CLINICAL ARTICLE

Risk Factors and Outcomes for Preoperative Asymptomatic Pulmonary Embolism in Patients Aged 60 Years and Over with Hip Fracture

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Objective: To investigate the risk factors for, and outcomes of, preoperative asymptomatic pulmonary embolism (PE) in patients ≥60 years old following delayed operation for hip fracture.

Methods: From March 2017 to December 2018, 90 patients aged ≥60 years with hip fracture who suffered a delay in surgery were recruited to this prospective study following admission to our hospital. Computed tomography pulmonary angiography (CTPA) was used to detect preoperative asymptomatic PE and calculated its incidence. Time from injury to admission, baseline characteristics, medical comorbidities, and blood biomarker levels were evaluated as potential risk factors. Logistic regression analysis was used to identify risk factors. Mortality and major bleeding events were recorded and compared between individuals with PE and without. Data were analyzed by *t*-test, Mann–Whitney U test, χ^2 test, Fisher's exact test, and logistic regression analysis.

Results: The incidence of preoperative asymptomatic PE was 18.9% (17/90 patients). In the univariate analysis, the risk factors for preoperative asymptomatic PE were male sex, hypertension, cerebrovascular accident, smoking, plasma D-dimer level, potassium level, urea level, creatinine level, and cysteine level. Multivariate logistic regression analysis showed that the risk of preoperative asymptomatic PE was higher in patients with hypertension (odds ratio [*OR*] = 10.048; 95% confidence interval [*CI*], 1.118–90.333), cerebrovascular accident (*OR* = 20.135; 95% *CI*, 1.875–216.164), smoking (*OR* = 48.741; 95% *CI*, 4.155–571.788), high plasma D-dimer levels (*OR* = 1.200; 95% *CI*, 1.062–157.300), and high plasma potassium levels (*OR* = 12.928; 95% *CI*, 1.062–157.300). All patients were followed up for 21.0 months (range, 2 to 36 months). Mortality within the first year postoperatively was higher in patients with PE (29.41% *vs* 9.59%, *P* = 0.046).

Conclusions: In view of the high incidence of preoperative asymptomatic PE and the inferior prognosis in individuals with PE, routine CTPA examination for preoperative asymptomatic PE could be useful for patients aged ≥60 years with hip fracture for whom surgery is delayed.

Key words: Hip fractures; Preoperative; Pulmonary embolism

Introduction

Pulmonary embolism (PE) is common cause of death in patients with hip fracture[1,2]. Due to trauma, extended bed rest, and underlying diseases, preoperative deep vein thrombosis (DVT) is confirmed in 2.60%–34.98% of patients who undergo preventive measures[3–5]. More than one-third of patients with DVT are confirmed to have PE, and in many such patients the PE is asymptomatic[6]. In older patients with hip fracture, this form of PE may progress to more serious complications, such as fatal PE during or after surgery. PE is responsible for 14% of deaths in patients with hip fracture[2]. Elderly patients with hip fracture have more medical com-

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Grant Sources: This research was supported by the Health Commission of Zhejiang Province, China (2018KY864, awarded to Fanglun Zhou).
Received 21 July 2020; accepted 9 February 2021

Orthopaedic Surgery 2021;13:958–965 • DOI: 10.1111/os.12983

Orthopaedic Surgery

orbidities and poorer general health[7], and thus require careful preoperative evaluation and optimization, often leading to delayed surgery. Operative delay in these patients is an important risk factor for DVT and PE[8,9]. Therefore, these patients have a higher possibility of preoperative PE. If PE is missed and not treated in time, there is a risk of progression of PE during and after operation. Hence, prevention and diagnosis of preoperative PE is important for older patients with hip fracture who undergo delayed surgery and more active screening may be helpful in such cases[10].

In most studies focusing on postoperative PE in high-risk patients, the incidence of and risk factors related to preoperative asymptomatic PE are unclear. Determining these factors and intervening where necessary may help judge the prognosis, reduce mortality, and improve patient outcomes. Very few previous studies have evaluated the incidence of preoperative asymptomatic PE in patients with hip fracture. Two studies reported the incidence of preoperative symptomatic PE of 1.0% and 3.7%, respectively[11,12]. In another study, PE was diagnosed by modified discrete cosine transform (MDCT), and the incidence of preoperative symptomatic and asymptomatic PE was 5.29%[13]. Factors that can lead to venous congestion, vascular endothelial damage and hypercoagulability are risk factors for venous thromboembolism (VTE). Park *et al.*[14] reported that high energy injury, history of VTE, and myeloproliferative disease were significant predictive factors of preoperative VTE in older patients with hip fracture. Another retrospective study[12] reported that multiple fractures, coexisting movement disorder, bed rest for more than 7 days, elevated levels of D-dimer, and fibrinogen led to an increase in the risk of VTE. In their retrospective study, Shin *et al.*[13] reported that subtrochanteric fracture, female patient, pulmonary disease, and previous VTE were associated with an increased risk of preoperative asymptomatic PE in older patients with hip fracture. However, all these previous studies were retrospective. In addition, these studies included both patients with DVT and PE. The outcomes of and risk factors for PE and DVT may be different. Therefore, separate evaluation of patients with these different statuses is necessary. To our knowledge, no prospective studies have been performed to evaluate the correlation between potential risk factors and preoperative asymptomatic PE in older patients with hip fracture.

In the present prospective study, we focus on this particular group who require more careful preoperative evaluation and optimization. The purposes of the current study were: (i) to calculate the incidence of preoperative asymptomatic PE in patients aged ≥60 years with hip fracture; (ii) to investigated the risk factors for preoperative asymptomatic PE; and (iii) to compare mortality and major bleeding events between individuals with PE and without. We hypothesized that operative delay time, baseline characteristics, medical comorbidities, and blood biomarker levels would be associated with preoperative asymptomatic PE, despite administration of thromboprophylaxis. To our knowledge, this is the first prospective study to assess the correlation between levels of biomarkers and preoperative asymptomatic PE in patients aged ≥60 years with hip fracture. Screening for identified risk factors may allow interventions to help reduce mortality and improve outcomes.

Materials and Methods

Inclusion and Exclusion Criteria

From March 2017 to December 2018, older patients (aged ≥60 years) with hip fracture who were admitted to our hospital were recruited to the present study. Figure 1 shows a flow chart detailing eligibility criteria for patient inclusion into the study. Inclusion criteria were as follows: (i) patients with hip fracture; and (ii) age: 60 years old and over. Exclusion criteria were as follows: (i) patients with multiple fractures; (ii) patients who did not require more careful preoperative evaluation and optimization, whose operations were performed within 48 h after admission; (iii) inability to perform computed tomography pulmonary angiography (CTPA) because of renal failure or iodine allergy; (iv) presence of PE-related symptoms; and (v) refused to participate in the study. Finally, 90 patients were included in the study.

Ethics Statement

This study was approved by the ethics committee at our hospital (Dong Ren Yi 2016-YX-148). All the patients provided written informed consent. Moreover, this study was carried out in accordance with the amended Declaration of Helsinki statement.

Potential Risk Factors for Pulmonary Embolism

Potential risk factors for PE were assessed for all study participants by obtaining detailed medical histories, performing physical examinations and and testing blood biomarker levels.

Anticoagulant Therapy

In our institution, patients aged ≥60 years with hip fracture undergo routine risk assessment for venous embolism (Caprini score) and bleeding after admission. After exclusion of risk factors for bleeding and other contraindications for anticoagulation, drugs (rivaroxaban [10 mg daily] or aspirin [100 mg daily] [Bayer, Du Leverkusen, North Rhine westphalanbai, Germany]) were administered once daily to prevent thrombosis until the day before surgery, and plantar vein pumps applied after admission (use was discontinued after VTE was diagnosed). After PE diagnosis, patients were given rivaroxaban (15 mg, twice daily) as anticoagulation therapy for approximately 1 week, which continued during the perioperative period (no anticoagulation therapy was used from 24 h before surgery to 8 h afterwards). Rivaroxaban (15 mg twice daily for 3 weeks, then changed to 20 mg once daily) was also used after discharge and anticoagulant therapy continued for at least 3 months. Prophylactic

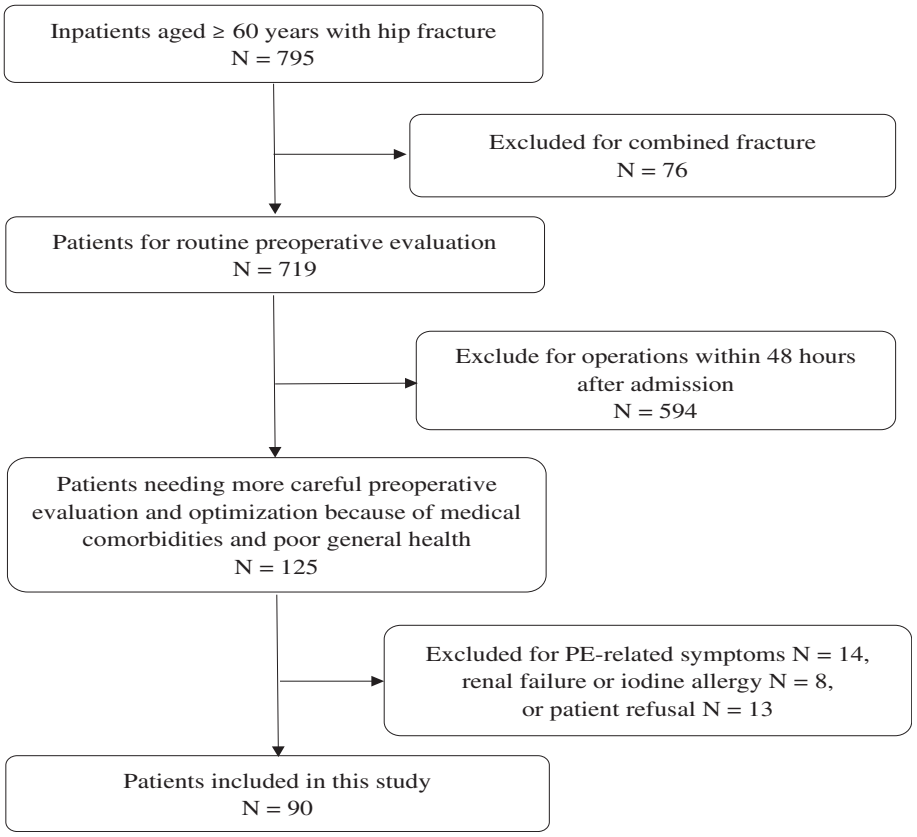

Fig. 1 Flow chart showing patient selection for inclusion in this study. 795 older patients (aged ≥ 60 years) with hip fracture who were admitted to our hospital were recruited to the present study. 705 patients were excluded because of operations within 48 h after admission (594 patients), combined fracture (76 patients), PE-related symptoms (14 patients), renal failure or iodine allergy (eight patients), and patient refusal (13 patients). Finally, 90 patients were included in the study.

anticoagulation was performed for at least 35 days in patients without PE.

Treatment Plan

Operations are generally performed within 48 h after admission (as quickly as possible) for older patients with hip fracture[15]. In the present study, operations were delayed for patients for whom further assessment of medical comorbidities or medical optimization was necessary. Routine preoperative examinations included arterial blood gas analysis; measurement of electrolytes, blood glucose, glycated hemoglobin, blood creatinine, urea, albumin, triglycerides, and cysteine; a full blood cell count; electrocardiography; echocardiography; and chest CT. Hip replacement was performed for patients with femoral neck fracture, and intramedullary nail placement (proximal femoral nail antirotation, PFNA) was performed for patients with femoral intertrochanteric fracture.

Diagnosis of Pulmonary Embolism

PE were objectively confirmed by CTPA. Compression ultrasound was used to confirm venous thrombosis of the lower extremity. After obtaining informed consent from the patients, CTPA was performed the day before scheduled surgery on a dual-source 64-row CT scanner (Philips Brilliance; Philips, Amsterdam, The Netherlands). Multidetector CTPA venography images were interpreted by two experienced senior professors who were blinded to the purpose of this study.

Delayed Surgery

Delayed surgery was defined as surgery performed more than 48 h after admission.

Outcome Measures

Symptoms of Pulmonary Embolism

Symptoms of PE were defined as hypotension, sweating, chest pain, dizziness, dyspnea, tachycardia, fainting, and low oxygen saturation (< 90%)[16].

Medical Comorbidities

Medical comorbidities included diabetes, hypertension, cancer, cardiac disease (including coronary heart disease and atrial fibrillation), pulmonary disease (including pneumonia, asthma, and chronic obstructive pulmonary disease), cerebrovascular accident, and rheumatic immune system diseases (including rheumatoid arthritis, ankylosing spondylitis, rheumatic polymyalgia, and autoimmune liver disease).

TABLE 1 Patient characteristics and risk factors for preoperative asymptomatic PE

Characteristic	All patients (N = 90)	Patients without PE (N = 73)	Patients with PE (N = 17)	*P* value
Sex				0.019*
Female	59 (65.6%)	52 (71.2%)	7 (41.2%)	
Male	31 (34.4%)	21 (28.8%)	10 (58.8%)	
Age (years), mean (SD)	81.2 (7.9)	81.2 (8.0)	81.2 (8.0)	0.974
Type of fracture				0.763
Femoral neck fracture	40 (44.4%)	33 (45.2%)	7 (41.2%)	
Intertrochanteric fracture	50 (55.6%)	40 (54.8%)	10 (58.8%)	
Left or right hip fracture				0.890
Left	49 (54.4%)	40 (54.8%)	9 (52.9%)	
Right	41 (45.6%)	33 (45.2%)	8 (47.1%)	
Current DVT	13 (14.4%)	9 (12.3%)	4 (23.5%)	0.237
Time from injury to admission (h)				0.645
Mean (SD)	18.9 (55.8)	14.7 (27.4)	56.1 (136.5)	
Median (Q1, Q3)	6 (3,18)	6 (3,18)	7 (4,15)	
Time from injury to CT scan (h)				0.564
Mean (SD)	73.4 (68.4)	66.2 (32.6)	104.6 (141.2)	
Median (Q1, Q3)	66 (46,74)	68 (47,74)	63 (36,74)	
Specific comorbidities				
Diabetes	10 (11.1%)	9 (12.3%)	1 (5.9%)	0.446
Hypertension	40 (44.4%)	29 (39.7%)	11 (64.7%)	0.062*
Cardiac disease	16 (17.8%)	12 (16.4%)	4 (23.5%)	0.491
Pulmonary disease	23 (25.6%)	17 (23.3%)	6 (35.3%)	0.307
Cerebrovascular accident	9 (10.0%)	5 (6.8%)	4 (23.5%)	0.039*
Cancer	11 (12.2%)	8 (11.0%)	3 (17.6%)	0.448
Previous VTE	3 (3.3%)	3 (4.1%)	0 (0%)	0.395
Rheumatic immune system diseases	5 (5.6%)	5 (6.8%)	0 (0%)	0.267
Smoking	14 (15.6%)	7 (9.6%)	7 (41.2%)	0.001*
Body mass index in kg/m^2, mean (SD)	20.77 (2.62)	20.95 (2.50)	19.98 (3.05)	0.168
Age-adjusted Charlson Comorbidity Index, mean (SD)	4.76 (1.37)	4.74 (1.35)	4.82 (1.47)	0.822

* These variables were included in the multivariate regression analysis at a *P* value of < 0.10. DVT, deep vein thrombosis; PE, pulmonary embolism; Q1, Q3, interquartile range; SD, standard deviation; VTE, venous thromboembolism.

TABLE 2 Results of first blood examination after admission

First blood examination after admissionMean (SD)	All patients (N = 90)	Patients without PE (N = 73)	Patients with PE (N = 17)	*P* value
D-dimer (mg/L)	7.2 (5.3)	6.7 (5.1)	9.5 (5.4)	0.050*
Arterial partial pressure of oxygen (mmHg)	75.3 (12.6)	74.4 (12.7)	79.2 (11.5)	0.163
Serum electrolyte				
K^+ (mmol/L)	3.9 (0.4)	3.9 (0.4)	4.1 (0.3)	0.01*
Na^+ (mmol/L)	142.1 (2.8)	142.0 (2.8)	142.4 (3.1)	0.539
Ca^+ (mmol/L)	2.2 (0.1)	2.2 (0.1)	2.2 (0.1)	0.551
Renal function				
Urea (mmol/L)	7.4 (2.4)	7.1 (2.3)	8.6 (2.5)	0.025*
Creatinine (mmol/L)	68.5 (22.9)	65.6 (22.2)	80.9 (21.9)	0.012*
Cysteine (mmol/L)	18.8 (9.4)	17.2 (5.0)	25.6 (17.7)	0.070*
Serum albumin (g/L)	36.3 (3.6)	36.4 (3.7)	35.9 (3.4)	0.586
Hemoglobin (g/L)	111.6 (19.1)	112.6 (18.4)	107.2 (22.1)	0.297
Platelet (× 10^9/L)	188.7 (55.0)	187.9 (54.0)	192.1 (60.7)	0.782

* These variables were included in the multivariate regression analysis at a *P* value of < 0.10. PE, pulmonary embolism; SD, standard deviation.

Blood Biomarker Levels

Initial blood samples were taken within 24 h of admission and used to determine plasma levels of D-dimer, electrolytes (potassium, sodium, and calcium), hemoglobin, platelets, urea, creatinine, cysteine, albumin, and arterial partial pressure of oxygen.

Mortality

The mortality was calculated within 30 days, 90 days, and 1 year after the operation.

TABLE 3 Multivariate logistic regression analysis of risk factors for asymptomatic PE

Characteristic	Adjusted Odds Ratio (95% CI)	*P* value
Sex		0.522
Male	1.0 (reference)	
Female	0.529 (0.075–3.711)	
Age (years)	0.892 (0.772–1.031)	0.123
Specific comorbidities		
Hypertension	10.048 (1.118–90.333)	0.039*
Cerebrovascular accident	20.135 (1.875–216.164)	0.013*
Smoking	48.741 (4.155–571.788)	0.002*
First blood examinations after admission		
D-dimer	1.200 (1.035–1.392)	0.016*
K^+	12.928 (1.062–157.300)	0.045*
Urea	1.203 (0.817–1.772)	0.350
Creatinine	0.998 (0.946–1.054)	0.953
Cysteine	1.133 (0.965–0.331)	0.127

* The difference was significant (*P* value < 0.05).

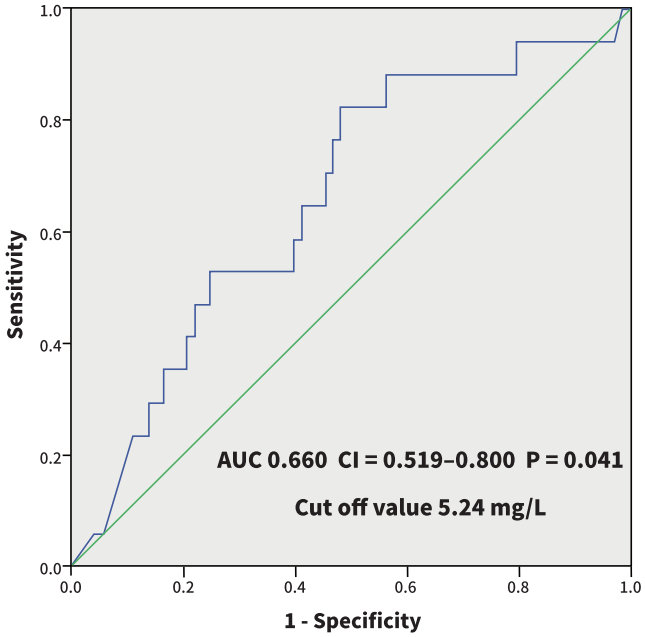

Fig. 2 Predictive value of D-dimer levels for pulmonary embolism. A value of >5.24 mg/L was discriminant. The sensitivity and specificity of the cut-off value (5.24 mg/L) were 82.4% and 52.1%, respectively, and the positive and negative predictive values were 28.6% and 92.7%, respectively. AUC, area under the receiver operating characteristic curve.

Major Bleeding Events

Major bleeding events were identified based on the recommendations of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis [17].

Statistical Analysis

Age, sex, body mass index, age-adjusted Charlson comorbidity index[18,19], type of fracture, side of fracture (right or left leg), thrombosis of lower limb, time from injury to admission, time from injury to CT scan, previous VTE, medical comorbidities, and results of first blood examination after admission were included in the analysis as potential risk factors. Normally distributed continuous were analyzed using the *t*-test, and the Mann–Whitney U test was used for skewed distributions of continuous variables. The chi-square test (or Fisher's exact test, where appropriate) was used to analyze categorical data. Variables with value <0.10 in univariate analysis were included in the multivariate regression analysis. The relationship between possible risk factors and preoperative PE was examined by multivariate logistic regression analysis. *P* values <0.05 were considered significant. Odds ratios (*ORs*) and 95% confidence intervals (*CIs*) are reported for all associations. All analyses were performed using the SPSS software (Version 22.0, SPSS, IBM, Armonk, NY, USA).

Results

Study Cohort Characteristics

Patient characteristics and specific comorbidities are summarized in Table 1. The study cohort comprised 31 men (34.4%) and 59 women (65.6%). Mean patient age was 81.2 ± 7.9 (range, 61–97) years. Mean time from injury to CTPA differed markedly, but not significantly, between patients with and without PE (66.2 ± 32.6 h *vs* 104.6 ± 141.2 h, *P* = 0.564); however, careful analysis of the data identified an extreme value among patients with PE and the difference between the groups was small on exclusion of this data, as supported by comparison of the median values (68 [47–74] *vs* 63 [36–74] h). No patient experienced adverse effects related to in this study.

Factors Associated with Asymptomatic Pulmonary Embolism: Univariate Analysis

The overall incidence of preoperative asymptomatic PE was 18.9% (17 of 90 patients) among all patients aged ≥60 years with hip fracture. Thrombus was located in the pulmonary trunk in three cases, of which two were associated with multiple branches of embolism, one case was only trunk embolism. Thrombus was located in pulmonary artery branches in 14 cases, including one case involving multiple branches and 13 cases involving only a single branch. Men were more susceptible to PE than women (58.8% *vs* 41.2%, respectively; *P* = 0.019). Patients with preoperative asymptomatic PE had a higher incidence of cerebrovascular accident (23.5% *vs* 6.8%, *P* = 0.039) and smoking (41.2% *vs* 9.6%, *P* = 0.001).

The results of the initial blood examination after hospital admission are presented in Table 2. Patients with PE had higher plasma levels of D-dimers (9.5 ± 5.4 *vs* 6.7 ± 5.1 mg/L, *P* = 0.050); potassium (4.1 ± 0.3 *vs* 3.9 ± 0.4 mmol/L, *P* = 0.018); urea (8.6 ± 2.5 *vs* 7.1 ± 2.3 mmol/L, *P* = 0.025); and creatinine (80.9 ± 21.9 *vs* 65.6 ± 22.2 mmol/L, *P* = 0.012).

TABLE 4 Mortality within the first 30 days, 90 days, 1 year postoperatively, and major bleeding

Mortality/Major bleeding	All patients (N = 90)	Patients without PE (N = 73)	Patients with PE (N = 17)	Multiple (with PE/without PE)	*P* value
30 days	1 (1.11%)	0 (0%)	1 (5.88%)		0.189
90 days	3 (3.33%)	1 (1.37%)	2 (11.76%)		0.090
1 year	12 (15.56%)	7 (9.59%)	5 (29.41%)	3.07	0.046
Major bleeding	2 (2.22%)	2 (2.74%)	0 (0%)		1.000

PE, pulmonary embolism.

Factors Associated with Asymptomatic Pulmonary Embolism: Multivariate Analysis

Variables in Tables 1 and 2 with *P* values <0.10 were included in multivariate logistic regression analysis. Age and sex were included in the multivariate logistic regression analysis as suspected confounders, because age and sex may have an impact on specific comorbidities and the results of blood tests. The results of multivariate logistic regression for PE are presented in Table 3. Sex, urea, and creatinine were significantly correlated with preoperative asymptomatic PE in univariate analysis; however, after adjusting for the other risk factors, the correlation with preoperative asymptomatic PE was not significant, as they were also associated with other factors. Multivariate logistic regression analysis showed that, after adjusting for other risk factors, higher susceptibility to PE was detected in patients with hypertension (*OR* = 10.048; 95% *CI*, 1.118–90.333); cerebrovascular accident (*OR* = 20.135; 95% *CI*, 1.875–216.164); or a smoking habit (*OR* = 48.741; 95% *CI*, 4.155–571.788). Plasma levels of D-dimers on the first day after admission were also significantly correlated with preoperative asymptomatic PE (*OR* = 1.200; 95% *CI*, 1.062–157.300), as were plasma potassium levels (*OR* = 12.928; 95% *CI*, 1.062–157.300).

Ability of Plasma D-dimer Levels to Predict Asymptomatic Pulmonary Embolism

Plasma D-dimer level within 24 h of admission was evaluated by receiver operating characteristic analysis. A value of >5.24 mg/L was discriminant. The area under the curve was 0.660 (95% *CI*, 0.519–0.800; *P* = 0.041) (Fig. 2). The sensitivity and specificity of the cut-off value (5.24 mg/L) were 82.4% and 52.1%, respectively, and the positive and negative predictive values were 28.6% and 92.7%, respectively.

Outcomes of Patients with Asymptomatic Pulmonary Embolism

One patient with preoperative asymptomatic PE died within 30 days of surgery. Mortality within the first 1 year postoperatively was higher in patients with PE (29.41% *vs* 9.59%, *P* = 0.046). No patients with PE had major bleeding events during anticoagulation treatment. Table 4 shows patient outcomes, including mortality within the first 30 days, 90 days, and 1 year postoperatively, and major bleeding.

Discussion

Incidence of Preoperative Asymptomatic Pulmonary Embolism

The overall incidence of preoperative asymptomatic PE in our study was 18.9%. Very few previous studies have evaluated the incidence of preoperative asymptomatic PE in older patients with hip fracture. Two studies reported very low incidences of preoperative PE of 1.0% and 3.7%[11,12]; however, only symptomatic PE was included. In another study, PE was diagnosed by MDCT, and the incidence of PE was 5.29%[13], including both symptomatic and asymptomatic types. DVT occurs in 62% of older patients with hip fracture who undergo a delayed operation (> 48 h after injury)[20]. In addition, 13.1% to 66.0% of patients with DVT may develop asymptomatic PE[8,16,21–24]. Therefore, our finding of a slightly higher incidence of preoperative asymptomatic PE is not unexpected.

Risk Factors

In the present study, five independent predictive factors for preoperative asymptomatic PE in patients of aged ≥60 years with hip fracture were identified: hypertension, cerebrovascular accident, smoking, and two biomarkers (potassium and D-dimers). Conversely, sex, age, type of fracture, side of fracture (right or left leg), lower limb thrombosis, time from injury to admission, and medical comorbidities (except for hypertension and cerebrovascular accident) were not significant predictors of preoperative asymptomatic PE on multivariate analysis. We also found that other biomarkers (determined from initial blood samples taken within 24 h of admission) were not significant predictors of preoperative asymptomatic PE, including the arterial partial pressure of oxygen and levels of sodium, calcium, hemoglobin, platelets, urea, creatinine, cysteine, and albumin.

One previous study concluded that women were more vulnerable to PE than men among elderly patients with hip fracture[13]; however, another study reported that men had a higher prevalence than women[25]. In the present study, the incidence of preoperative asymptomatic PE was higher in men than women, while multivariate regression analysis showed that male sex was not a risk factor for preoperative asymptomatic PE in older patients with hip fracture.

Hypertension

Hypertension was correlated with an increased risk of preoperative asymptomatic PE in this study. This result is consistent with those of other studies[26–28] and may be attributable to the hypercoagulable state of the blood[26].

Cerebrovascular Accident

We also found that cerebrovascular accident was another risk factor for preoperative asymptomatic PE in patients aged ≥60 years with hip fracture. Stroke with limb paresis is a risk factor for PE in the general population[28]. Additionally, movement disorder in patients with femoral neck fracture is a risk factor for preoperative VTE[12], and limb paralysis and motor dysfunction are common in patients who have experienced cerebrovascular accidents.

Smoking

In the present study, smoking was an independent risk factor for the incidence of preoperative asymptomatic PE in patients aged ≥60 years with hip fracture. Smoking is associated with an increased incidence of PE[29]. A previous study showed that a history of smoking was the only risk factor for early PE in patients with trauma[30]. Smoking can increase the levels of fibrinogen and tissue factor, aggravate blood viscosity, and eventually lead to a prethrombotic state[31]. Twenty percent of smokers are in a hypercoagulable state[32]. Further, a meta-analysis of 32 observational studies showed that smoking can increase the prevalence of VTE, including PE[33].

Plasma D-dimer Levels

The present study also investigated the relationship between plasma D-dimer levels and preoperative asymptomatic PE. We found that an elevated plasma D-dimer level within 24 h of admission was an independent risk factor for preoperative asymptomatic PE, consistent with a previous report[12]. D-dimers become elevated after tissue injury, and the D-dimer level is higher in patients who have experienced trauma. The diagnostic value of D-dimer has not been confirmed in patients with trauma. Two studies[34,35] have proposed D-dimer cut-off values for diagnosis of DVT in patients with lower limb fracture, with encouraging results. The cut-off points were 1 mg/L (sensitivity, 100%; specificity, 71%) and 3 mg/L (sensitivity, 88.37%; specificity, 96.96%). In the present study, we found that a D-dimer level of 5.24 mg/L was discriminative for the presence of asymptomatic PE in patients aged ≥60 years with hip fracture; however, the sensitivity and specificity were relatively low (82.4% and 52.1%, respectively). Hence, plasma D-dimer level may be a potentially useful biomarker for the diagnosis of preoperative asymptomatic PE after hip fracture.

Plasma Potassium Levels

Electrolyte balance may be related to the coagulation state and increased risk of VTE[36,37]. Therefore, electrolytes were included in the analysis as potential risk factors in the present study. To the best of our knowledge, no previous study has established the relationship between plasma potassium levels and the occurrence of PE in patients with hip fracture. In the present study, a significantly elevated plasma level of potassium was observed in patients with PE; however, the reason for this association is unknown.

Outcomes

Autopsy-validated PE is a common cause of death in older patients with hip fracture subjected to delayed surgery[2]. Our study shows that patients with preoperative asymptomatic PE have poorer clinical outcomes compared with those without PE. Preoperative asymptomatic PE may indicate poor prognosis and may develop into intra- or post-operative fatal PE. Since many fatal PE are asymptomatic and difficult to detect clinically, preoperative investigation should be routinely performed for patients with a hip fracture for whom surgery is delayed.

Limitation

This study has some inherent limitations. Firstly, the patient sample in this study was relatively small, as the number of participants was limited by the exclusion of those whose operations were performed within 48 h after admission. Secondly, we have not commented whether there was any influence on the rate of asymptomatic PE as a consequence of their VTE prophylactic regime. We recognized that this could be a potential bias. Nevertheless, we report a high incidence of preoperative asymptomatic PE in older patients with hip fracture. In addition, we identify risk factors predicting preoperative asymptomatic PE and demonstrate that this condition is associated with inferior patient outcomes.

Further investigations are needed to identify ways to reduce mortality by intervention to address risk factors in these patients. This will be the focus of our subsequent research, to allow clinical application of our findings.

Conclusions

As there have only been a very few studies reporting the risk factors for, and outcomes of preoperative asymptomatic PE in older patients with hip fracture, this study provides valuable clinical implications for identifying pulmonary embolism and reducing mortality in these patients.

In view of the high incidence of preoperative asymptomatic PE and the inferior prognosis in individuals with PE, routine CTPA examination for preoperative asymptomatic PE could be useful for patients aged ≥60 years with hip fracture for whom surgery is delayed.

Author contributions

Guo-hong Xu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. Fang-lun Zhou, Li-hong Wang, Cheng-qian Dai, Guo-jian Shentu contributed substantially to the study design, data analysis and interpretation. Fang-lun Zhou drafted the manuscript and all authors contributed

substantially to its revision. All authors are in agreement with the manuscript.

Conflict of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. Sheikh HQ, Hossain FS, Aqil A, Akinbamijo B, Mushtaq V, Kapoor H. A comprehensive analysis of the causes and predictors of 30-day mortality following hip fracture surgery. Clin Orthop Surg, 2017, 9: 10–18.
2. Perez JV, Warwick DJ, Case CP, Bannister GC. Death after proximal femoral fracture—an autopsy study. Injury, 1995, 26: 237–240.
3. Bengoa F, Vicencio G, Schweitzer D, Lira MJ, Zamora T, Klaber I. High prevalence of deep vein thrombosis in elderly hip fracture patients with delayed hospital admission. European Journal of Trauma and Emergency Surgery. 2020, 46: 913–917.
4. Song K, Yao Y, Rong Z, Shen Y, Zheng M, Jiang Q. The preoperative incidence of deep vein thrombosis (DVT) and its correlation with postoperative DVT in patients undergoing elective surgery for femoral neck fractures. Arch Orthop Trauma Surg, 2016, 136: 1459–1464.
5. Cho YH, Byun YS, Jeong DG, Han IH, Park YB. Preoperative incidence of deep vein thrombosis after hip fractures in Korean. Clin Orthop Surg, 2015, 7: 298–302.
6. Boc A, Vene N, Košmelj K, Mavri A. Impact of asymptomatic pulmonary embolism on the long-term prognosis of patients with deep venous thrombosis. Semin Thromb Hemost, 2017, 43: 24–29.
7. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. BMJ, 2005, 331: 1374.
8. Smith EB, Parvizi J, Purtill JJ. Delayed surgery for patients with femur and hip fractures-risk of deep venous thrombosis. J Trauma, 2011, 70: E113–E116.
9. Hefley FG, Nelson CL, Puskarich-May CL. Effect of delayed admission to the hospital on the preoperative prevalence of deep-vein thrombosis associated with fractures about the hip. J Bone Joint Surg Am, 1996, 78: 581–583.
10. Shin WC, Lee SM, Suh KT. Recent updates of the diagnosis and prevention of venous thromboembolism in patients with a hip fracture. Hip Pelvis, 2017, 29: 159–167.
11. Nam JH, Kim DH, Yoo JH, Hwang JH, Chang JD. Does preoperative mechanical prophylaxis have additional effectiveness in preventing postoperative venous thromboembolism in elderly patients with hip fracture?-retrospective case-control study. PLoS One, 2017, 12: e0187337.
12. Xia ZN, Xiao K, Zhu W, *et al*. Risk assessment and management of preoperative venous thromboembolism following femoral neck fracture. J Orthop Surg Res, 2018, 13: 291.
13. Shin WC, Woo SH, Lee SJ, Lee JS, Kim C, Suh KT. Preoperative prevalence of and risk factors for venous thromboembolism in patients with a hip fracture: an indirect multidetector CT venography study. J Bone Joint Surg Am, 2016, 98: 2089–2095.
14. Park JS, Jang JH, Park KY, Moon NH. High energy injury is a risk factor for preoperative venous thromboembolism in the patients with hip fractures: a prospective observational study. Injury, 2018, 49: 1155–1161.
15. Roberts KC, Brox WT. AAOS clinical practice guideline: Management of hip Fractures in the elderly. J Am Acad Orthop Surg, 2015, 23: 138–140.
16. García-Fuster MJ, Fabia MJ, Furió E, *et al*. Should we look for silent pulmonary embolism in patients with deep venous thrombosis. BMC Cardiovasc Disord, 2014, 14: 178.
17. Schulman S, Angerås U, Bergqvist D, *et al*. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost, 2010, 8: 202–204.
18. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol, 1994, 47: 1245–1251.
19. Koppie TM, Serio AM, Vickers AJ, *et al*. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer, 2008, 112: 2384–2392.
20. Zahn HR, Skinner JA, Porteous MJ. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. Injury, 1999, 30: 605–607.
21. Meignan M, Rosso J, Gauthier H, *et al*. Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. Arch Intern Med, 2000, 160: 159–164.
22. Hughes MJ, Stein PD, Matta F. Silent pulmonary embolism in patients with distal deep venous thrombosis: systematic review. Thromb Res, 2014, 134: 1182–1185.
23. Stein PD, Matta F, Musani MH, Diaczok B. Silent pulmonary embolism in patients with deep venous thrombosis: a systematic review. Am J Med, 2010, 123: 426–431.
24. Tzoran I, Saharov G, Brenner B, *et al*. Silent pulmonary embolism in patients with proximal deep vein thrombosis in the lower limbs. J Thromb Haemost, 2012, 10: 564–571.
25. Tagalakis V, Kondal D, Ji Y, *et al*. Men had a higher risk of recurrent venous thromboembolism than women: a large population study. Gend Med, 2012, 9: 33–43.
26. Tan L, Qi B, Yu T, Wang C. Incidence and risk factors for venous thromboembolism following surgical treatment of fractures below the hip: a meta-analysis. Int Wound J, 2016, 13: 1359–1371.
27. Goldhaber SZ, Grodstein F, Stampfer MJ, *et al*. A prospective study of risk factors for pulmonary embolism in women. JAMA, 1997, 277: 642–645.
28. Goldhaber SZ. Pulmonary embolism. Lancet, 2004, 363: 1295–1305.
29. Gregson J, Kaptoge S, Bolton T, *et al*. Cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol, 2019, 4: 163–173.
30. Gambhir S, Grigorian A, Ashbaugh A, *et al*. Early versus late pulmonary embolism in trauma patients: not all pulmonary embolisms are created similarly. J Surg Res, 2019, 239: 174–179.
31. Salahuddin S, Prabhakaran D, Roy A. Pathophysiological mechanisms of tobacco-related CVD. Glob Heart, 2012, 7: 113–120.
32. Nielsen VG, Hafner DT, Steinbrenner EB. Tobacco smoke-induced hypercoagulation in human plasma: role of carbon monoxide. Blood Coagul Fibrinolysis, 2013, 24: 405–410.
33. Cheng YJ, Liu ZH, Yao FJ, *et al*. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med, 2013, 10: e1001515.
34. Bakhshi H, Alavi-Moghaddam M, Wu KC, Imami M. Banasiri M. D-dimer as an applicable test for detection of posttraumatic deep vein thrombosis in lower limb fracture. Am J Orthop, 2012, 41: E78–E80.
35. Yang Y, Zan P, Gong J. Cai M. d-dimer as a screening marker for venous thromboembolism after surgery among patients younger than 50 with lower limb fractures. Clin Appl Thromb Hemost, 2017, 23: 78–83.
36. Janvrin SB, Davies G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery. Br J Surg, 1980, 67: 690–693.
37. Martin G, Bennett-Guerrero E, Wakeling H, *et al*. A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle, or 6% hetastarch in saline during major surgery. J Cardiothorac Vasc Anesth, 2002, 16: 441–446.