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Incidence of and risk factors for preoperative deep vein thrombosis in elderly patients with end-stage osteoarthritis following total knee arthroplasty: a retrospective cohort study

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Abstract

Background Deep vein thrombosis (DVT) is a common and serious risk in elderly patients with knee osteoarthritis (OA), making preoperative detection crucial. Despite this, identifying OA patients at high risk for preoperative DVT and appropriately targeting them for venous ultrasound screening remains a challenge. There is limited research-based evidence on the risk factors for preoperative DVT in elderly patients with end-stage OA. We examined the incidence of and risk factors for preoperative DVT in elderly patients with end-stage OA scheduled for total knee arthroplasty.

Methods We retrospectively analyzed the demographic data (age, sex, body mass index, current smoking, alcohol consumption, walking status, and Barthel index score), medical history, and laboratory test indices of 1411 patients with end-stage OA aged ≥ 60 years scheduled for total knee arthroplasty from January 2015 to December 2018. Risk factors for preoperative DVT were evaluated by univariate and multivariate logistic analyses. Receiver operating characteristic analysis was performed to determine optimal cut-off values.

Results The incidence of preoperative DVT was 4.5% (63 of 1411 patients). Seven independent risk factors were correlated with preoperative DVT in the multivariate logistic regression: age (odds ratio [OR], 1.073; $P=0.002$), D-dimer concentration (OR, 1.173; $P=0.003$), hyperlipidemia (OR, 2.038; $P=0.045$), atrial fibrillation (OR, 4.004; $P=0.033$), chronic renal failure (OR, 6.732; $P=0.008$), chronic obstructive pulmonary disease (COPD) (OR, 8.721; $P=0.001$), and walking status (wheelchair) (OR, 2.697; $P=0.002$). The optimal cut-off values for predicting preoperative DVT were 0.585 μg/mL for the D-dimer concentration (area under the curve [AUC], 0.769; $P<0.001$) and 72.5 years for age (AUC, 0.668; $P<0.001$).

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Conclusion Among elderly patients with end-stage OA, venous ultrasonography to rule out DVT risk should be prioritized in those with a high D-dimer concentration (> 0.585 μg/mL), high age (> 72.5 years), hyperlipidemia, atrial fibrillation, chronic renal failure, COPD, and walking status (wheelchair).

Keywords Deep vein thrombosis, Total knee arthroplasty, Osteoarthritis, Ultrasonography

Introduction

Total knee arthroplasty (TKA) has become a widely used surgical treatment for end-stage knee osteoarthritis (OA) during the past decade, significantly improving patients' quality of life, pain levels, and physical function [1, 2]. However, perioperative complications, particularly the risk of deep vein thrombosis (DVT), remain a significant concern and require further investigation.

DVT is a common complication following TKA. Without prophylaxis, the risk of developing asymptomatic DVT ranges from 35 to 84% [3]. Even with routine thromboprophylaxis, approximately 0.63% of patients still develop symptomatic DVT [4]. Additionally, the incidence of preoperative DVT in patients with OA before undergoing TKA ranges from 2.6 to 17.4% [5–8]. Notably, preoperative DVT may lead to intraoperative embolus dislodgement. Because fresh blood clots do not adhere tightly to the vessel wall, they may easily dislodge and cause a pulmonary embolism (PE) [9]. Furthermore, preoperative DVT has been linked to an increased risk of postoperative DVT [10]. Therefore, efficient identification of preoperative DVT in patients with knee OA is of particular importance.

Ultrasonography has been suggested as an effective method of preoperative DVT detection [11]. Although ultrasonography is a valuable diagnostic tool, performing ultrasound examinations for preoperative screening in all patients with OA is considered overuse [12]. Patients with OA who are at high risk for DVT should be prioritized for ultrasonography screening. Several studies indicate that those undergoing TKA are more likely to develop preoperative DVT if they have conditions such as rheumatoid arthritis (RA), connective tissue disease, revision TKA, a high D-dimer level (> 0.5 μg/mL), or age of > 75 years [5, 7, 13]. However, there is little research-based evidence on the risk factors for preoperative DVT in elderly patients with end-stage OA, especially those related to patients' medical history.

Thus, the aim of this study was to investigate the incidence of and risk factors for preoperative DVT in elderly patients with end-stage OA scheduled for TKA. We hypothesized that certain risk factors are significantly associated with preoperative DVT and that identifying these factors will help improve screening and prevention strategies.

Materials and methods

Study participants

This retrospective cohort study was conducted at Peking Union Medical College Hospital from January 2015 to December 2018 and involved 1411 patients with knee OA, selected from a total of 1969 patients. The inclusion criteria were an age ≥ 60 years, end-stage knee OA, and scheduled primary TKA. The exclusion criteria were other types of arthritis (e.g., RA, traumatic osteoarthritis, ankylosing spondylitis, and hemophilic arthritis), absence of lower extremity ultrasonography examination, and incomplete medical records. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (IRB number: K3692). The research followed the Declaration of Helsinki guidelines, and the ethics committee waived the requirement for informed consent because the study used a retrospective design and the data were anonymized. Figure 1 shows that 1411 patients with end-stage knee OA were finally enrolled in the study.

Data collection

The hospital's information system was used to obtain the patients' clinical data, including sex, age, body mass index, current smoking, alcohol consumption, walking status, and Barthel index (BI) score. Walking status included three categories: walking independently, using a mobility aid, and using a wheelchair.

We assessed the patients' history of illnesses, including hypertension, diabetes, hyperlipidemia, coronary atherosclerotic heart disease, atrial fibrillation (AF), coronary stent implantation, chronic renal failure (CRF), Parkinson's disease (PD), osteoporosis, depression, arteriosclerosis obliterans, cerebral infarction, lower extremity varicose veins, and chronic obstructive pulmonary disease (COPD).

Several laboratory parameters were measured, including coagulation markers (D-dimer, fibrinogen, international normalized ratio, and activated partial thromboplastin time), routine blood indices (platelets, white blood cells, neutrophils, and hemoglobin), and high-sensitivity C-reactive protein.

Preoperative DVT determination

For diagnosis of DVT, the patients underwent lower extremity venous ultrasound 1 to 3 days preoperatively. These scans were conducted on the bilateral lower extremities to detect venous thrombosis in the proximal

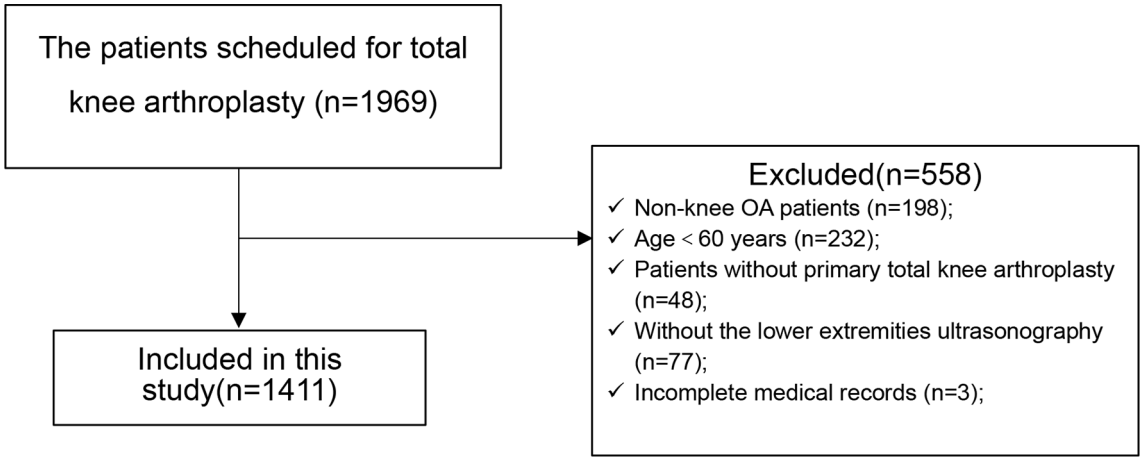

Fig. 1 Flow chart of study inclusion and exclusion criteria

veins (common femoral, femoral, and popliteal veins) and distal veins (posterior tibial, peroneal, soleal, and sural veins). In this study, a positive case was defined as the diagnosis of DVT on lower extremity venous ultrasound, regardless of whether the DVT was located on affected side (with OA) or the contralateral side. Additionally, both proximal or distal DVT were included as positive cases.

Data analyses

The data were analyzed using SPSS Version 24.0 (IBM Corp., Armonk, NY, USA). The sample data were analyzed using the Kolmogorov–Smirnov test to evaluate their conformity to a normal distribution. Normally distributed continuous variables are presented as mean±standard deviation, and the means of the two groups were compared using Student's t test. Non-normally distributed continuous variables are presented as median and interquartile range; the Mann–Whitney U test was used to determine the distribution difference. The chi-square test or Fisher's exact test was performed for categorical variables such as numbers and proportions.

To include all potential risk factors, variables with a P value of <0.1 in the univariate analysis were entered into the multivariate logistic analysis to determine the risk factors for preoperative DVT in patients with OA. A stepwise forward (LR) multivariate logistic regression analysis was conducted with an entry probability of 0.05 and a removal probability of 0.1 for variables associated with categorical outcomes (development of DVT) in the univariate analysis. A P value of <0.05 indicated statistical significance.

A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for continuous variables that were statistically significant (P<0.05) according to multivariate logistic regression. These were determined by maximizing the Youden index (sensitivity+specificity−1). Additionally, the sensitivity, specificity, and area under the ROC curve (AUC) were determined.

Results

Participant selection

After application of the exclusion criteria, 1411 elderly patients with end-stage knee OA (241 men, 1170 women) were included in the study (Fig. 1). The patients' mean age was 69.2±5.8 years (range, 60–91 years).

Baseline characteristics

The incidence of preoperative DVT was 4.5% (63 of 1411 patients). The univariate analysis revealed statistical differences in the walking status (walking independently, mobility aid, or wheelchair) between the DVT group (63 patients) and non-DVT group (1348 patients) (P<0.001). Patients with DVT had a higher prevalence of comorbidities, including CRF (4.8% vs. 0.6%, P=0.011) and COPD (6.3% vs. 0.7%, P=0.002). Additionally, patients with DVT were older (72.5±5.8 vs. 69.1±5.8 years, P<0.001), had higher D-dimer levels (1.4±1.8 vs. 0.7±1.3 μg/mL, P<0.001), and had lower BI scores (88.3±9.6 vs. 91.6±6.4, P=0.013) (Table 1).

Univariate and multivariate logistic regression analyses for DVT risk factors

A multivariate logistic analysis was performed using the variables with a P value of <0.1 in the univariate analysis (age, BI score, walking status, hyperlipidemia, AF, CRF, COPD, white blood cells, neutrophils, and D-dimer level). After adjusting for confounding variables, the findings indicated that age (odds ratio [OR], 1.073; 95% confidence interval [CI], 1.026–1.123; P=0.002), D-dimer (OR, 1.173; 95% CI, 1.054–1.305; P=0.003), hyperlipidemia (OR, 2.038; 95% CI, 1.015–4.094; P=0.045), AF (OR,

Table 1 Distribution and differences in demographic characteristics between DVT and non-DVT groups

Variable	Total (*n*=1411)	DVT group (*n*=63)	Non-DVT group (*n*=1348)	*P* value
Age (years)	69.2±5.8	72.5±5.8	69.1±5.8	<0.001*
Gender				0.547
Male	241(17.1)	9(14.3)	232(17.2)	
Female	1170(82.9)	54(85.7)	1116(82.8)	
BMI	27.0±3.6	27.0±3.3	27.0±3.6	0.862
BI score	91.5±6.6	88.3±9.6	91.6±6.4	0.013*
Walking status				<0.001*
Walking independently	894(63.4)	24(38.1)	870(64.5)	
Mobility aid	285(20.2)	15(23.8)	270(20.0)	
Wheelchair	232(16.4)	24(38.1)	208(15.5)	
Current smoking	83(5.9)	2(3.2)	81(6.0)	0.509
Alcohol consumption	93(6.6)	3(4.8)	90(6.7)	0.728
Hypertension	856(60.7)	39(61.9)	817(60.6)	0.837
Diabetes	280(19.8)	15(23.8)	265(19.7)	0.419
Hyperlipidemia	146(10.3)	11(17.5)	135(10.0)	0.058
Coronary atherosclerotic heart disease	152(10.8)	10(15.9)	142(10.5)	0.182
Atrial fibrillation	22(1.6)	3(4.8)	19(1.4)	0.071
Coronary stent implantation	51(3.6)	3(4.8)	48(3.6)	0.878
Chronic renal failure	11(0.8)	3(4.8)	8(0.6)	0.011*
Parkinson's disease	6(0.4)	1(1.6)	5(0.4)	0.240
Osteoporosis	500(35.4)	22(34.9)	478(35.5)	0.930
Depression	15(1.1)	2(3.2)	13(1.0)	0.142
Arteriosclerosis obliterans	23(1.6)	1(1.6)	22(1.6)	1.000
Cerebral infarction	89(6.3)	4(6.3)	85(6.3)	1.000
Lower extremity varicose veins	31(2.2)	3(4.8)	28(2.1)	0.326
COPD	13(0.9)	4(6.3)	9(0.7)	0.002*
D-dimer (μg/mL)	0.7±1.3	1.4±1.8	0.7±1.3	<0.001*
Fbg (g/L)	3.1±6.5	3.0±0.6	3.1±6.7	0.134
INR	1.0±0.1	1.0±0.2	1.0±0.1	0.702
APTT (s)	27.4±4.8	27.4±4.0	27.4±4.9	0.706
hs-CRP (mg/L)	4.3±21.9	4.3±6.6	4.3±22.4	0.111
PLT (10^9/L)	222.3±57.7	234.4±69.3	221.7±57.1	0.350
WBC (10^9/L)	6.0±2.0	6.4±1.7	6.0±2.0	0.088
NEUT (10^9/L)	3.5±2.5	3.8±1.4	3.5±2.5	0.050
HGB (g/L)	131.8±13.9	129.9±14.7	131.9±13.9	0.198

*P<0.05. Abbreviations: BMI, body mass index; BI, Barthel Index; COPD, chronic obstructive pulmonary disease; Fbg, fibrinogen; INR, international normalized ratio; APTT, activated partial thromboplastin time; hs-CRP, high-sensitivity C-reactive protein; PLT, platelets; WBC, white blood cell; NEUT, neutrophil; HGB, hemoglobin

4.004; 95% CI, 1.121–14.304; P=0.033), CRF (OR, 6.732; 95% CI, 1.628–27.831; P=0.008), COPD (OR, 8.721; 95% CI, 2.484–30.623; P=0.001), and walking status (wheelchair) (OR, 2.697; 95% CI, 1.446–5.030; P=0.002) were independent risk factors for preoperative DVT in elderly patients with end-stage OA (Table 2). Additionally, the following factors were identified as significant predictors of preoperative DVT in elderly patients with end-stage OA: high age (B=0.071), high D-dimer concentration (B=0.160), hyperlipidemia (B=0.712), AF (B=1.387), CRF (B=1.907), COPD (B=2.166), and walking status (wheelchair) (B=0.992) (Table 2).

Determination of cut-off values of continuous variables

The ROC curve of age and D-dimer level is shown in Fig. 2. On the basis of the ROC curve analysis for predicting preoperative DVT (Table 3), the optimal cut-off values were 72.5 years for age (AUC, 0.668; 95% CI, 0.601–0.735; P<0.001) and 0.585 μg/mL for the D-dimer level (AUC, 0.769; 95% CI, 0.710–0.828; P<0.001).

Discussion

The most important finding of the present study is that 4.5% of elderly patients with end-stage OA scheduled for TKA had preoperative DVT. In addition, the D-dimer level, age, hyperlipidemia, AF, CRF, COPD, and walking status (wheelchair) were identified as risk factors for preoperative DVT in our study.

Wakabayashi et al. [7] found a higher incidence of preoperative DVT (17.4%) in patients undergoing TKA than observed in our study (4.5%). This difference may be explained by their inclusion of patients with RA and those undergoing revision TKA, both of which are independent risk factors for preoperative DVT. Moreover, one meta-analysis showed that patients with RA are more likely than patients with OA to develop DVT after TKA [14]. Similarly, Sato et al. [15] reported a higher incidence of preoperative DVT (14.7%) among patients with OA, RA, and idiopathic osteonecrosis. They performed lower extremity ultrasounds only on patients with a D-dimer level of ≥1 μg/mL or those deemed by physicians to be at high risk for DVT (683 of 1236 patients, 55.3%). However, our results were comparable to those of Sun et al. [13], who limited their study cohort to patients with primary OA. They reported that the prevalence of preoperative DVT before TKA was 5.53%. Therefore, the differences between patients with RA and OA should be acknowledged when assessing the risk of preoperative DVT.

The D-dimer level can be measured to predict DVT risk [16, 17]. Our study showed that the D-dimer level was associated with the risk of preoperative DVT in elderly patients with end-stage OA. The D-dimer cut-off value used in our study (>0.58 μg/mL) was similar to that reported by Jiang et al. [5], who found that preoperative DVT in patients with end-stage OA was associated with a D-dimer level of >0.5 μg/mL. In Europe and North America, a D-dimer level of <0.5 μg/mL is used to rule out DVT in non-surgical patients [18]. Similarly, a higher D-dimer level is a reliable marker of hypercoagulability,

Table 2 Univariate and multivariate logistic regression analysis of risk factors associated with preoperative DVT

Variable	Univariate analysis OR (95% CI)	*P*	B	Multivariate analysis OR (95% CI)	*P*
Age (years)	1.099 (1.054–1.145)	<0.001	0.071	1.073 (1.026–1.123)	0.002
D-dimer (μg/mL)	1.202 (1.087–1.329)	<0.001	0.160	1.173 (1.054–1.305)	0.003
Hyperlipidemia	1.901 (0.968–3.731)	0.062	0.712	2.038 (1.015–4.094)	0.045
Atrial fibrillation	3.497 (1.007–12.144)	0.049	1.387	4.004 (1.121–14.304)	0.033
Chronic renal failure	8.375 (2.167–32.366)	0.002	1.907	6.732 (1.628–27.831)	0.008
COPD	10.087 (3.019–33.701)	<0.001	2.166	8.721 (2.484–30.623)	0.001
Walking status		<0.001			0.007
Walk	1.0 (reference)			1.0 (reference)	
Mobility aid	2.014 (1.042–3.894)	0.037	0.534	1.706 (0.864–3.368)	0.124
Wheelchair	4.183 (2.329–7.513)	<0.001	0.992	2.697 (1.446–5.030)	0.002
BI score	0.950 (0.925–0.976)	<0.001			
WBC (10^9/L)	1.060 (0.978–1.149)	0.157			
NEUT (10^9/L)	1.029 (0.965–1.097)	0.387			
Constant			-8.831		<0.001

Abbreviations BI, Barthel Index; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; NEUT, neutrophil

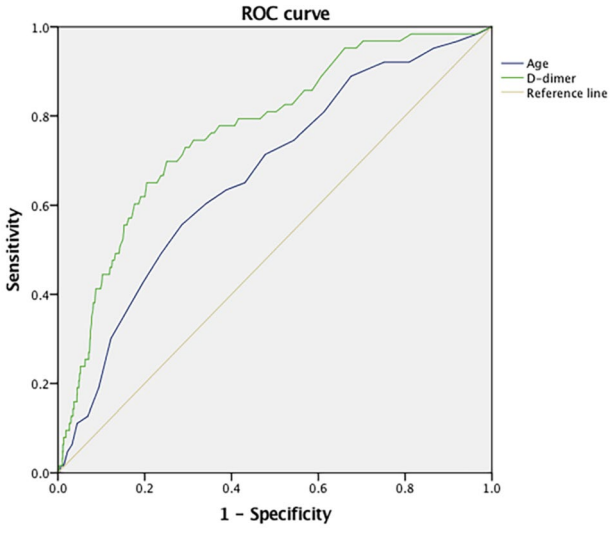

Fig. 2 ROC curve of age and D-dimer

indicating a higher risk of thrombosis and enhancing the negative predictive value [19]. Consequently, it has been suggested that a D-dimer cut-off value of 0.585 μg/mL should be used in elderly patients with end-stage OA to rule out DVT prior to surgery. Nevertheless, the specific D-dimer cut-off value should be considered based on the impact of surgical factors. In addition, predicting postoperative DVT based on the preoperative D-dimer level may be challenging. Most studies have shown that D-dimer testing is not accurate for predicting or diagnosing postoperative DVT after TKA [20–23]. Both joint arthroplasty and thrombosis may increase the D-dimer level during the acute postoperative period, making it difficult to distinguish between D-dimer increases caused by thrombosis and those caused by surgery. Therefore, an increase in the D-dimer level may be a useful biomarker for predicting preoperative DVT before total joint arthroplasty without being influenced by surgical factors.

Our study showed that age was a risk factor for preoperative DVT. Imai et al. [24] and Wu et al. [25] also reported that age was associated with preoperative DVT before TKA. Elderly patients, particularly women aged>60 years, have been shown to be at an increased risk of DVT [26]; however, our study found no evidence that gender affects the development of DVT. Because of the high incidence of comorbidities such as hypertension, diabetes, hyperlipidemia, and heart failure, these patients are more susceptible to coagulation activation [27]. In addition, hyperlipidemia was identified as a risk factor for preoperative DVT in our study. Hyperlipidemia may aggravate the endothelial dysfunction caused by high cholesterol levels, contributing to venous thrombosis progression [28]. Thus, elderly patients aged>72.5 years with hyperlipidemia are more likely to develop preoperative DVT and should be closely monitored.

The association between AF and the risk of preoperative DVT was further demonstrated in our study. Wang et al. [29] also indicated that patients with AF had a higher risk of DVT than those without AF (adjusted hazard ratio [HR], 1.74; 95% CI, 1.36–2.24). Because of the disruption of physiological hemostatic mechanisms, AF is associated with an increased risk of pathological thrombus

Table 3 ROC curve analysis to determine the optimal cut-off value

Variable	Cut-off value	Youden index	Sensitivity	Specificity	Area under the curve (95%CI)	*P* value
Age (years)	72.5	0.271	55.6%	71.5%	0.668 (0.601–0.735)	<0.001
D-dimer (μg/mL)	0.585	0.447	69.8%	74.9%	0.769 (0.710–0.828)	<0.001

formation [30]. However, Enga et al. [31] found that AF was only associated with DVT for the first 6 months after diagnosis (HR, 6.20; 95% CI, 3.37–11.39), whereas no relationship existed beyond this time period. This may be attributed to the patient's hesitation when dealing with the diagnosis of AF, which delays the initiation of heart rate control and anticoagulation administration [31]. However, another study showed that the incidence of DVT after TKA was not higher in patients with than without AF [32]. Patients with AF were switched from preoperative oral anticoagulants (warfarin, rivaroxaban, or dabigatran) to low-molecular-weight heparin (LMWH) bridging therapy. This was continued until oral anticoagulants therapy was resumed after TKA wound drain removal. These findings suggest that LMWH bridging therapy can effectively prevent thrombosis events in patients with AF after TKA. Our findings therefore suggest that adherence to anticoagulation for thromboprophylaxis in patients with AF might be poor, and further studies of medication adherence in patients with AF are needed.

All stages of chronic kidney disease (CKD) significantly increase the risk of DVT, encompassing conditions such as nephrotic syndrome, end-stage renal disease (ESRD), and kidney transplantation [33]. Wattanakit et al. [34] showed an almost two-fold increased risk of DVT among patients with stage 3/4 CKD compared with the risk among those who had normal renal function in the general population. Furthermore, patients with stage 5 CKD, also known as ESRD, are at higher risk of developing DVT. In an Asian study population, patients with ESRD had a higher incidence of DVT than those without ESRD (adjusted HR, 13.92; 95% CI, 9.25–20.95) [35]. Additionally, patients with ESRD undergoing total joint arthroplasty had a higher risk of DVT than patients without ESRD (OR, 1.4; $P=0.03$) [36]. Stage 3–5 CKD is referred to as CKF. Our study showed that elderly patients with end-stage OA who had CKF were at increased risk for preoperative DVT. Hemostatic derangements may contribute to this increased risk and include activated procoagulants, decreased endogenous anticoagulants, enhanced platelet activity, and decreased fibrinolysis [33]. In addition, patients with ESRD commonly require long-term dialysis, and repeated punctures of arteriovenous fistulas may increase embolus formation. However, LMWH or fondaparinux for treatment of DVT is not recommended in patients with ESRD [37] because of concerns about drug accumulation and increased bleeding risks. Therefore, future research should focus on choosing the most appropriate anticoagulant and balancing the anticoagulant dosage in patients with ESRD to prevent DVT.

Our study showed that COPD was a risk factor for preoperative DVT. Similar results have been obtained in studies of femoral and pelvic fractures [38] and intertrochanteric fractures [39]. Patients with COPD are at increased risk of thromboembolic events because of various mechanisms such as systemic inflammation, hypoxemia, oxidative stress, endothelial dysfunction, and prothrombotic conditions [40]. Additionally, the persistence of chronic hypoxia causes severe impairment in daily activities, resulting in venous stasis and hypercoagulability in the lower limbs and thus increasing the risk of thrombosis. Patients with COPD are likely to develop DVT; however, it is more likely to be combined with PE [41]. Therefore, when a patient has decreased oxygen saturation and an increased heart rate, it is essential not only to consider COPD as a possible cause but also to perform computed tomography pulmonary angiography to rule out PE.

Our study also showed that walking status (wheelchair) was a risk factor for preoperative DVT. Patients using a wheelchair upon admission may be incapable of independently performing activities of daily living and experience limited mobility. As a result of poor physical activity, thrombosis is more likely to occur secondary to inadequate blood circulation and increased venous stasis, which is a key factor in DVT development [42]. However, active ankle movement can significantly improve venous outflow and capacity, helping to prevent DVT [43]. In addition, compared with intermittent pneumatic compression, active ankle exercise can produce the same effect as increasing venous outflow [44]. Therefore, patients with declining ambulatory ability are recommended to increase the amount of active ankle exercises performed while in bed.

Our study had some limitations. Because this was a retrospective study, some DVT risk factors may have been omitted, resulting in biased results. Additionally, this study only included elderly patients with end-stage knee OA (age of ≥60 years). The inclusion of an etiology-specific population and age-factor considerations may limit the generalizability of the results. For example, patients with RA, ankylosing spondylitis, and traumatic OA were not included. Another limitation is that our study results were obtained from a single center and cannot be widely extrapolated. Hence, prospective multicenter studies are needed to validate our results and examine other risks associated with DVT in patients with RA.

Conclusion

In our study, 4.5% of elderly patients with end-stage OA were found to have preoperative DVT. Moreover, elevated D-dimer levels (>0.585 μg/mL), age of >72.5 years, hyperlipidemia, atrial fibrillation, chronic renal failure, chronic obstructive pulmonary disease, and a wheelchair-dependent status were all associated with an increased risk of preoperative DVT.

Abbreviations

TKA	total knee arthroplasty
DVT	deep vein thrombosis
PE	pulmonary embolism
OA	osteoarthritis
RA	rheumatoid arthritis
ROC	receiver operating characteristic
OR	odds ratio
AUC	area under the ROC curve

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Author contributions
Conceptualization, Methodology, Data curation, Funding acquisition, Writing - original draft: YFG, NG, YPZ, XPH. Data curation, Formal analysis: YPC, AMG, WH. Investigation, Resources: XSW, JL, JJ, WWQ, YZ. Visualization, Supervision: YFM, WNL. Project administration, Writing - review & editing: YPZ, XPH. All authors read and approved the final manuscript to be published.

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Data availability
As a result of restrictions regarding ethical approval involving patient data and anonymity, the datasets generated and/or analysed during this study are not available publicly, but may be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of the Peking Union Medical College Hospital (K3692). The ethics committee waived the requirement for informed consent because this study was retrospective and the data are anonymous.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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