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Parapneumonic effusion is a risk factor for VTE in hospitalized patients with community-acquired pneumonia: a retrospective cohort study

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Abstract

Background Venous thromboembolism (VTE) is a major, frequent, and potentially fatal health issue worldwide. Community-acquired pneumonia (CAP) is one of the leading causes of hospitalization and parapneumonic pleural effusion (PPE) is a relatively common complication of pneumonia. Whether PPE is a risk factor for VTE in hospitalized patients with CAP has not been studied before.

Methods We retrospectively reviewed all patients diagnosed with CAP admitted to our center from 1 January to 31 August in 2019. The clinical and laboratory data were collected from medical records. Univariate and multivariable logistic regression analysis were used to assess the VTE related risk factors. Subgroup analysis was conducted to investigate the potential correlation between PPE and VTE among distinct subsets of hospitalized patients diagnosed with CAP.

Results This retrospective cohort study included 703 inpatients and 73 patients were confirmed VTE. In multivariable logistic regression analysis, PPE, age, sex, gender, D-dimer, and pneumonia severity index score, were significantly correlated with VTE. Several laboratory parameters within the PPE group demonstrated significant elevated levels compared to the non-PPE cohort, encompassing inflammatory markers such as neutrophils, C reaction protein, D-dimer, as well as some coagulation indicators including platelets, and prothrombin time.

Conclusion PPE is an independent risk factor for hospitalized CAP patients. The patients with PPE have a higher level of inflammation response. Medical clinicians should pay more attention to VTE and improve its prevention and therapeutic strategies among hospitalized CAP patients.

Keywords Venous thromboembolism, Parapneumonic pleural effusion, Risk factors, Community-acquired pneumonia, Inpatients

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Introduction

Venous thromboembolism (VTE) is a major, frequent, and potentially fatal health issue in the general population worldwide. It is reported that the annual incidence of VTE in the United States was 123 cases per 100,000 persons and in European countries it is 131 per 100,000 persons [1, 2]. VTE often occurs insidiously or asymptomatically and was associated with increased risk of short-term all-cause mortality [3]. In recent years, awareness of VTE disease has been increased due to the widespread use of imaging studies and the increased sensitivity of imaging techniques. Nowadays, clinicians are increasingly encountering patients with VTE, including pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT), resulting in the increased importance of VTE awareness in daily clinical practice [4].

Several VTE risk factors including acute infection process have been identified in previous studies and hospitalized patients with pre-existing lung disease are at a significantly increased risk of VTE [5, 6]. The possible mechanism by which acute infection causes VTE is that infection can induce local or systemic inflammatory reactions, thereby affecting endothelial cell function and leading to subsequent vessel wall damage [7]. Infection is a chronic risk factor and acute trigger for the occurrence of VTE [8]. Community-acquired pneumonia (CAP) is one of the leading causes of hospitalization among respiratory patients, but there are few analyzes of risk factors for VTE in hospitalized patients with CAP [9].

Parapneumonic pleural effusion (PPE) refers to the pathogenic accumulation of fluid adjacent to pneumonia which is relatively a common complication of pneumonia and the most common type of exudative pleural effusion, occurring in 20 to 40% of inpatients with pneumonia [10]. The formation of PPE involves an increase in permeability and the possible damage to vascular endothelium, blockage of blood flow due to mechanical compression, and hypercoagulability due to inflammatory stimulation. Whether PPE is a risk factor for VTE in hospitalized patients with CAP has not been studied before.

Methods

Study population

We retrospectively reviewed all patients diagnosed with CAP admitted to our center from 1 January to 31 August in 2019. All diagnoses were confirmed by two physicians. Wells score was used to assess the patient's pre-test probability of developing VTE and assist in determining whether to perform VTE screening tests on admission [11]. Patients falling into the likely group and unlikely group with elevated age-adjusted D-dimer value would complete screening tests for VTE [12]. The patients were selected according to the inclusion criteria as follows: (i) confirmed diagnosis of CAP [13] (ii) patients screened for VTE within 48 h of admission by compression ultrasonography (CUS), or computed tomography pulmonary angiogram (CTPA) or lung ventilation/perfusion (V/Q) scan. The exclusion criteria were as follows: (i) patients receiving anticoagulant treatment on admission. (ii) critically ill patients admitted to respiratory intensive care unit.

Confirmed diagnosis of VTE

The diagnostic criterion for DVT by ultrasonography was incomplete compressibility of the vein and absence or reduction of blood flow signal. The diagnosis of PTE should be considered if CTPA shows a segmental or more proximal filling defect or a V/Q scan yields a high probability for PTE.

Clinical and laboratory data collection

The clinical and laboratory data were collected from medical records including age, gender, smoking status, bedridden time, body mass index (BMI), thrombosis prevention status and pulmonary comorbidities. Serum levels of white blood cell (WBC), neutrophils, hemoglobin (Hb), hematocrit (HCT), platelet (PLT), prothrombin time (PT), activated partial prothrombin time (APTT), C reaction protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer from peripheral blood at diagnosis, pneumonia severity index (PSI) score, were collected. PSI score is a tool to assess the severity of CAP and used widely at our center [14]. A higher PSI stage means more severe CIP. For the purposes of simplification, the hospitalized patients were divided into two groups based on risk stratification, stage IV/V or stage III.

Risk assessment of VTE

The cumulative score of VTE risk assessment and its corresponding risk level were assessed for CAP patients. Our analysis focused on the values of these variables obtained from the records closest to the time of admission. Two extensively trained researchers calculated the scores independently. Pertaining to the Padua Prediction Score (PPS) [15], categorization aligned with the American College of Chest Physicians (ACCP) guidelines, a score of ≥ 4 was defined as the "high-risk" group. As for Caprini Risk Assessment Model (RAM) [16], the guidelines indicated that categorization as "low risk" for scores between 0 and 1, "intermediate risk" for a score of 2, "high risk" for scores ranging from 3 to 4, and "highest risk" for scores surpassing 5.

Diagnosis and classification of PPE

The diagnosis and categorization of PPE were substantiated by a consensus reached by at least two clinicians based on comprehensive assessment including clinical manifestations, imaging, pleural fluid analysis and

microbiological findings [17, 18]. Uncomplicated parapneumonic effusion (UPPE) was characterized by the patient's positive response solely to antibiotic therapy. On the other hand, complicated parapneumonic effusion (CPPE) was defined when non-suppurative effusions required drainage and other procedures. The diagnosis of empyema was established upon the identification of pus within the pleural space [19–21].

Statistical analyses

All statistical analyses were performed with SPSS 23.0 and R version 4.1.0. Mean and standard deviation or median and interquartile range were used to describe continuous variables appropriately. For continuous variables, T test or nonparametric test was used. Chi-squared test was used to compare the incidence rates of VTE in different categories. Risk factors were analyzed by logistic regression and relative risk odds ratio (OR) and 95% confidence interval (CI) were calculated. Two-sided test $p < 0.05$ was considered as statistically significant.

Results

Patient characteristics

Among the initial 1048 participants screened for CAP, 345 patients were excluded based on specific exclusion criteria delineated in Fig. 1. Within our cohort study conducted from January to August 2019, a total of 703 hospitalized CAP patients (comprising 428 males and 275 females) were included for analysis. During their hospitalization, 73 patients were confirmed VTE by CUS, CTPA and V/Q scan, of which 1 patient (1.37%) were diagnosed with DVT and PTE, 5 patients (6.85%) had PTE only, 67 patients (91.78%) had DVT only. Among the DVT cases, 17 (25.0%) were classified as proximal DVT and 51 (75.0%) as isolated distal DVT. Prevalent pulmonary comorbidities included PPE at 6.26%, chronic obstructive pulmonary disease (COPD) at 26.46%, asthma (17.50%), bronchiectasis (14.22%), interstitial lung diseases (17.64%), and miscellaneous conditions (4.41%) encompassing pulmonary vasculitis, obstructive sleep apnea-hypopnea syndrome (OSAHS) and lung cancer, among others. (as illustrated in Table 1)

Clinical characteristics related with VTE

Table 1 indicates the clinical and laboratory variables associated with VTE on admission. The median age was 64.0 years (interquartile range [IQR], 57.0–72.0). Patients in the VTE group were older than the non-VTE group (median 69.0 vs. 64.0, $p < 0.001$). The median scores of Padua Prediction Score (PPS) (3.0 vs. 2.0, $p < 0.001$) and Caprini risk assessment Model (RAM) (4.0 vs. 3.0, $p < 0.001$) were higher in the VTE group. Between the two groups, gender, smoking status, bedridden time (>72 h), the values of WBC, HGB, HCT, PLT, PT, APTT and ESR showed no significant difference. The clinical indicators which showed significant differences between VTE and non-VTE group are shown as follows: age, BMI, PPS, Caprini RAM, thromboprophylaxis, neutrophils, D-dimer, CRP, and PPE.

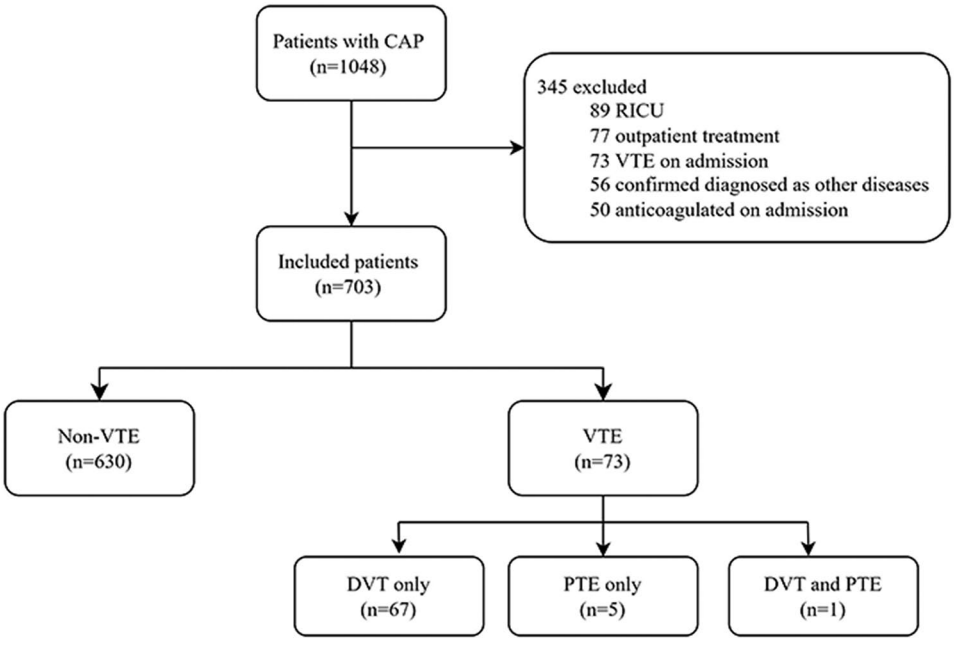

Fig. 1 Flow diagram of the study population VTE: venous thromboembolism; PTE: pulmonary thromboembolism; DVT: deep vein thrombosis

Table 1 Baseline characteristics of patients with and without VTE

Patient characteristics	Total *N* = 703	Patients without VTE *N* = 630	Patients with VTE *N* = 73	*p* value
Age (years)	64.0 (57.0–72.0)	64.00 (57.0–71.0)	69.0 (62.0–79.0)	< 0.001*
Male	428 (60.88)	376 (59.68)	52 (71.23)	0.056
BMI (kg/m^2)	23.82 ± 3.83	23.95 ± 3.85	22.57 ± 3.41	0.009*
Smoking history	364 (51.78)	322 (51.11)	42 (57.53)	0.298
Bedridden time (> 72 h)	121 (17.21)	103 (16.35)	18 (24.66)	0.075
PPS (score)	2.00 (1.00–3.00)	2.00 (1.00–2.00)	3.00 (2.00–6.00)	< 0.001*
Caprini RAM (score)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	4.00 (3.00–6.00)	< 0.001*
Thromboprophylaxis	109 (15.5)	70 (11.11)	39 (53.42)	< 0.001*
Laboratory tests on admission				
WBC (×10^9/L)	6.71 (5.29–8.93)	6.63 (5.24–8.88)	7.06 (5.68–9.36)	0.073
Neutrophils (%)	62.70 (55.00–72.25)	62.30 (54.30–71.18)	69.10 (59.10–77.80)	0.002*
HGB (g/L)	129.00 (117.00–140.00)	129.00 (117.00–141.00)	128.00 (113.00–137.00)	0.078
HCT (%)	37.60 (34.60–40.90)	37.70 (34.70–41.00)	37.30 (32.90–40.10)	0.069
PLT (×10^9/L)	229.00 (181.00–276.00)	229.50 (181.25–274.00)	220.00 (181.00–285.00)	0.448
PT (s)	11.80 (11.30–12.43)	11.80 (11.30–12.40)	11.90 (11.20–13.00)	0.660
APTT (s)	24.90 (23.00–27.00)	24.90 (23.15–26.90)	24.90 (22.50–27.70)	0.928
D-dimer (ng/mL)	517.51 (300.00–1175.42)	467.88 (285.84–977.83)	1423.67 (790.00–2467.31)	< 0.001*
ESR (mmol/h)	19.00 (7.00–36.00)	19.00 (7.00–37.00)	18.50 (10.00–28.25)	0.930
CRP (mg/dL)	0.71 (0.32–3.15)	0.69 (0.30–2.68)	1.19 (0.46–6.62)	0.009*
Types of pulmonary comorbidity				
PPE	44 (6.26)	33 (5.24)	11 (15.07)	0.002*
COPD	186 (26.46)	166 (26.35)	20 (27.40)	0.848
Asthma	123 (17.50)	108 (17.14)	15 (20.55)	0.469
Bronchiectasis	100 (14.22)	94 (14.92)	6 (8.22)	0.121
Interstitial lung disease	124 (17.64)	110 (17.16)	14 (19.18)	0.715
Others	31 (4.41)	26 (4.13)	5 (6.85)	0.448

Data are presented as means ± SD and median (interquartile range) for continuous variables, counts (proportions) for categorical. Abbreviations: VTE: venous thromboembolism; BMI: body mass index; PPS: Padua Prediction Score; RAM: risk assessment Model; WBC: white blood count; HGB: hemoglobin; HCT: hematocrit; PLT: platelet count; PT: prothrombin time; APTT: activated partial thromboplastin time; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PPE: parapneumonic effusion; COPD: chronic obstructive pulmonary disease. * Statistically significant between the two groups

Table 2 Multivariable logistic regression analysis of VTE risk factors

Variables	OR	(95%CI)	*P*	Adjusted OR	(95%CI)	Adjusted *P*
PPE (yes or no)	3.21	1.55–6.67	0.002	2.44	1.12–5.33	0.025
Age	1.06	1.03–1.08	< 0.001	1.05	1.02–1.08	< 0.001
Sex (male or female)	1.67	0.98–2.85	0.058	1.76	1.01–3.08	0.048
D-dimer ≥ 500 ng/mL (yes or no)	5.04	2.71–9.37	< 0.001	3.73	1.96–7.11	< 0.001
PSI score (IV/V or III)	4.29	1.87–9.81	< 0.001	2.63	1.08–6.39	0.033

Abbreviations: VTE: venous thromboembolism; PPE: parapneumonic effusion; PSI: pneumonia severity index; OR, odds ratio; CI, confidence interval

PPE is an independent VTE risk factor for hospitalized CAP patients

In multivariable logistic regression analysis, PPE (yes or no), age, gender, D-dimer ≥ 500 ng/mL (yes or no), PSI score (stage IV/V or III) were significantly correlated with VTE, as shown in Table 2. There is no correlation between PPE and D-dimer (Collinearity tolerance 0.991; Variance Inflation Factor 1.009), which means they are independent risk factors for VTE in hospitalized CAP patients.

Subgroup analysis

As depicted in Fig. 2, subgroup analysis was conducted to investigate the potential correlation between PPE and VTE among distinct subsets of hospitalized patients diagnosed with CAP. The findings revealed that within subgroups devoid of bronchiectasis or asthma, categorized as low risk based on PPS, with a BMI of 25 or less, and aged over 65 years, the existence of PPE is a risk factor for VTE incidence. Notably, there were no notable disparities observed between groups with varying levels of D-dimer, and PPE was a discernible risk factor for VTE

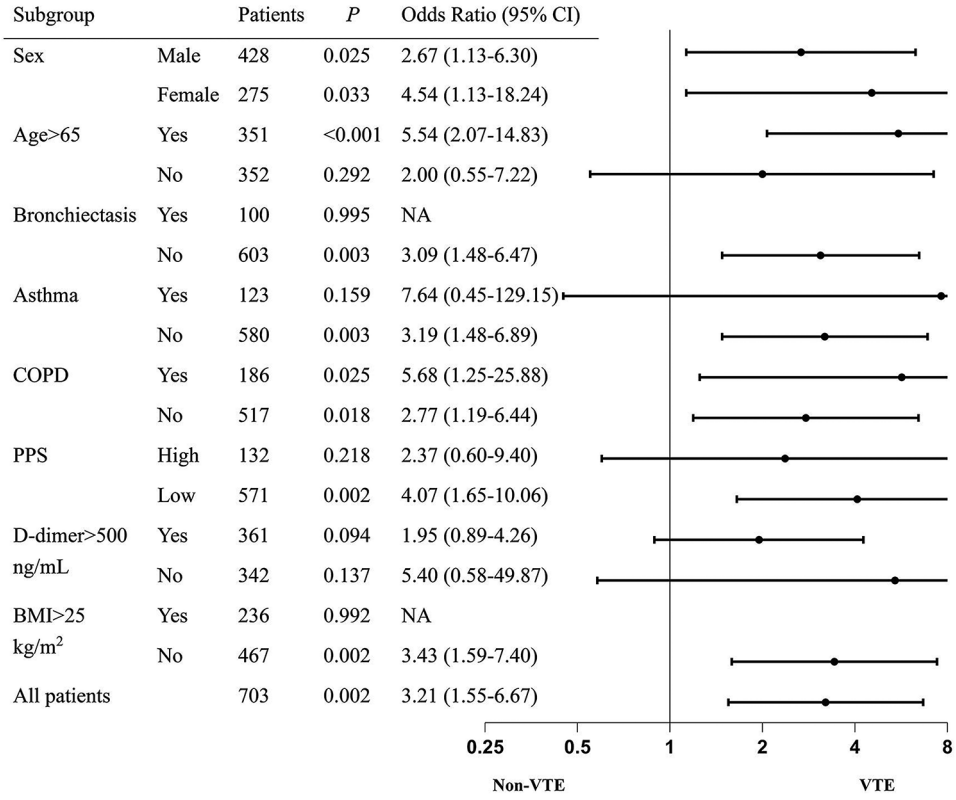

Fig. 2 Subgroup analysis about the potential correlation between PPE and VTE among different subsets of hospitalized patients diagnosed with CAP
COPD: chronic obstructive pulmonary disease; PPS: Padua Prediction Score; BMI: body mass index

Table 3 Comparison of patients with and without PPE

Patient characteristics	Patients without PPE *N* = 659	Patients with PPE *N* = 44	*p* value
Neutrophils (%)	62.20 (54.30–71.70)	68.95 (65.20–75.98)	< 0.001*
HGB (g/L)	129.00 (117.00–141.00)	124.50 (109.00–137.00)	0.043*
PLT ($\times 10^9$/L)	227.00 (179.5–271.00)	315.00 (202.25–377.25)	< 0.001*
PT (s)	11.80 (11.20–12.40)	12.35 (11.50–13.12)	0.002*
D-dimer (ng/mL)	485.53 (292.21–1044.72)	1615.94 (850.50–3995.70)	< 0.001*
CRP (mg/dL)	0.69 (0.30–2.65)	3.15 (0.64–7.48)	< 0.001*
VTE	62 (9.41)	11 (25.00)	0.002*

across populations both with and without COPD and individuals of all genders.

CAP Patients with PPE have higher inflammatory markers

The risk of VTE occurrence significantly elevated among the PPE group ($p = 0.002$). To ascertain the underlying factors responsible for the increased prevalence of VTE in hospitalized CAP patients with PPE, a comparative analysis was undertaken to evaluate patient characteristics between cohorts with and without PPE, and the results are presented in Table 3; Fig. 3. Among the CAP patients presenting with PPE, a total of 44 individuals received a confirmed diagnosis of PPE, comprising 32 cases of UPPE, 8 cases of CPPE, 3 instances of empyema. No statistically significant differences were observed among the distinct subcategories of PPE. Furthermore, several laboratory parameters within the PPE group demonstrated significant elevated levels compared to the non-PPE cohort, encompassing inflammatory markers such as neutrophils, CRP, D-dimer, as well as some coagulation indicators including hemoglobin, platelets, and PT.

Discussion

VTE is correlated with a heightened global medical burden and constitutes the third most prevalent cause of mortality on a global scale [22, 23]. An expeditious risk stratification of patients, coupled with the discernment of those patients at high risk, holds the potential to optimize therapeutic interventions [24]. Previous studies have

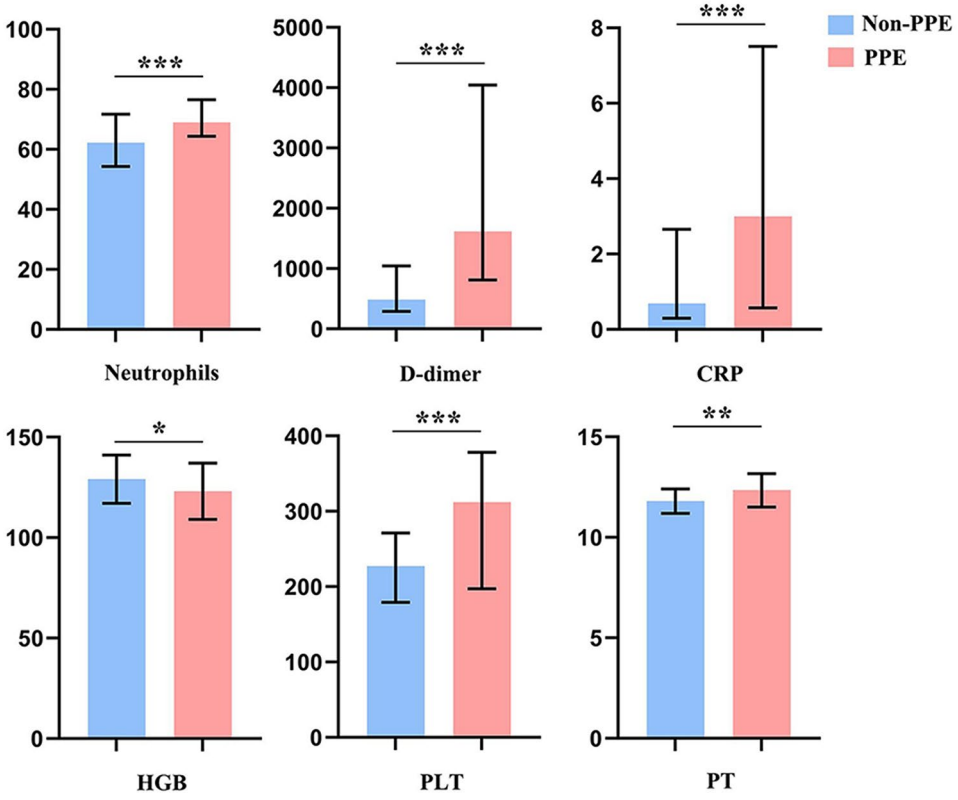

Fig. 3 Comparison of patients with and without PPE Data are presented as median (interquartile range) for continuous variables, counts (proportions) for categorical. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared by Nonparametric test

demonstrated that patients with acute or chronic inflammatory diseases are at higher risk of initial and recurrent VTE and inflammatory molecules and immune cells are acknowledged as pivotal contributors to thrombosis [25].

Pneumonia remains a leading cause of hospitalization worldwide [26]. Two retrospective cohort studies revealed a notable 2- to 3-fold increased risk of acute venous thrombosis among patients diagnosed with pneumonia [8, 27]. Nevertheless, given that the extent to which this risk is causal is uncertain, it may be imperative to acquire insights into risk cohorts in whom the risk is additionally increased. To study this, we conducted a retrospective study to identify risk factors associated with the risk of VTE in hospitalized CAP patients.

The findings from expansive international clinical investigations revealed that the prevalence of VTE ranged between 4.96% and 14.90%. Moreover, one study showed that the occurrence of DVT specifically among CAP inpatients in elderly communities was determined to be 26.3% [28]. In the current study, the incidence of VTE among hospitalized CAP patients was 10.4% (73/703). The differences in incidence across studies were related to the inclusion population and the selection strategy. Due to the significantly increased incidence of VTE in critically ill patients, the patients in intensive care unit (ICU) were excluded from this study. As a result, this may actually underestimate the influence of PPE on development of VTE. Since patients with pneumonia and PPE are associated with adverse Clinical outcomes, such as higher mortality, higher admission rate, and longer hospital stays [29]. Further investigation needs to be conducted among pneumonia patients hospitalized in ICU and general ward. Notably, more than half(53.42%) of the patients who received thromboprophylaxis developed VTE in our study. This suggests that thromboprophylaxis was not associated with a reduction in VTE occurrence, aligning with findings from another study on VTE prophylaxis in acutely medically ill patients [30]. However, in our cohort, there were no cases of fatal VTE, and 91.78% of the patients had isolated DVT. It has been reported that the incidence of fatal VTE ranges from 5 to 10% in hospitalized patients without prophylaxis [31, 32]. These findings indicate that, although thromboprophylaxis may not prevent the development of VTE, it could effectively reduce the incidence of fatal VTE.

In our study, CAP patients with VTE exhibited advanced age compared to their counterparts without VTE and there was no difference in the gender distribution. A meta-analysis showed that older age, elevated levels of CRP, D-dimer, and the presence of infections are all risk factors for the incidence of VTE in hospitalized patients [33]. Barba's research group found that

surpassing the age of 70 years old was an independent risk factor for VTE, which may be linked to diminished muscle activity and tone, as well as the presence of degenerative vascular lesions prevalent in the elderly population [34].

To our knowledge, this is the first study to demonstrate that PPE is an independent risk factor for CAP patients. In the subsequent analysis, PPE group exhibited elevated concentrations of neutrophils, CRP, D-dimer, PT and PLT, thereby signifying an augmented inflammatory state. Meanwhile, the formation process of PPE includes increased pleural permeability, vascular endothelial damage, and inflammation, which results in the generation of pro-inflammatory cytokines that foster coagulation and leads to the occurrence of venous thrombosis, where the inflammatory and coagulation system are coupled through a common activation pathway. Through the identification of specific risk factors including PPE, individuals with an elevated susceptibility to the development of VTE can be discerned at an earlier stage. This early recognition enables the implementation of more judicious VTE prevention measures for hospitalized CAP patients, complementing existing clinical risk scoring systems. In addition, the higher VTE rate in PPE patients may just be a reflection of the fact that PPE tends to develop in a more advanced stage in pneumonia. However, after considering pneumonia severity (PSI score), PPE is an independent VTE risk factor for hospitalized CAP patients in our study.

D-dimer is a marker of fibrinolytic activity and has been reported to be elevated in CAP patients [35]. The more severe the injury induced by infection, the more disordered the coagulation fibrinolysis system. The increased D-dimer level has been confirmed in patients with VTE in many literatures, but they did not demonstrate the best D-dimer cut-off level. The current study revealed that the levels of D-dimer of the VTE group and PPE group were higher than corresponding counterparts. Furthermore, we conducted an analysis to ascertain whether D-dimer concentrations exceeding 500 ng/mL could be identified as a potential VTE risk factor. The researchers found the D-dimer value was positively correlated with the pneumonia severity index score and the plasma D-dimer value was an independent risk factor for COPD patients [36, 37].

There were several limitations in the current study. Firstly, it was a single-center, retrospective cohort study with selective bias in identifying risk factors and patient selection. Inevitably, the retrospective nature of the study prevents validation of the accuracy of the data interrogated. Thus, more attention should be paid to the future prospective and multicenter studies. Secondly, the small numbers of VTE and PPE rates in subgroup analysis might preclude definitive conclusion and generalizability of the results. Thirdly, microbiological detail, allied standardized treatments and other confounding variables should be collected and considered in future studies.

Conclusion

PPE is an independent risk factor for hospitalized CAP patients. The patients with PPE have a higher level of inflammation response. Medical clinicians should pay more attention to VTE and improve its prevention and therapeutic strategies among hospitalized CAP patients.

Abbreviations

VTE	Venous thromboembolism
CAP	Community-acquired pneumonia
PPE	Parapneumonic pleural effusion
PTE	Pulmonary thromboembolism
DVT	Deep vein thrombosis
CUS	Compression ultrasonography
CTPA	Computed tomography pulmonary angiogram
V/Q	Ventilation/perfusion
BMI	Body mass index
WBC	White blood cell
Hb	Hemoglobin
HCT	Hematocrit
PLT	Platelet
PT	Prothrombin time
APTT	Activated partial prothrombin time
CRP	C reaction protein
ESR	Erythrocyte sedimentation rate
PPS	Padua Prediction Score
ACCP	American College of Chest Physicians
RAM	Risk Assessment Model
UPPE	Uncomplicated parapneumonic effusion
CPPE	Complicated parapneumonic effusion
OR	Odds ratio
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
OSAHS	Obstructive sleep apnea-hypopnea syndrome

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Author contributions

XYS: Concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, manuscript preparation, manuscript editing, and manuscript review. YXZ: Concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, and manuscript preparation. FSY: Data acquisition and data analysis. SFD: Data acquisition and statistical analysis. QYC: Data acquisition and statistical analysis. XJJ: Data acquisition and data analysis. YHY: Concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, manuscript editing, and manuscript review.All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Because this is an observational study, written informed consent was waived off from individual patients. Permission for data analysis was approved by

the Ethics Committee of the Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine, Capital Medical University, Beijing, China.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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