



Risk factors for venous thromboembolism in patients with pneumonia in the pre-COVID-19 era: a meta-analysis and systematic review

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Background: Elevated risk of venous thromboembolism (VTE) in patients with coronavirus disease 2019 (COVID-19) pneumonia has been recognized, while the risk factors associated with VTE in patients with non-COVID-19 pneumonia remain to be defined. This study aimed to conduct a meta-analysis and systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify potential risk factors for VTE in patients with pneumonia from the pre-COVID-19 era.

Methods: PubMed, EMBASE, and Cochrane Library were searched. Two reviewers performed screening, full-text review, and extraction. Risk factors and odds ratio (OR) were estimated.

Results: Of 595 articles identified, six studies were included. Pooled analysis suggested that age ≥ 60 years [OR =2.75, 95% confidence interval (CI): 2.55–2.97, $P < 0.001$], mechanical ventilation (MV) (OR =9.48, 95% CI: 8.24–10.91, $P < 0.001$), hypertension (OR =1.41, 95% CI: 1.09–1.83, $P = 0.010$), diabetes (OR =1.49, 95% CI: 1.36–1.64, $P < 0.001$), heart failure (OR =3.15, 95% CI: 1.05–9.41, $P = 0.040$) and cancer (OR =2.86, 95% CI: 2.07–3.95, $P < 0.001$) were associated with higher risk for deep vein thrombosis in patients with pneumonia. While age ≥ 60 years (OR =2.46, 95% CI: 2.21–2.73, $P < 0.001$), bacterial pneumonia (OR =3.80, 95% CI: 1.65–8.73, $P = 0.002$), hyperlipidemia (OR =1.55, 95% CI: 1.00–2.41, $P = 0.049$), heart failure (OR =2.70, 95% CI: 2.05–3.56, $P < 0.001$), chronic obstructive pulmonary disease (OR =4.73, 95% CI: 3.11–7.17, $P < 0.001$) and cancer (OR =2.90, 95% CI: 2.39–3.53, $P < 0.001$) were risk factors for pulmonary embolism in patients with pneumonia.

Conclusions: Patients with non-COVID-19 pneumonia, particularly those with advanced age, MV, cardiovascular comorbidities or cancer, warrant individualized management during hospitalization. Our findings could contribute to refining risk prediction models and further risk stratification for VTE in patients with pneumonia in clinical practice.

Keywords: Pneumonia; venous thromboembolism (VTE); deep venous thrombosis; pulmonary embolism; meta-analysis

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Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), has become a substantial contributor to the global burden of disease (1). Studies have shown (2,3) that VTE is the third most common cardiovascular disease just behind myocardial infarction and stroke, with an annual incidence of more than 10 million people globally.

Infection has traditionally been considered as a transient weak risk factor of VTE, while hospitalization for acute illness is a transient strong risk factor (1). Schmidt *et al.* (4) reported that patients with respiratory tract infections had the highest incidence rate ratio of VTE compared to those with other hospital-diagnosed infections, including urinary tract, skin and intra-abdominal infection. This elevated rate ratio of VTE persisted throughout a 26-week follow-up period. A large case-control study (5) additionally disclosed that patients with acute respiratory infection, including acute laryngitis, acute bronchitis, pneumonia, and productive cough, were at increased risk of both DVT and PE for an entire year post-infection. D-dimer is elevated after infection, making it unsuitable as a VTE-specific

indicator in patients with pneumonia (6). Therefore, it is urgent to identify specific population for enhanced screening strategies and VTE prophylaxis.

Over the past few years, a significant rise in VTE incidence has been observed among patients with coronavirus disease 2019 (COVID-19) pneumonia (7-9). Several studies have indicated that advancing age, cancer, elevated D-dimer levels upon admission (10), and critical illness (11,12) may serve as independent risk factors for VTE in COVID-19 patients. However, the clinical characteristics and risk factors for patients with pneumonia in pre-COVID-19 era have not been specifically investigated. To date, there has been no formal systematic review or meta-analysis on this topic.

Given the distinct biological and pathological characteristics, related publications of COVID-19 were intentionally excluded to avoid irreconcilable heterogeneity. Evaluation of VTE risk factors in real-world settings among pneumonia patients could facilitate meticulous clinical management, potentially augmenting survival outcomes. Our study aimed to review previous literature and to investigate the risk factors for VTE in pneumonia patients prior to the COVID-19 pandemic. This research provides insights to appropriate clinical management and the development of risk prediction models further. We present this article in accordance with the PRISMA reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-926/rc>).

Methods

Literature search and selection criteria

In this meta-analysis, PubMed, Embase, and Cochrane Library were searched until November 2022, utilizing the keywords “Venous thromboembolism”, “Pulmonary Embolism”, “Venous Thrombosis”, “Deep Vein Thrombosis”, “Pneumonia” and “risk factor” singly or in combination. Detailed search strategy was listed in [Appendix 1](#). All references from the reviewed articles were manually examined to guarantee that all relevant articles were included.

Highlight box

Key findings

- In patients with pneumonia, age ≥ 60 years, illness severity, bacterial pneumonia and comorbidities were associated with higher risk for venous thromboembolism (VTE).

What is known and what is new?

- Patients with coronavirus disease 2019 (COVID-19) pneumonia have a significant higher incidence of VTE. Advanced age, cancer, elevated D-dimer levels upon admission, and critical illness may serve as independent risk factors.
- Our study provides evidence of the risk factors for VTE in patients with pneumonia in pre-COVID-19 era.

What is the implication, and what should change now?

- Our findings can aid in identifying patients at a higher risk of VTE, improving risk stratification, and guiding the development of risk prediction models. Multicenter, well-designed original studies are needed in the future. Physicians should pay more attention to patients with pneumonia who have these risk factors for VTE.

Following the eligibility criteria, two authors (XFY and XLF) independently reviewed titles and abstracts, initially excluding obvious irrelevant literature and then re-evaluating the full text. They reached a consensus according to the inclusion criteria as follows: (I) the study design was case control or cohort study; (II) patients with pneumonia and VTE; (III) studies presented in English only. Studies were excluded if: (I) studies that did not report relevant risk factors; (II) patients diagnosed with COVID-19; (III) research lacking full text, with incomplete information, or posing inability to conduct data extraction. When data availability or selection was in dispute, the decision was made after discussion or consultation with a third person.

Data extraction and quality assessment

The data extracted included the author, year, study design, country, sample size, sex, age, BMI, the type of VTE and the odds ratio (OR) [95% confidence interval (CI)] of related risk factors. Two researchers (F.X. and Y.T.) independently conducted literature quality evaluations using the Newcastle-Ottawa Scale (NOS) (13) for cohort and case-control study. A study acquiring 0 to 4 stars was considered low-quality, while that achieving 5 to 9 stars was considered high quality. After completing the quality evaluation, the same two authors cross-checked the evaluation results and discussed or consulted with a third reviewer to resolve on any inconsistent results. The meta-analysis was performed based on the related items of the PRISMA guideline (14).

Data synthesis and statistical analysis

STATA 15.1 (15) was used to analyze the data. OR (95% CI) was used to analyze the risk factors of subtype of cardiovascular and cerebrovascular disease. A P value <0.05 was considered to be statistically significant. I^2 was used to evaluate heterogeneity. If the heterogeneity test was $P \geq 0.1$ and $I^2 \leq 50\%$, it indicated that there was homogeneity between studies, and the fixed effects model was used for combined analysis; if $P < 0.1$, $I^2 > 50\%$, it indicated that the study was heterogeneous, sensitivity analysis was used to find the source of heterogeneity. If the heterogeneity was still large, the random effects model would be employed, or alternatively, the combination of results would be forgone in favor of a descriptive analysis. Since there were no more than 5 articles in the study for each indicator, no publication bias detection was carried out in this study.

Results

Study selection and quality assessment

There were 595 articles identified according to the search strategy. After the exclusion of duplicates, 301 articles were screened. A total of 223 articles were considered eligible for full-text evaluation. After reviewing the full-text, we excluded studies that reported on COVID-19, lacked risk factor analysis or had unavailable data. Finally, 6 studies (16-21) were included in the final analysis according to the inclusion and exclusion criteria. The process and the results of the literature screening are shown in *Figure 1*. The Newcastle-Ottawa Scale (NOS) score used for quality assessment was equal to or above 6, indicating that all these studies had a high level of methodological quality (*Table 1*).

Baseline characteristics of the included studies

A total of six studies were included in this meta-analysis, consisting of two case-control studies (20,21) and four cohort studies (16-19), with a total sample size of 162,011 patients. Among these studies, four were conducted in Asia (16,18,20,21), while the remaining two were conducted in Europe (17) and America (19). Two studies focused on both DVT and PE with a total of 79,548 patients, two research specifically investigated on DVT with a total of 595 patients, while the remaining two studies focused solely on PE with a total of 2,458 patients (*Table 1*).

Meta-analysis of risk factors for perioperative VTE in patients with pneumonia

The meta-analysis findings are summarized in *Table 2*. When significant heterogeneity was detected, sensitivity analysis was performed by excluding studies with possible sources of heterogeneity and recalculating the combined statistics.

Demographic factors

Age

Masrouha *et al.* (17) reported that age ≥ 60 years was significantly associated with an increased risk of DVT (OR = 2.75, 95% CI: 2.55–2.97, $P < 0.001$; *Table 2, Figure 2A*). Additionally, pooled results showed that age ≥ 60 was significantly associated with an increased risk of PE (OR = 2.46, 95% CI: 2.21–2.73, $P < 0.001$, $I^2 = 0.0\%$; *Table 2, Figure 2A*).

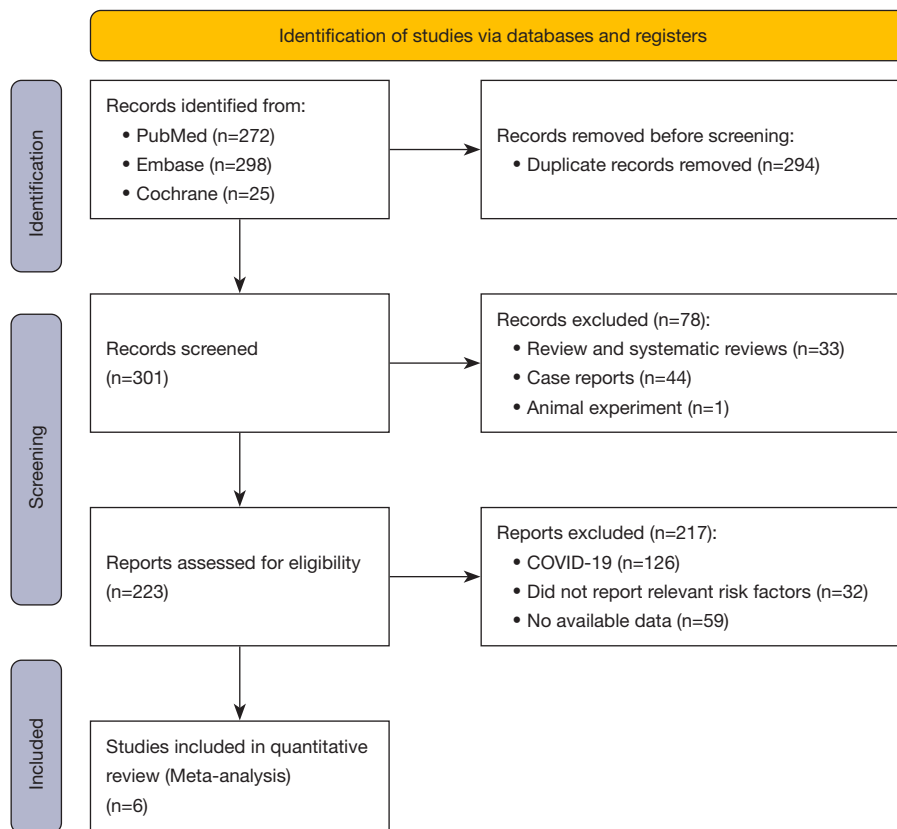


Figure 1 Flow chart summarizing evidence search and study selection.

Table 1 Baseline characteristics and quality assessment of included studies

Author	Year	Study design	Country	Sample size	Sex (male/female)	Age (years)	BMI (kg/m ²)	VTE	NOS score
Chen <i>et al.</i> (16)	2015	Cohort	China	94,640	62,225/32,415	66.0±17.8	NA	DVT + PE	7
Masrouha <i>et al.</i> (17)	2016	Cohort	Lebanon	2,302	1,287/1,015	49.5	NA	DVT + PE	7
Zhang <i>et al.</i> (18)	2015	Cohort	China	2,387	NA	NA	NA	PE	6
Obi <i>et al.</i> (19)	2018	Cohort	USA	71	61/10	40.5±13.6	34.7±10.1	PE	6
Cui <i>et al.</i> (20)	2021	Case-control	China	90	69/21	68 [57–78]	23.8±4.0	DVT	8
Ma <i>et al.</i> (21)	2022	Case-control	China	505	NA	82.75	27.7±5.5	DVT	7

BMI, body mass index; VTE, venous thromboembolism; NOS, Newcastle-Ottawa Scale; DVT, deep vein thrombosis; PE, pulmonary embolism; NA, not available.

Gender

Two studies reported the association between gender and the risk of DVT. The pooled results revealed no significant association between gender and the risk of DVT (OR =1.00, 95% CI: 0.83–1.21, P=0.992, I²=0.0%; *Table 2*,

Figure 2B). Four articles reported the association between gender and the risk of PE, and the pooled analysis did not find any significant difference between the two groups (OR =1.24, 95% CI: 0.94–1.65, P=0.132, I²=57.6%; *Table 2*, *Figure 2B*).

Table 2 Risk factors associated with DVT or PE in patients with pneumonia

Variables	Heterogeneity	OR	95% CI	P value
DVT				
Gender	$I^2=0\%$, $P=0.821$	1.00	0.83–1.21	0.992
Age ≥ 60 years	NA	2.75	2.55–2.97	<0.001
Mechanical ventilation	$I^2=39.9\%$, $P=0.197$	9.48	8.24–10.91	<0.001
Bacterial pneumonia	$I^2=98.9\%$, $P<0.001$	3.85	0.87–17.01	0.075
Hypertension	NA	1.41	1.09–1.83	0.010
Diabetes	$I^2=0\%$, $P=0.475$	1.49	1.36–1.64	<0.001
Hyperlipidemia	NA	1.18	0.77–1.81	0.451
Heart failure	$I^2=95.9\%$, $P<0.001$	3.15	1.05–9.41	0.040
Cancer	$I^2=63.4\%$, $P=0.098$	2.86	2.07–3.95	<0.001
PE				
Gender	$I^2=57.6\%$, $P=0.069$	1.24	0.94–1.65	0.132
Age ≥ 60 years	$I^2=0\%$, $P=0.915$	2.46	2.21–2.73	<0.001
Bacterial pneumonia	$I^2=88.1\%$, $P<0.001$	3.80	1.65–8.73	0.002
Hypertension	$I^2=84.9\%$, $P=0.010$	1.83	0.62–5.40	0.274
Diabetes	$I^2=63.7\%$, $P=0.064$	1.01	0.68–1.50	0.970
Hyperlipidemia	$I^2=31.7\%$, $P=0.226$	1.55	1.00–2.41	0.049
Heart failure	$I^2=0\%$, $P=0.807$	2.70	2.05–3.56	<0.001
Chronic obstructive pulmonary disease	$I^2=37.3\%$, $P=0.024$	4.73	3.11–7.17	<0.001
Cancer	$I^2=0\%$, $P=0.578$	2.90	2.39–3.53	<0.001

DVT, deep vein thrombosis; PE, pulmonary embolism; OR, odds ratio; CI, confidence interval; NA, not available.

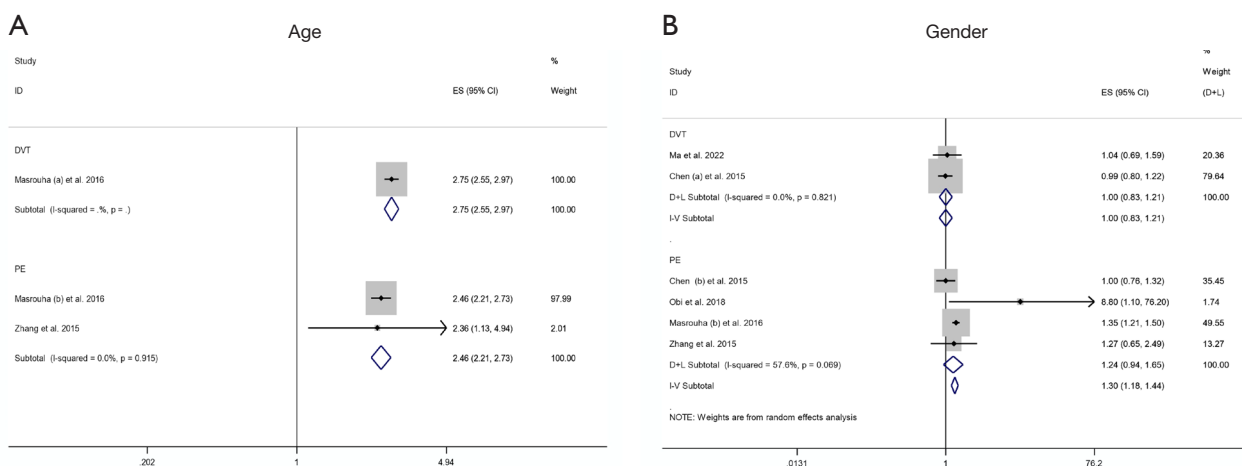


Figure 2 Meta-analysis of demographic factors associated with VTE occurrence in patients with pneumonia. (A) Age; (B) gender. VTE, venous thromboembolism.

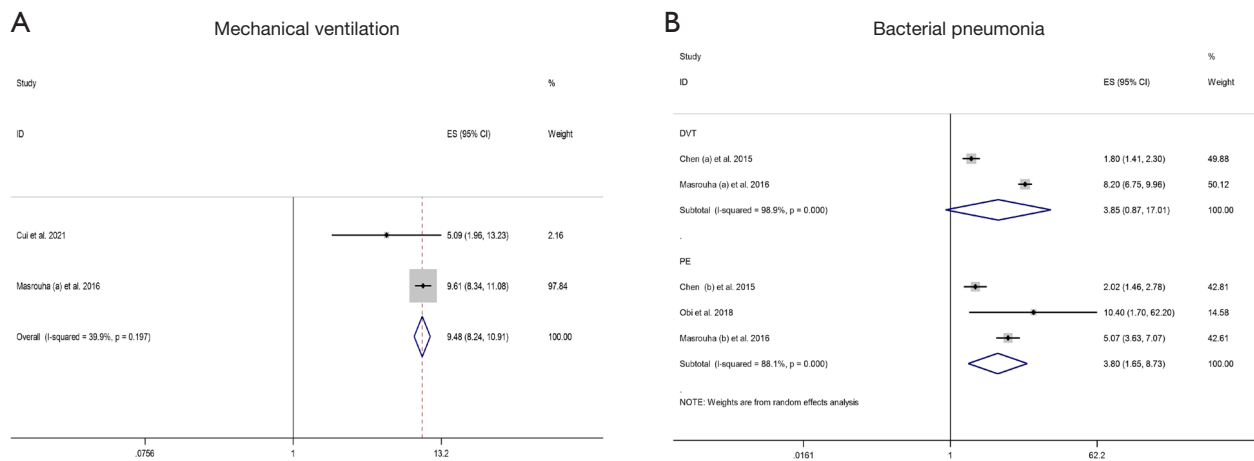


Figure 3 Meta-analysis of clinical factors associated with VTE occurrence in patients with pneumonia. (A) Mechanical ventilation; (B) bacterial pneumonia. VTE, venous thromboembolism.

Clinical risk factors

Mechanical ventilation (MV)

Two studies reported the association between MV and the risk of DVT. The pooled results showed that patients with MV had a significantly higher rate of DVT (OR = 9.48, 95% CI: 8.24–10.91, $P < 0.001$; *Figure 3A*).

Bacterial pneumonia

Two studies reported the association between bacterial pneumonia and the risk of DVT. The pooled results indicated that there was no significant association between bacterial pneumonia and the risk of DVT (OR = 3.85, 95% CI: 0.87–17.01, $P = 0.075$; *Figure 3B*). Three studies explored the association between bacterial pneumonia and the risk of PE. The analysis showed that patients with bacterial pneumonia had significantly higher risk of PE (OR = 3.80, 95% CI: 1.65–8.73, $P = 0.002$; *Figure 3B*).

Comorbidities

Hypertension

Chen *et al.* (16) reported that hypertension was significantly associated with an increased risk of DVT (OR = 1.41, 95% CI: 1.09–1.83, $P = 0.010$; *Figure 4A*). Additionally, two studies explored the association between hypertension and the risk of PE and the pooled results showed that there was no significant association between hypertension and the risk of PE (OR = 1.83, 95% CI: 0.62–5.40, $P = 0.274$; *Figure 4A*).

Diabetes

Two studies reported the association between diabetes and the risk of DVT. The pooled analysis showed that patients with diabetes had a significantly higher DVT incidence rate (OR = 1.49, 95% CI: 1.36–1.64, $P < 0.001$; *Figure 4B*) with no heterogeneity ($I^2 = 0.0%$, $P = 0.475$). Three studies explored the association between diabetes and the risk of PE, and the pooled results revealed that diabetes was not associated with an increased risk of PE (OR = 1.01, 95% CI: 0.68–1.50, $P = 0.970$; *Figure 4B*).

Hyperlipidemia

Chen *et al.* (16) reported that there was no significant association between hyperlipidemia and the risk of DVT (OR = 1.18, 95% CI: 0.77–1.81, $P = 0.451$; *Figure 4C*). Additionally, there were two studies explored the association between hypertension and the risk of PE. The pooled results showed that hyperlipidemia was significantly associated with an increased risk of PE (OR = 1.55, 95% CI: 1.00–2.41, $P = 0.049$; *Figure 4C*).

Heart failure

There were two studies reported the association between heart failure and the risk of DVT. The pooled results showed that heart failure was significantly associated with an increased risk of DVT (OR = 3.15, 95% CI: 1.05–9.41, $P = 0.040$; *Figure 4D*). Three studies explored the association between heart failure and the risk of PE, and the pooled results showed that heart failure was significantly associated

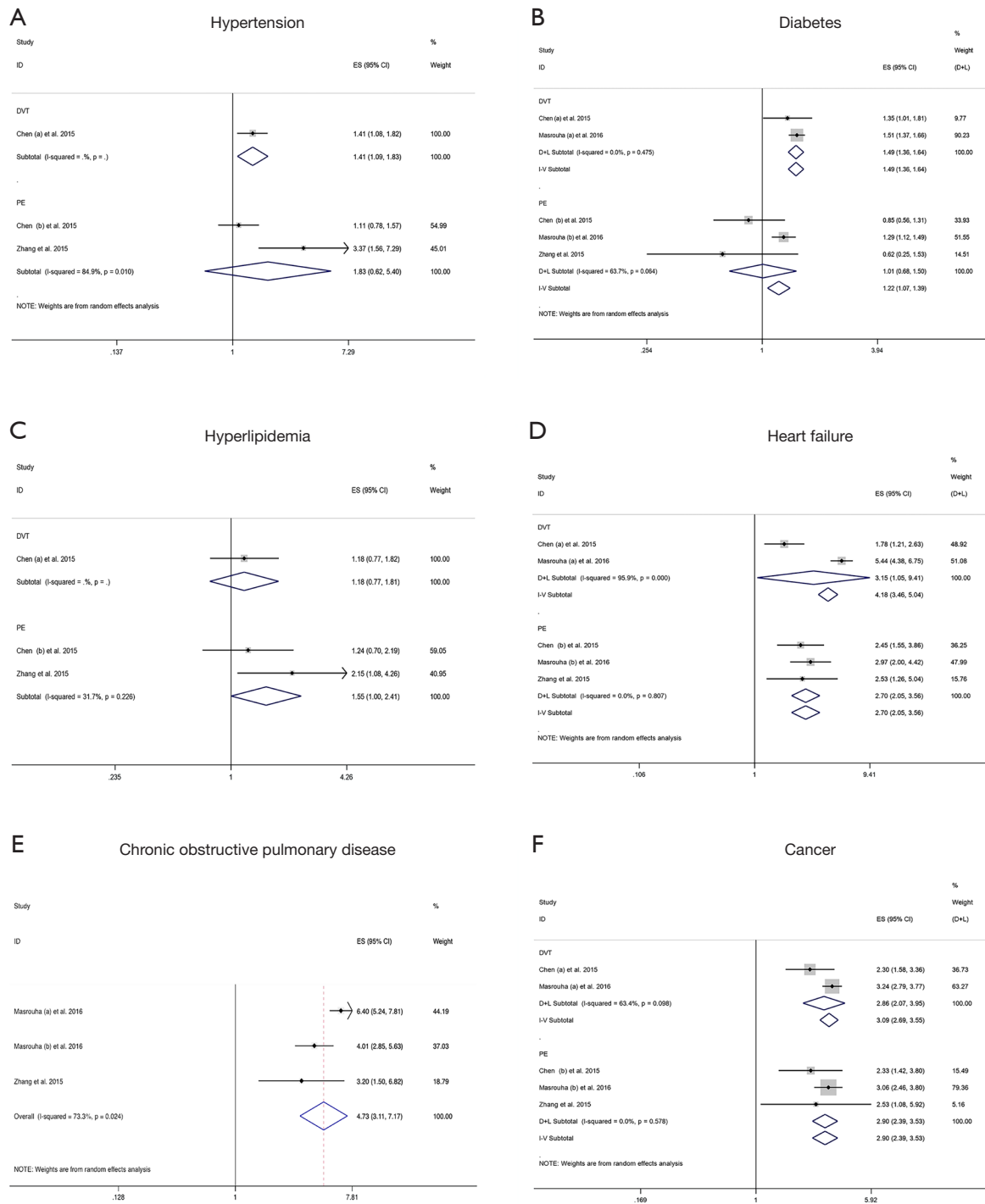


Figure 4 Meta-analysis of comorbidities associated with VTE occurrence in patients with pneumonia. (A) Hypertension; (B) diabetes; (C) hyperlipidemia; (D) heart failure; (E) chronic obstructive pulmonary disease; (F) cancer. VTE, venous thromboembolism.

with an increased risk of PE (OR =2.70, 95% CI: 2.05–3.56, $P < 0.001$; *Figure 4D*).

Chronic obstructive pulmonary disease (COPD)

Three studies examined the relationship between COPD and the risk of PE. The combined results revealed a notably elevated rate of PE in patients with COPD (OR =4.73, 95% CI: 3.11–7.17, $P < 0.001$; *Figure 4E*).

Cancer

Two studies reported the association between cancer and the risk of DVT and three studies reported the association between cancer and the risk of PE. The pooled analysis showed that cancer was both significantly associated with an increased risk of DVT (OR =2.86, 95% CI: 2.07–3.95, $P < 0.001$; *Figure 4F*) and PE (OR =2.90, 95% CI: 2.39–3.53, $P < 0.001$; *Figure 4F*).

Sensitivity analysis

Sensitivity analysis eliminated each included study one by one, and performed a summary analysis on the remaining studies to assess whether a single included study had an excessive impact on the results of the entire meta-analysis. No studies were found to have a significant impact on the findings, suggesting that the results of this study were reliable and stable (*Figures S1–S5*).

Discussion

In this systematic review and meta-analysis, we summarized several potential risk factors of VTE in patients with pneumonia. Our study is the first to focus on risk factors of VTE in patients with pneumonia in the pre-COVID era. Our findings can serve as a basis for future studies aiming at risk assessment of different types of pneumonia or newly emerging infections. A significant correlation was observed between age (≥ 60 years), heart failure, and cancer with elevated risk of both DVT and PE. However, gender did not seem to contribute. MV, hypertension and diabetes were predominantly associated with an increased prevalence of DVT, while bacterial pneumonia, hyperlipidemia and COPD were associated with an increased risk of PE.

Advanced age is an important component in the current VTE risk assessment models such as the Caprini score and the Pauda score. The susceptibility of VTE related to age is thought to stem from endothelial dysfunction and unusual platelet activity which is frequently observed in

older people (22). MV, an indicator of pneumonia severity, presented to be a moderate to strong risk (OR =9.48, $P < 0.001$) for DVT in patients with pneumonia. Extended durations of MV, especially invasive, has been identified as an independent risk factor for VTE by Knudson *et al.* (23) Procedures commonly used during invasive MV, such as sedation and immobilization, may exacerbate blood stasis and further increase the risk of DVT. However, the correlation between MV and PE in patients with pneumonia remains unclear due to data limitations in the included studies.

Our meta-analysis revealed that various comorbidities could contribute to the occurrence of VTE in patients with pneumonia, including cancer, heart failure, hypertension, diabetes mellitus, hyperlipidemia and COPD. Cancer is identified as a strong and persistent risk factor for VTE (24). However, anticoagulation management for cancer-associated VTE is complex due to potential hemorrhagic complications, drug interactions, and inconvenience of low molecular weight heparin (25). Our review indicated that cancer significantly increased the risk of both DVT and PE in patients with pneumonia, making them a high-risk group of thrombosis. Additionally, we noted a significant association between heart failure and VTE. A meta-analysis reported a relative risk of 1.51 (95% CI: 1.36–1.68) for VTE in heart failure patients admitted to hospital, despite prophylactic anticoagulation (26). With the rising aging population, it is essential to raise physicians' awareness of the association between heart failure and VTE. Preventive strategies should be endorsed to counteract this preventable and financially burdensome condition. As for patients with both pneumonia and cardiovascular diseases, our results echoed the conclusions of Ageno *et al.* (27) They revealed that hypertension, diabetes mellitus and hyperlipidemia were associated with higher risk of VTE. However, a comparative analysis from the Emerging Risk Factors Collaboration (ERFC) and UK biobank by Gregson *et al.* found inconsistent associations of VTE with diabetes and blood pressure on the general population (28). Another meta-analysis of prospective studies evaluating the relationship between traditional cardiovascular risk factors and VTE also found negative associations (29), a discrepancy that may be attributed to overlooked confounding variables such as age and BMI (29). Our results revealed that patients with pneumonia and existing cardiovascular risk factors may be predisposed to elevated VTE, facilitating better refinement of VTE risk assessment model for specific patient groups. COPD is a

prevalent respiratory comorbidity. Previous investigations have shown that hospital admissions resulting from acute exacerbations of COPD significantly increased the risk of VTE (30,31). Our study emphasized this relationship and further showed that COPD itself can exacerbate the likelihood of developing PE in pneumonia patients, possibly due to the persistent inflammation and deterioration of the pulmonary vascular bed inherent in COPD (32). Compared with COVID-19 pneumonia, several meta-analyses suggested that there was no apparent correlation between these comorbidities and VTE in COVID-19 patients. This difference may potentially be attributed to the significant inflammatory response triggered by COVID-19, which could be more influential than the impact of comorbidities (33,34).

In our meta-analysis, bacterial pneumonia itself was found to be an independent risk factor of VTE. Previous studies have documented a link between respiratory infection and VTE (5,35,36). An analysis from Registro Informatizado de la Enfermedad Tromboembolica venosa (RIETE) registry (37) found that patients with respiratory tract infections were more likely presented with PE initially than patients with other infections. Obi *et al.* (19) found that bacterial pneumonia remained to be a strong risk factor of VTE in H1N1 viral pneumonia, especially of PE. Yet, there were not enough studies comparing different pathogens.

Our study has several limitations. Firstly, the study was based on a relatively small dataset comprising only six studies. Thus, it is difficult to identify more pneumonia-specific risk factors, especially from prospective cohorts. Secondly, the primary studies did not contain relevant data, such as clinical manifestations, laboratory metrics, or thromboprophylactic management. Thirdly, our analysis did not have enough specificity as we were unable to perform subgroup analyses based on the severity of pneumonia due to insufficient data. Given these constraints, there is an urgent requirement for more multicenter, well-designed original studies with superior rigor and breadth to validate and potentially enhance our results.

Conclusions

Through systematically reviewing the eligible studies, the present meta-analysis identified relevant risk factors for VTE in patients with pneumonia in the pre-COVID-19 era, mainly advanced age, illness severity and comorbidities. These findings have the potential to assist in identifying patients at a higher risk of VTE, improving

risk stratification, and guiding the development of risk prediction models. Due to the limited data available in the included articles, further high-quality research is warranted to confirm our findings.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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