ALB level (<36.45 g/L, OR

3.370, 95% CI 1.393-8.152, p = 0.007), and low P level (<3.650 mmol/L, OR 2.886, 95% CI 1.092-7.627, p = 0.033) were risk factors for DVT on admission in AIFPs. Hosmer-Lemeshow test indicated this model's fitness was good (χ^2 = 2.274, p = 0.810).

Table II: Categorical variables by thresholding significantly associated continuous variables from laboratory tests.

Variables	Non-DVT (n = 93)	DVT (n = 37)	Maximum Youden's index	p-value
ALB <36.45 g/L	35 (37.6%)	24 (64.9%)	0.272	0.005
K<3.650 mmol/L	11 (11.8%)	13 (35.1%)	0.233	0.002
IP <1.075 mmol/L	55 (59.1%)	29 (78.4%)	0.192	0.038
Ca <2.045 mmol/L	12 (12.9%)	12 (32.4%)	0.249	0.010
D-Dimer >6.005 mg/L	30 (32.3%)	22 (59.5%)	0.272	0.004
FDP >20.78 ug/ml	31 (33.3%)	22 (59.5%)	0.261	0.006

All data are presented as count and percentage and compared by Chi-squared test. ALB: albumin, K: Serum potassium, IP: Inorganic phosphorus, Ca: Serum calcium, FDP: Fibrinogen degradation products.

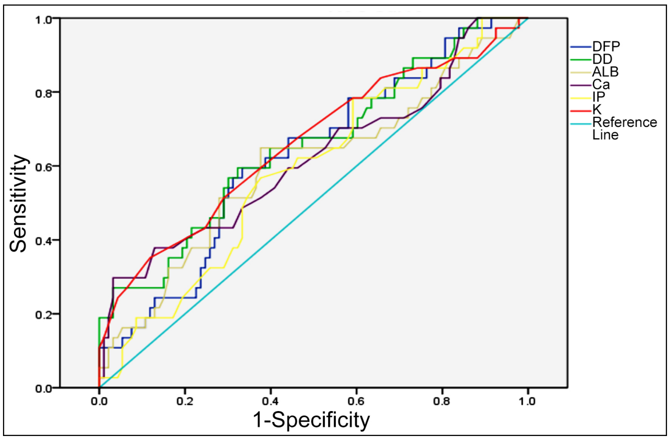

Figure 1: ROC curve for logistic regression model of significant DVT-associated continuous variables.
ALB: Albumin, K: Serum potassium, IP: Inorganic phosphorus, Ca: Serum calcium, FDP: Fibrinogen degradation products.

DISCUSSION

DVT is often associated with fractures, especially in aged hip fracture patients.[9] Currently, most studies of DVT on admission after hip fractures have focused on elderly patients aged over 60 years. Fan *et al.* demonstrated that DVT developed in 20.8% of AIFPs on admission.[5] Zuo *et al.* reported that 20.1% of intertrochanteric fracture patients had DVT on admission.[10] This study demonstrated that the prevalence of DVT on admission was 28.5% in AIFPs over 80 years old, which was higher than previous results. Age increases the risk of in-hospital venous thrombus embolism.[7] The older age of patients in this study might explain the high prevalence of DVT. It is worth noting that this study provides the first evidence of DVT on admission in AIFPs over 80 years old. Moreover, the incidence of proximal central and mixed DVT was 32.4%, which was not low compared to 12.2% in the study of Xing *et al*.[11] On the other hand, the incidence of distal DVT was 67.6%, including calf muscular vein thrombosis which can develop commonly after hip fractures and is usually asymptomatic.[12] Increasing evidence has shown no difference in the occurrence of pulmonary embolism or death between asymptomatic and symptomatic DVTs.[13] It points out the necessity to perform routine DVT screening in AIFPs on admission.

In this study, high D-dimer level, low ALB level, and low P level were risk factors for DVT on admission in AIFPs. D-dimer is a common index for venous thromboembolism and can be upregulated in hip fracture patients along with the activation of the coagulation process. The threshold value of D-dimer for DVT diagnosis is controversial. Xing *et al.* reported the diagnostic D-dimer threshold was 5.035 mg/L in patients with hip fracture, whose mean age was 78.72 ± 8.68 years.[11] It has been reported in many previous studies that the level of D-dimer increases with age.[14] As this study shows, the threshold value of D-dimer was 6.005 mg/L with a sensitivity of 0.595 and a specificity of 0.677, which is higher than that reported in the study of Xing *et al*.[11] It may be because of the higher mean age of enrolled AIFPs in this study. Hypoalbuminaemia is a common nutritional disorder in older hip fracture patients and is related to the complications and prognosis in orthopaedic patients.[15]

Hypoalbuminaemia triggers hyperfibrinogenaemia and platelet aggregability, which might explain the association between hypoalbuminaemia and DVT.[16] Zuo *et al*. demonstrated that reduced ALB (<31.7 g/L) was positive for DVT in elderly patients with intertrochanteric fractures.[10] Zhao *et al*. revealed that ALB <35 g/L contributed to DVT in AIFPs.[17] Here, the authors demonstrated that reduced ALB also contributed to DVT on admission in AIFPs, and the ALB threshold was 36.45 g/L, which is similar to previous studies.[10,17] Hypokalaemia is often caused by limited dietary intake, comorbidities, and multiple drugs, including diuretics and corticosteroids, and is popular in older people with an incidence of 3.4-20%.[18,19] A study conducted by Zhang *et al.* revealed that preoperative low levels of K was linked to early symptomatic DVT after posterior lumbar spine surgery with OR of 0.241.[20] A major finding in this study was that reduced serum K (<3.650 mmol/L) was associated to DVT, with a sensitivity of 0.351 and a specificity of 0.882, which is in agreement with the results of Zhang *et al*.[20] Within the physiological range, increased serum K inhibits platelet aggregation and reduces the sensitivity of platelet to thrombin and other agonists.[21] This might explain the protective role of serum K in DVT risk suppression. Future studies are needed to elaborate the relationship of DVT between low K level.

This study has some limitations. First, the sample size of enrolled patients was small, most likely due to the older age of patients and relatively short enlisting time, which might cause some selective bias and undermine the significance of some variables. As all the patients came from one hospital for treatment, these results might not be universal or generalisable. In addition, all factors for DVT, such as some comorbidities, genetic factors, drug use, and pre-fall status of mobility, were not completely collected because of the retrospective study design. Finally, the causes of DVT were not probed. Therefore, large-scale, multi-centred studies with systematic and comprehensive indicators are needed for the validation and enrichment of the results in this study.

CONCLUSION

The frequency of DVT on admission was 28.5% in AIFPs over 80 years old and elevated D-dimer levels, reduced ALB levels as well as reduced K concentrations were shown to be correlated to DVT.

Timely correction of reduced serum levels of ALB and K may be useful in the prevention of DVT, and large-scale, multi-centred studies with systematic indicators are needed to validate and enrich these findings.

ETHICAL APPROVAL:

Approval from the Ethical Board of the China-Japan Friendship Hospital (ERB No. 2023-KY-145) was obtained and this was carried out in accordance with the instructions of the Declaration of Helsinki.

PATIENT'S CONSENT:

Patient's consent is not required for this retrospectively designed study.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

QZ, XX, XC, HY, YY, YC: Design, execution, and analysis of the manuscript.

All authors approved the final version of the manuscript to be published.

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