

# Silent Pulmonary Embolism in Deep Vein Thrombosis: Relationship and Risk Factors

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## Abstract

**Purpose:** This study aimed to evaluate risk factors for silent pulmonary embolism (PE) in symptomatic deep vein thrombosis (DVT) and investigate the relationship between DVT and silent PE.

**Methods:** This was a single-centre, retrospective cohort study. Between 5 January 2015 and 31 December 2021, consecutive patients with symptomatic DVT received CT pulmonary angiography and CT venography were analyzed. Patient demographics, comorbidities, risk factors, and image findings were analyzed. The group differences were compared using a Chi-square test, Fisher's exact test, independent t test, or Mann-Whitney U test. Multivariate regression was used to determine predictive factors for silent PE.

**Results:** A total of 355 patients (mean age,  $60.5 \pm 16.6$  years) were included. The incidence of silent PE was 43.1%. The main or lobar pulmonary arteries were affected in 53.6% of patients, which is more often found in iliofemoral DVTs (56.6% vs 26.7%,  $p = .027$ ). The multivariate analysis showed male patients ( $p = .042$ ; OR 1.59; 95% CI, 1.02–2.50), inferior vena cava involvement ( $p = .043$ ; OR 1.81; 95% CI, 1.02–3.20) and D-dimer value  $> 3.82 \mu\text{g/ml}$  ( $p < .001$ ; OR 2.32; 95% CI, 1.43–3.77) were risk factors for silent PE. Unilateral DVT patients with ipsilateral iliac vein compression had a lower incidence of silent PE (28.8% vs 52.9%,  $p < .001$ ).

**Conclusion:** Iliofemoral DVT was associated with a more proximal PE. The male patients, inferior vena cava involvement, and D-dimer  $> 3.82 \mu\text{g/ml}$  were risk factors for silent PE. Ipsilateral iliac vein compression reduced the incidence of silent PE.

## Keywords

deep vein thrombosis, pulmonary embolism, risk factors, iliac vein compression, D-dimer

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## Introduction

Silent pulmonary embolism (PE) is known to be prevalent in deep vein thrombosis (DVT) patients. Previous studies have reported the incidence of silent PE in DVT patients ranging from 11% to 46% for high-probability pulmonary scintigraphy.<sup>1</sup> However, up to 72% of incidence has been reported when computed tomography pulmonary angiography (CTPA) was used for screening.<sup>2</sup> Considering the high incidence, potential severe consequences, and the benefits of baseline imaging for individualizing subsequent treatment regimens, routine screening for silent PE in DVT patients has been advocated.<sup>1–5</sup> However, screening for silent PE was associated with added cost,<sup>6</sup> radiation and contrast medium induced nephropathy.<sup>7,8</sup>

Moreover, the opponents thought therapeutic anticoagulation was also sufficient for DVT patients with concomitant silent PE.<sup>9</sup> For these reasons, European Society of Vascular Surgery guidelines did not recommend routine screening for silent PE in new diagnosed DVT patients.<sup>10</sup>

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As mentioned above, routine screening for silent PE in DVT is still under debate. Considering the potential advantages and disadvantages, screening in selected DVT patients with a high risk of silent PE seems more reasonable. Several studies have found that increased age,<sup>1</sup> male,<sup>4,5</sup> D-dimer level,<sup>6,11</sup> proximal DVT,<sup>1,5,11,12</sup> right side DVT,<sup>5</sup> unprovoked DVT,<sup>5,12</sup> and coexisting heart disease<sup>4,5</sup> were associated with a higher incidence of silent PE. However, the relationship between DVT characteristics and silent PE has not been well elucidated. Moreover, the risk factors for silent PE in DVT patients have not been well documented.

This study aimed to evaluate the incidence and extent of silent PE in symptomatic DVT patients and its relationship with the DVT characteristics. The risk factors for the occurrence of silent PE are analyzed. These results may help establish an individualized screening plan, thus avoiding unnecessary radiation exposure and risk of kidney injury.

## Methods

### Study Design and Patients

Between 5 January 2015 and 31 December 2021, consecutive symptomatic DVT patients admitted to our department were retrospectively analyzed. The inclusion criteria were DVT patients absent of manifestation (dyspnea, chest pain, hypotension, dizziness, fainting, sweating, tachycardia, and low oxygen saturation) suggestive of PE and underwent both CTPA and CT venography (CTV). Exclusion criteria were chronic DVT, upper extremity DVT, previously indwelled inferior vena cava (IVC) filter, and symptomatic PE. Two reviewers (SYD and SHB) independently searched the electronic medical record system and picture archiving and communication system to identify eligible patients. Patient demographics (age and sex), delay from symptom onset to admission, comorbidities (hypertension, diabetes, neurovascular disease, and peripheral arterial disease), risk factors for DVT (thrombophilia, immobilization, recent surgery, obesity, varicose veins, estrogen use, active cancer, peripartum and previous DVT history) were collected. The imaging information regarding DVT characteristics (IVC involvement, involved extremities, and proximal/distal DVT), iliac vein compression, and location of PE were also recorded. The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the study hospital approved this study protocol, and informed consent was waived.

### Diagnostic Methods for Venous Thromboembolism (VTE) and Iliac Vein Compression

DVT was initially confirmed with whole leg ultrasound scanning (including iliac, common femoral, femoral, popliteal, and calf veins) by GE LOGIO 9 (GE Healthcare, USA) or Philips IU22 (Philips, Amsterdam, Netherlands) using high-frequency or multifrequency probes.

The combined CTPA and CTV was routinely performed within 48 h after DVT diagnosis using a 128-slice CT (Dual Source CT, SOMATOM Definition Flash, Siemens, Germany) in the same examination session.<sup>13</sup> In all patients, a 40-ml iodinated contrast medium (Visipaque, 320 mg/ml, GE Health Care, Ireland) was administered via the cubital vein at a rate of 4 ml/s for pulmonary artery scanning. After the CTPA examination, another 80-ml contrast medium was administered for CTV. After 2 min of the second administration, CT scanning from the level of the first lumbar vertebra to the toes was performed. DVT or PE was confirmed if one or more intraluminal filling defects were present in the deep veins and pulmonary arteries. The degree of iliac vein compression was calculated using  $(1-D1/D2) \times 100\%$ , where D1 is the minimum diameter at the point of maximum compression, and D2 is the minimum diameter at the common iliac vein caudal to the obstruction.<sup>14</sup> Compression degree  $>50\%$  was considered iliac vein compression. The interpretation of CTPA was based on the initial radiologist's reading. Two independent radiologists not involved in this study calculated the degree of iliac vein compression.

### D-dimer Test and Treatment for VTE

The plasma D-dimer was tested within 24 h after admission using a quantitative enzyme-linked immunosorbent assay provided by the central laboratory of the study hospital. A D-dimer value  $>500$  ng/ml was considered abnormal.<sup>15</sup> For patients aged  $>50$  years, the age-adjusted threshold ( $\text{age} \times 10$  ng/ml) was used.<sup>16</sup> All patients received therapeutic anticoagulant therapy during hospitalization using low-molecular-weight heparin (Enoxaparin sodium injection, Sanofi, France) and then switched to warfarin with a target international normalized ratio ranging from 2.0 to 3.0, or Rivaroxaban 20 mg once daily before discharge. Anticoagulant therapy would last at least 3–6 months based on the recurrence risk factors and bleeding risks. Adjunctive treatments for DVT, including IVC filter placement, catheter-directed thrombolysis, percutaneous mechanical thrombolysis, balloon angioplasty and/or stent placement for iliac vein compression, were performed according to the individualized treatment regimen.

### Statistical Analysis

The distribution of continuous data was tested using the Kolmogorov-Smirnov test. Data with normal distribution were presented as mean  $\pm$  standard deviation. Data with asymmetric distribution were presented as the median and interquartile range (IQR). Student's t test or Mann-Whitney U test was used to compare the difference between continuous data, and the chi-square test or Fisher's exact test was used for count data. Predictive factors for PE were assessed with logistic regression; the univariate approach was followed by multivariate analysis. The predictive power of D-dimer as a suspected diagnosis was evaluated using ROC curves. The area under the curve and the Youden index were calculated. Data were analyzed using the SPSS statistical package (26.0, IBM SPSS Statistics, USA). A  $p$  value  $<.05$  was considered statistically significant.

## Results

### Patients

A total of 519 patients with symptomatic DVT who underwent both CTPA and CTV were identified. One hundred and sixty-four patients were excluded for reasons: 42 patients with chronic DVT, 83 patients with symptomatic PE, 35 patients with previously indwelled IVC filter, and four patients with upper extremity DVT. Finally, 355 patients were included in the present study, and the flow chart of patient inclusion is presented in Figure 1. The mean age of included patients was  $60.5 \pm 16.6$  years, and 53.8% of these patients were male. The median delay from symptom onset to admission was 7 days (IQR, 3–15 days). The patients' leading comorbidities were hypertension and diabetes, which presented in 39.4% and 16.1% of patients. The major risk factors for DVT were immobilization (24.5%) and previous DVT history (15.2%) (Table 1). Unilateral and bilateral DVT were presented in 74.1% and 25.4% of patients. The remaining two patients had isolated IVC thrombosis. Proximal DVT was the most common type, and iliofemoral DVT accounted for 85.1% of all DVT types. Of note, IVC involvement was found in 18.9% of patients. Right side DVT accounted for 33.1% of all unilateral DVTs.

### Incidence and Extent of Silent PE and Relationship between Silent PE and DVT

The overall incidence of silent PE was 43.1% (153/355) in this study. The main pulmonary, lobar, and segmental arteries were affected in 28.1%, 25.5%, and 46.4% of patients. Of note, more silent PE occurred in right side DVT compared to left side DVT (40.4% vs 27.9%,  $p = .035$ ) (Table 1). More bilateral DVT

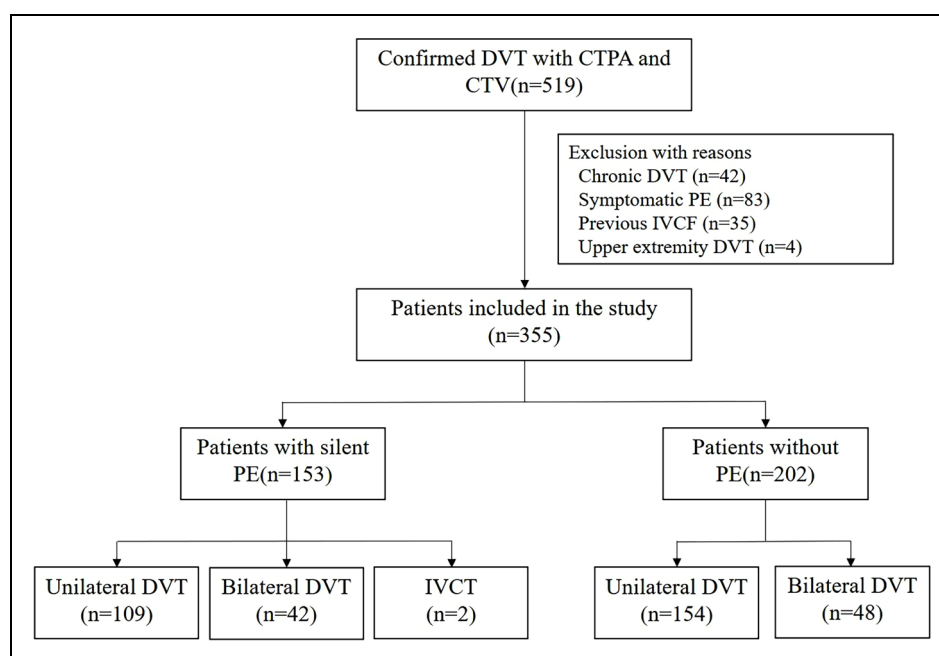
developed silent PE compared to unilateral DVT, but this difference was not significant (46.7% vs 41.4%,  $p = .429$ ). For patients with silent PE, iliofemoral DVT was associated higher incidence of main or lobar pulmonary artery involvement (56.6% vs 26.7%,  $p = .027$ ).

### Predictive Value of D-dimer

The median D-dimer value of included patients was  $6.0 \mu\text{g/ml}$  (IQR, 2.7–11.1  $\mu\text{g/ml}$ ). The D-dimer level of patients with silent PE was significantly higher than patients without PE ( $p = .01$ ). The predictive value of the D-dimer was analyzed by ROC curves. D-dimer value  $> 3.82 \mu\text{g/ml}$  was discriminant (area under the curve: 0.58,  $p = .01$ ) for predicting silent PE with a sensitivity of 76.5% and a specificity of 42.1% (Figure 2). The positive predictive value for this value was 50%, and the negative predictive value was 70.2%.

### Risk Factors for Silent PE

Risk factors for silent PE in DVT patients were tested by univariable analysis (Table 1). Compared with the patients without PE, higher male proportion, median D-dimer level, and IVC involvement proportion were found in patients with silent PE. Besides, there are significantly more patients with a D-dimer value  $> 3.82 \mu\text{g/ml}$  in the patients with silent PE than those without PE. Multivariate logistic regression analysis showed male patients (odds ratio (OR) 1.59; 95% confidence interval (CI), 1.02–2.50), IVC involvement (OR 1.81; 95% CI, 1.02–3.20), D-dimer value  $> 3.82 \mu\text{g/ml}$  (OR 2.32; 95% CI, 1.43–3.77) were risk factor for the occurrence of silent PE (Table 2).



**Figure 1.** Flowchart of patient inclusion and distribution of DVT in patients with and without silent PE.

**Table 1.** Demographics, Comorbidities, Risk Factors, and Characteristics of DVT Patients with and without Silent PE.

Variable	All Patients (n = 355)	Silent PE (n = 153)	No PE (n = 202)	P value
Male	191 (53.8%)	94 (61.4%)	97 (48.0%)	.012
Mean age	60.5 ± 16.6	59.0 ± 16.0	61.7 ± 17.0	.131
Median delay from symptom to admission (IQR)	7 (3–15)	7 (4–15)	7 (3–15)	.475
Symptom duration ≤ 7d	205 (57.7%)	92 (60.1%)	113 (55.9%)	.429
Median D-dimer (µg/ml) (IQR)	6.0 (2.7–11.1)	6.8 (4.0–13.0)	5.2 (2.2–9.6)	.010
D-dimer > 3.82 µg/ml	234 (65.9%)	117 (76.5%)	117 (57.9%)	<.001
Comorbidities				
Hypertension	140 (39.4%)	54 (35.3%)	86 (42.6%)	.165
Diabetes	57 (16.1%)	25 (16.3%)	32 (15.8%)	.899
Coronary heart disease	21 (5.9%)	11 (7.2%)	10 (5.0%)	.376
Cardiac insufficiency	6 (1.7%)	5 (3.3%)	1 (0.5%)	.221
Neurovascular disease	46 (13.0%)	19 (12.4%)	27 (13.4%)	.792
Peripheral arterial diseases	8 (2.3%)	4 (2.6%)	4 (2.0%)	.970
Risk factors				
Thrombophilia	6 (1.7%)	5 (3.3%)	1 (0.5%)	.112
Immobilization	87 (24.5%)	34 (22.2%)	53 (26.2%)	.384
Recent surgery	40 (11.3%)	17 (11.1%)	23 (11.4%)	.935
Obesity	41 (11.5%)	15 (9.8%)	26 (12.9%)	.371
Varicose veins	22 (6.2%)	11 (7.2%)	11 (5.4%)	.500
Estrogen use	7 (2.0%)	3 (2.0%)	4 (2.0%)	1.000
Cancer	33 (9.3%)	12 (7.8%)	21 (10.4%)	.412
Peripartum	11 (3.1%)	2 (1.3%)	9 (4.5%)	.166
Previous DVT	54 (15.2%)	24 (15.7%)	30 (14.9%)	.828
Thrombus distribution				
IVC involved	67 (18.9%)	41 (26.8%)	26 (12.9%)	.001
Proximal	326 (91.8%)	143 (93.5%)	183 (90.6%)	.151
Iliofemoral	302 (85.1%)	136 (88.9%)	166 (82.2%)	.079
Isolated IVC thrombosis	2 (0.6%)	2 (1.3%)	0	.185
Bilateral extremities	90 (25.4%)	42 (27.5%)	48 (23.8%)	.429
Unilateral extremity	263 (74.1%)	109 (71.2%)	154 (76.2%)	
Light side	176 (66.9%)	65 (59.6%)	111 (72.1%)	
Right side	87 (33.1%)	44 (40.4%)	43 (27.9%)	.035*

Data are presented as n (%) or mean ± standard deviation unless stated otherwise.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; IQR, interquartile range; IVC, inferior vena cava.

\*P value was calculated by comparing the number of patients between right side DVT and left side DVT.

### The Relationship between Iliac Vein Compression and Silent PE

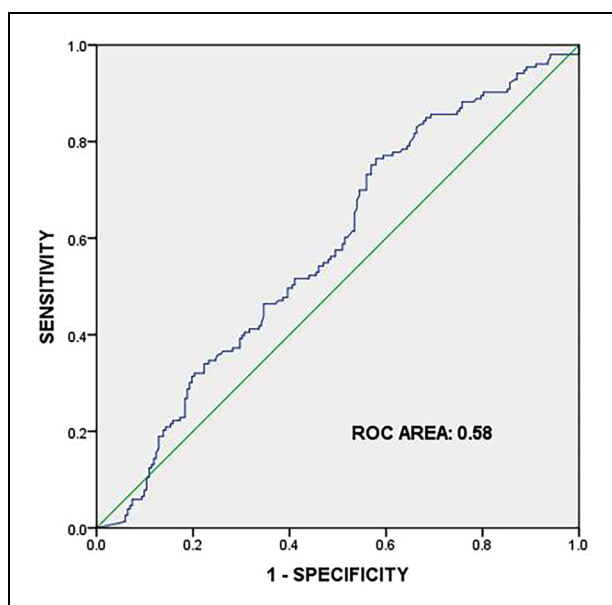
Iliac vein compression was identified in 47.5% (125/263) of patients with unilateral DVT. Compared with right iliac vein compression, the incidence of left iliac vein compression was significantly higher (59.1% vs 24.1%,  $p < .001$ ). Unilateral DVT with ipsilateral iliac vein compression was associated reduced incidence of silent PE (28.8% vs 52.9%,  $p < .001$ ). Subgroup analysis showed similar result for left side DVT (26.9% vs 51.4%,  $p = .001$ ), whereas this difference was not significant for right side DVT (38.9% vs 54.5%,  $p = .189$ ) (Table 3).

### Discussion

This study showed that right side DVT was associated with a higher incidence of silent PE than left side DVT. Iliofemoral DVT did not increase the incidence of silent PE, whereas iliofemoral DVT was associated with more proximal thrombi in

pulmonary arteries. The male patients, IVC involvement, and D-dimer value > 3.82 µg/ml were risk factors for the occurrence of PE. For unilateral DVT, ipsilateral iliac vein compression was a protective factor for developing silent PE.

Undetected baseline silent PE may be subsequently mistakenly diagnosed as new PE due to failed anticoagulant therapy, which may lead to unnecessary IVC filter placement.<sup>17</sup> The main pulmonary artery involvement in silent PE is possible,<sup>4,6</sup> and pulmonary hypertension may ensue.<sup>10</sup> Of note, approximately 25% of patients with chronic thromboembolism pulmonary hypertension (CTEPH) do not report any episode of symptomatic PE,<sup>18</sup> which suggests silent PE is also an important risk factor for CTEPH.<sup>19</sup> In the present study, up to 53.6% of main or lobar pulmonary artery involvement was found in silent PE, which means a nonnegligible number of patients have a potential risk of pulmonary hypertension. The present study also showed that iliofemoral DVT was associated with a more proximal PE. These results suggest that screening for PE in iliofemoral DVT may benefit individualized anticoagulation to counter the risk of long-term pulmonary hypertension.



**Figure 2.** Predictive value of D-dimer for silent pulmonary embolism in patients with deep vein thrombosis using ROC analysis.

**Table 2.** Multivariate Regression Analysis of Risk Factors for Silent PE in DVT Patients.

Risk Factors	OR (95% CI)	P value
Gender		
Female	1.00	
Male	1.59 (1.02–2.50)	.042
IVC involvement		
IVC not involved	1.00	
IVC involvement	1.81 (1.02–3.20)	.043
D-dimer		
D-dimer $\leq$ 3.82 ug/ml	1.00	
D-dimer $>$ 3.82 ug/ml	2.32 (1.43–3.77)	$<.001$

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; OR, odds ratio; CI, confidence interval; IVC, inferior vena cava.

Li et al found that the patients with prior silent PE had an increased incidence of symptomatic PE during catheter-directed thrombolysis treatment, and a prophylactic IVC filter may be recommended for these patients.<sup>20</sup> This result suggests that screening for baseline silent PE may benefit patients who receive pharmacomechanical mechanical thrombectomy. DVT with concomitant silent PE was also associated with an increased incidence of VTE recurrence compared to isolated DVT.<sup>1,21,22</sup> Moreover, Tzoran et al found that the risk of symptomatic PE increased 4.8-fold in patients with silent PE in the first two weeks of anticoagulant therapy.<sup>23</sup> As mentioned above, selective silent PE screening in high-risk patients may be worthwhile despite the added cost, radiation, and risk of contrast medium related nephropathy.

Previous studies have demonstrated that right side DVT was associated with a high risk of symptomatic PE than left side DVT.<sup>24,25</sup> Moreover, Li et al found right side DVT was also

**Table 3.** The Presence of Iliac Vein Compression in Unilateral Lower Extremity DVT Patients with Silent PE and Without PE.

Variable	All Patients (n = 263)	Silent PE (n = 109)	No PE (n = 154)	P value
Iliac vein compression	125 (47.5%)	36 (33.0%)	89 (57.8%)	$<.001$
Right side DVT				
Iliac vein compression	21 (8.0%)	8 (7.4%)	13 (8.4%)	.189
No iliac vein compression	66 (25.1%)	36 (33.0%)	30 (19.5%)	
Left side DVT				
Iliac vein compression	104 (39.5%)	28 (25.7%)	76 (49.4%)	.001
No iliac vein compression	72 (27.4%)	37 (33.9%)	35 (22.7%)	

Data are presented as n (%) unless stated otherwise.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

associated with increased risk for silent PE, and they assume the iliac vein compression may play a role in this difference.<sup>5</sup> In the present study, more silent PE was found in right side DVT than left side DVT (40.4% vs 27.9%,  $p = .035$ ), which is consistent with previous publications. In addition, the present study evaluated the relationship between iliac vein compression and silent PE. We found left side iliac vein compression was more common than right side (59.1% vs 24.1%,  $p < .001$ ). Furthermore, unilateral DVT with ipsilateral iliac vein compression was associated reduced incidence of silent PE (28.8% vs 52.9%,  $p < .001$ ). These may explain why right side DVTs were more vulnerable to silent PE. Of note, subgroup analysis of right side DVT also showed that iliac vein compression reduced the incidence of silent PE, whereas the difference was not significant (38.9% vs 54.5%,  $p = .189$ ). The limited number of iliac vein compression in right side DVT may be responsible for this insignificance. Several studies reported that proximal DVT significantly increased the incidence of silent PE.<sup>1,5,11,12</sup> However, other studies showed that the incidence of PE was not related to the level of DVT.<sup>2,4,6,26</sup> In the present study, the more proximal DVTs also had a higher silent PE incidence, but this difference did not reach a statistical significance.

This study showed that male patients had a 1.59-fold risk of silent PE compared to females. Li et al and Lopez-Beret et al also found that silent PE was significantly more common in male DVT patients.<sup>4,5</sup> Moreover, males were more vulnerable to secondary PE and recurrent VTE.<sup>27,28</sup> However, the relationship between sex and silent PE in DVT patients has not been elucidated. Thus, further studies are urgent to illustrate the relationship between sex and silent PE in DVT. In most previous studies, the extent of DVT was only evaluated by ultrasound scan or venography. Thus, the incidence of IVC involvement and its correlation with silent PE has not been studied. Intuitively, DVT with the IVC involvement has a relatively higher incidence of PE compared to isolated lower extremity DVT.<sup>29</sup> The present study showed IVC involvement in DVT

patients was a risk factor for silent PE. This result suggests that DVT with IVC involvement should be treated more carefully. D-dimer testing was associated with a high negative predictive value and a low positive predictive value for VTE diagnosis.<sup>16</sup> Our study demonstrated that DVT patients with silent DVT had a significantly higher D-dimer level than those without PE, which is consistent with previous studies.<sup>6,12</sup> García-Fuster et al reported that a D-dimer value of 578 ng/ml (quantitative turbidimetric assay) was discriminative of PE occurrence, whereas the sensitivity and specificity were low.<sup>6</sup> In this study, we found that the D-dimer value of 3.82 µg/ml (sensitivity: 76.5%, specificity: 42.1%) was discriminative of PE occurrence. Different D-dimer assay methods and corresponding cut-offs used in the two studies may explain these different discriminants. The multivariate regression model showed that the D-dimer value >3.82 µg/ml was associated with an approximately 2.3-fold risk of silent PE. Thus, screening for silent PE in DVT patients with a D-dimer value >3.82 µg/ml might be reasonable. Anticoagulant therapy avoids thrombus extension,<sup>30</sup> thus reducing the incidence of PE. That means delayed admission and anticoagulant therapy may result in increased PE incidence. However, our study showed that both delay from symptom onset to admission and symptom duration >7 days were not related to silent PE incidence. Further studies are required to elucidate this issue.

There are some limitations to the present study. First, this is a single-center retrospective study, and the number of patients was relatively small for assessing risk factors in the multivariate statistical models. Moreover, limited by the retrospective design, selection bias and confounding factors may have compromised the results. Second, some patients received therapeutic anticoagulation before the blood sample was collected, which may somewhat have influenced the results. Third, the cost-effectiveness of screening was not analyzed. Fourth, patients with previous DVT history were not excluded, and the previous PE may be mistakenly diagnosed as new silent PE, leading to the overestimated silent PE incidence.

## Conclusions

Iliofemoral DVT was associated with a more proximal silent PE than non-iliiofemoral DVTs. The male patients, IVC involvement, and D-dimer value >3.82 µg/ml were risk factors for the occurrence of silent PE. Unilateral DVT with ipsilateral iliac vein compression was associated with a reduced silent PE incidence.

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Not applicable.

## Authors' Contributions

Study design: Gu Jianping and Wang Tao. Data collection: Shi Yadong, Su Haobo and Yuan Yuan. Data analysis: Huang Hao and Lu Zhaoxuan. Writing: Shi Yadong and Chen Liang

## Availability of Data and Materials

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

## Consent for Publication

Not applicable.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


## Ethics Approval and Consent to Participate

The Institutional Review Board of the study hospital approved this study protocol, and informed consent was waived.

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