

**Venous thromboembolic events in patients with COVID-19: A systematic  
review and meta-analysis**

Ting Wu<sup>1,2,#</sup>, Zhihong Zuo<sup>1,3,#</sup>, Deyi Yang<sup>1,3</sup>, Xuan Luo<sup>4</sup>, Liping Jiang<sup>3</sup>, Zaxian Xia<sup>5,6</sup>,  
Xiaojuan Xiao<sup>1</sup>, Jing Liu<sup>1</sup>, Mao Ye<sup>7</sup>, and Meichun Deng<sup>1,3,6,\*</sup>

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<sup>1</sup> Department of Biochemistry and Molecular Biology & Hunan Province Key Laboratory of Basic and Applied Hematology, School of Life Sciences, Central South University, Changsha, Hunan 410013, China

<sup>2</sup> Department of Cardiovascular Medicine, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, China

<sup>3</sup> Xiangya School of Medicine, Central South University, Changsha, Hunan 410013, China

<sup>4</sup> Hunan Yuanpin Cell Biotechnology Co., Ltd, Changsha, Hunan 410129, China

<sup>5</sup> Department of Cell Biology, School of Life Sciences, Central South University, Changsha, Hunan 410013, China

<sup>6</sup> Hunan Key Laboratory of Animal Models for Human Diseases, Hunan Key Laboratory of Medical Genetics & Center for Medical Genetics, School of Life Sciences, Central South University, Changsha, Hunan 410013, China

<sup>7</sup> Molecular Science and Biomedicine Laboratory, State Key Laboratory for

Chemo/Biosensing and Chemometrics, College of Biology, College of Chemistry and Chemical Engineering, Collaborative Innovation Center for Molecular Engineering for Theranostics, Hunan University, Changsha, Hunan, China

#These authors contributed equally to this work.

\*Corresponding author.

Dr. Meichun Deng:

Phone: +86-731-82650230; fax: +86-731-82650230.

E-mail address: dengmch@csu.edu.cn (M. Deng)

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## Abstract

**Background** High incidence of venous thromboembolic complications in COVID-19 patients was noted recently.

**Objective** This study aimed to explore the factors associated with prevalence of venous thromboembolism (VTE) in COVID-19 patients.

**Methods** A literature search was conducted in several online databases. Fixed effects meta-analysis was performed for the factors associated with prevalence of VTE in COVID-19 patients.

**Results** A total of 39 studies were analyzed in this analysis. The incidence of pulmonary embolism and VTE in severe COVID-19 patients were 17% (95% CI, 13%–21%) and 42% (95% CI, 25%–60%), respectively. VTE were more common among individuals with COVID-19 of advance age. Male COVID-19 patients are more likely to experience VTE. Higher levels of white blood cell (WBC; WMD =  $1.34 \times 10^9/L$ ; 95% CI,  $0.84$ – $1.84 \times 10^9/L$ ), D-dimer (WMD = 4.21 ug/mL; 95% CI, 3.77 –4.66 ug/mL), activated partial thromboplastin time (APTT; WMD = 2.03 s; 95% CI, 0.83 –3.24 s), fibrinogen (WMD = 0.49 ug/mL; 95% CI, 0.18 –0.79 g/L) and C-reactive protein (CRP; WMD = 21.89 mg/L; 95% CI, 11.44 –32.34 mg/L) were commonly noted in COVID-19 patients with VTE. Patients with lower level of lymphocyte (WMD =  $-0.15 \times 10^9/L$ ; 95% CI,  $-0.23$  –  $-0.07 \times 10^9/L$ ) was at high risk of developing VTE. The incidence of severe condition (OR = 2.66; 95% CI, 1.95–3.62) was more likely to occur among COVID-19 patients who developed VTE.

**Conclusion** VTE is a common complication in severe COVID-19 patients and thromboembolic events are also associated with adverse outcomes.

**Keywords:** COVID-19, incidence, clinical features, risk factors, venous thromboembolism, older people.

### Keypoints:

- It is urgent to pay much attention to high incidence of venous thromboembolic complications of COVID-19 patients
- This study aimed to explore the factors associated with prevalence of venous thromboembolism in COVID-19 patients
- The levels of white blood cells, lymphocyte, D-dimer, APTT, fibrinogen and CRP were closely associated with prevalence of venous
- The occurrence of thromboembolic events are significant predictors of adverse outcomes

## Introduction

Up to September 23rd, 2020, 30 million COVID-19 cases and more than 970 thousand deaths were reported globally. The virus that causes COVID-19 is a new type of highly diverse enveloped positive single-stranded RNA virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The clinical manifestations of COVID-19 are varied, ranging from asymptomatic to severe, including acute respiratory distress syndrome and multi-organ failure [2, 3], of which some severe cases developed into death due to hyperinflammation and respiratory dysfunction [4]. Histopathology of COVID-19 patients indicated diffuse alveolar damage and inflammatory infiltrates in lungs and pathological changes in extra-pulmonary sites, such as gastrointestinal and cardiovascular organs [5-7]. Even though the pathogenesis of COVID-19 was not fully uncovered, direct viral damage [8], systemic hyperinflammation [9], dysregulation of immune system [10] and ACE2-related pathway [11] were believed to participate in the process [12]. In term of therapeutics, remdesivir, a promising anti-viral agent, gives the potential reduction in time to clinical improvement [13]. Patients treated with remdesivir got better clinical status than the standard group [14]. Corticosteroid also plays its role in reducing escalation of care and improving clinical outcomes [15, 16]. Besides, convalescent plasma therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases [17, 18]. Currently, several vaccines also have gone through different stages of clinical trials [19, 20]. Although both treatment and vaccination are encouraging, large clinical trials are needed for next validation.

Coagulation function in patients with COVID-19 is significantly deranged compared with healthy people [21]. Hyperinflammation caused by SARS-CoV-2 infection elevated level of many pro-inflammatory cytokines [22, 23], which triggers multiple procoagulant pathways and disrupts anticoagulant system, leading to thrombotic microangiopathy [24]. IL-6 is reported to be the most important mediator for cytokine-induced coagulation activation [25]. It is well-known that endothelial cell injury caused by SARS-CoV-2 can strongly activates the coagulation system via exposure of tissue factor (TF). Moreover, the spike protein of the virus downregulates the expression of ACE2 by mediating its engagement, resulting in activation of the renin-angiotensin system, followed by facilitating platelet adhesion and aggregation [26]. In addition, complement system activation partly functions in the disordered coagulant network, founded on the observation of terminal complement components deposit in lungs [27]. In clinical practice, approximately 20% of COVID-19 patients, and almost all patients with

severe and critical COVID-19, had severe coagulation abnormalities [28, 29]. Patients with COVID-19 and coagulopathy were characterized by increased D-dimer levels, a modest decrease in platelet count, and a prolongation of the prothrombin time, some of which are positively associated with disease severity [30, 31] and an increased risk of death [32, 33]. Recently, high rates of venous thromboembolism (VTE) in critically ill patients with COVID-19 were reported [34]. Researches showed COVID-19 patients developed venous thrombosis and embolism in lungs, lower extremities, heart, brain, and even skin, contributing to tissue necrosis, ischemic stroke, and even death [35-37]. It is urgent to pay much attention to venous thromboembolic complications in COVID-19 patients.

### **Methods**

This study was registered in PROSPERO, with registration No. CRD42020189157.

#### **Search strategy**

A literature search was conducted in the EMBASE, PubMed, Web of Science, MedRxiv, and Biorxiv databases using the following search terms: “SARS-CoV-2,” “coronavirus,” “COVID-19,” “2019-nCoV,” “thrombus,” “thrombosis,” and “embolism,” alone or in combination, without language restrictions. Included articles were published before and on September 11th, 2020.

#### **Inclusion and exclusion criteria**

The following inclusion criteria were used: (1) type of participants: patients ( $\geq 18$ -years-old) who were infected with SARS-CoV-2 and (2) type of study; and studies that provide information with respect to medical history, laboratory results, and clinical outcomes of COVID-19 patients who developed VTE, which was defined as a composite of PE (pulmonary embolism) and DVT (deep vein thrombosis). Studies that included venous thromboembolic and non-venous thromboembolic groups were analyzed to explore the factors associated with the prevalence of venous thromboembolic events. Criteria in this analysis for severe COVID-19 patients included severe and/or critical cases, which were defined by the World Health Organization (Clinical management of COVID-19: interim guidance). Adults with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: (1) respiratory rate  $> 30$  breaths/min; (2) severe respiratory distress; or (3)  $SpO_2 < 90\%$  on room air were regarded as severe COVID-19. Patients needing respiratory support or presenting with or presenting with sepsis or developing multiple organ dysfunction were classified as critical cases. The following exclusion criteria were used: (1) study design: case reports, reviews, comments, letters, and abstracts, (2) type of participants: patients  $< 18$ -years-old, pregnant women, and animals, and (3) insufficient information concerning evaluation rates.

## **Study selection**

All studies from the electronic search were uploaded into Endnote X9 and duplicates were removed. Two independent investigators reviewed remaining identified trials to confirm that they fulfilled the inclusion criteria. Finally, reference lists of included studies were screened to assess other potentially relevant studies. All disagreements were discussed and solved after rechecking the source data with a third investigator; in all cases one person recognized an error.

## **Data extraction**

Two reviewers extracted data by using a predefined data extraction form. The extracted data included: last name of the first author, geographical region, event (thrombosis and/or embolism, *N*), sample size (*N*), minimum, mean and maximum age (years), percentage of male patients (%), subtypes of thromboembolic events, and study design. We employed the Newcastle-Ottawa scale (NOS) for quality assessment of included trials. NOS scores of at least six were considered high quality studies. All disagreements were resolved through discussion.

## **Statistical analysis**

The odds ratio (OR) and weighted mean difference (WMD) were employed to compare dichotomous and continuous variables, respectively. All results are reported with 95% confidence intervals (CIs). Data presented as median (range) or median (interquartile range [IQR]) were transferred to the form of mean (standard deviation [SD]) [38]. The effect estimates of outcomes were pooled by using fixed-effects models. A random-effects model was applied when significant heterogeneity was detected. Heterogeneity was estimated by using the  $I^2$  value, and  $I^2 > 50\%$  was considered significant. The sensitivity analyses were performed by excluding one study at a time to observe the changes in outcome. The publication bias was assessed by Egger's test and Begg's test ( $P < 0.10$ ). All statistical analyses were performed with Stata 12.0 statistical software (Stata Corporation, College Station, Texas, USA).

## **Results**

### **Selection of included studies and Study Characteristics**

A total of 1562 relevant articles were identified by searching several online databases. Figure 1 presented the screening and selection process of the eligible trials. This meta-analysis included 39 studies [39-77], of which 30 articles were retrospective studies and 9 were prospective studies. Among these studies, 7 were from China, 13 from France, 3 from Netherlands, 6 from The United States, 4 from The United Kingdom, 3 from Spain, 2 from Switzerland and 1 from Russia. The characteristics of the included trials were listed in Table 1. The results of the quality assessments were presented in

Table 1.

### **Incidence and clinical features of COVID-19 patients with VTE**

The pooled meta-analysis results indicated that the overall incidences of PE and VTE in patients with severe COVID-19 were 17% (95% CI, 13%–21%) and 42% (95% CI, 25%–60%), respectively. The average age of COVID-19 patients with venous thromboembolic events was 64.5 (95% CI, 63.23–65.76) and the body mass index (BMI) was 27.22 kg/m<sup>2</sup> (95% CI, 25.70–28.75 kg/m<sup>2</sup>), which was significantly higher than the normal range. The proportion of male patients was 69% (95% CI, 61%–77%). The laboratory results revealed that neutrophil counts ( $7.62 \times 10^9/L$ ; 95% CI,  $6.57$ – $8.68 \times 10^9/L$ ), fibrinogen levels (6.01 g/L; 95% CI, 5.29–6.72 g/L), D-dimer levels (7.47 µg/mL; 95% CI, 6.34–8.60 µg/mL), and C-reactive protein (CRP) levels (136.99 mg/L; 95% CI, 103.60–170.37 mg/L) were significantly higher in COVID-19 patients with thromboembolic events than in control COVID-19 patients. In addition, decreased lymphocyte counts ( $0.77 \times 10^9/L$ ; 95% CI,  $0.70$ – $0.84 \times 10^9/L$ ) were observed. These results demonstrated that 45% (95% CI, 24%–67%) of COVID-19 patients who developed VTE developed severe or critical condition (Table 2).

### **Factors associated with prevalence of VTE**

Thromboembolic events were more prevalent among individuals with COVID-19 of advanced age (WMD = 2.31; 95% CI, 0.92–3.70). Male COVID-19 patients were more likely to experience a venous thromboembolic event (OR = 1.42; 95% CI, 1.18–1.71) (Figure 2). The pooled results show that the presence of comorbidities in COVID-19 patients, including hypertension (OR = 0.94; 95% CI, 0.75–1.18), diabetes (OR = 0.93; 95% CI, 0.74–1.19), cardiovascular diseases (OR = 1.22; 95% CI, 0.80–1.87), coronary artery disease (OR = 1.27; 95% CI, 0.72–2.25), respiratory diseases (OR = 0.72; 95% CI, 0.46–1.14), and malignant diseases (OR = 0.87; 95% CI, 0.60–1.27), was not associated with the prevalence of venous thromboembolic events (Appendix 2). Few differences in BMI (WMD =  $-0.22 \text{ kg/m}^2$ ; 95% CI,  $-0.72$  to  $0.28 \text{ kg/m}^2$ ) were noted between COVID-19 patients with and without VTE (Appendix 3). COVID-19 patients who developed thromboembolic events had higher white blood cell counts (WBC; WMD =  $1.34 \times 10^9/L$ ; 95% CI,  $0.84$ – $1.84 \times 10^9/L$ ) and lower lymphocyte counts (WMD =  $-0.15 \times 10^9/L$ ; 95% CI,  $-0.23$  to  $-0.07 \times 10^9/L$ ) than COVID-19 patients without thromboembolic events (Figure 2). COVID-19 patients with elevated D-dimer levels (WMD = 4.21 µg/mL; 95% CI, 3.77–4.66 µg/mL), higher fibrinogen (WMD = 0.49 g/L; 95% CI, 0.18–0.79 g/L), longer activated partial thromboplastin time (APTT; WMD = 2.03 s; 95% CI, 0.83–3.24 s), or higher CRP levels (WMD = 21.89 mg/L; 95% CI, 11.44–32.34 mg/L) had a higher risk of developing thromboembolic events (Figure 3). However, hemoglobin levels (WMD =  $-1.30 \text{ g/L}$ ; 95% CI,  $-4.63$  to  $2.03 \text{ g/L}$ ), platelet counts (WMD =  $3.26 \times 10^9/L$ ; 95% CI,  $-10.09$



to  $16.62 \times 10^9/L$ ), neutrophil counts (WMD =  $1.03 \times 10^9/L$ ; 95% CI, -0.06 to  $2.12 \times 10^9/L$ ) were not significant predictors of thromboembolic events in COVID-19 patients (Appendix 3). In addition, COVID-19 patients who developed thromboembolic events were more likely (OR = 2.66; 95% CI, 1.95–3.62) to develop severe condition or need critical care (Figure 3).

#### **Publications bias and Sensitivity analysis**

Our result suggested no possible publication bias in the pooled result of the outcomes (Appendix 1). Our sensitivity analysis revealed no significant differences in the outcomes except for the pooled results of fibrinogen and neutrophil (Appendix 4).

#### **Discussion**

A total of 39 studies were analyzed and the following conclusions were drawn. Venous thromboembolic event was a common complication in severe COVID-19 patients. Advanced age, gender and levels of WBC and lymphocyte might be closely associated with prevalence of venous thromboembolic events. Inflammatory factors, such as CRP, may be involved in the occurrence of venous thromboembolic events. D-dimer, APTT and fibrinogen can be served as significant predictors of venous thromboembolic events in patients with COVID-19 infections. In addition, venous thromboembolic events were associated with adverse outcomes.

Individuals at any age can be infected with SARS-CoV-2, however, older individuals are the most vulnerable to experiencing an aggressive form of COVID-19. It was reported that viral load was associated with advanced age [78]. Furthermore, there was a strong age gradient in the risk of death among patients with COVID-19. According to the analysis including 72,314 cases, an overall case fatality rate (CFR) was 2.3%, while CFR was 8% in patients aged 70 to 79 years and 14.5% in patients aging 80 and older [79]. Unsurprisingly, there was a similar pattern, regardless of the geographic region. In another analysis in Korea, the overall CFR was much higher in older people compared with 11,344 confirmed cases [80]. In France, an average death rate was 0.0001% in young patients and 8.3% in patients older than age 80 [81]. In Asia, Europe and North America, 10% mortality rate was observed in those 65 years of age or older, which was much higher than patients who were younger [82]. In this scenario, the dynamical remodeling of immune response with aging could be essential explanation. As age advances, reduced production of native T and B cells and dysfunction of innate immune cells were observed. This series of changes associated with age affecting the immune system was denominated as immunosenescence [83]. Innate immunity serves as the first line to against pathogen invasion and successful mounting of type I interferons (IFN) secreted by infected cells should be able to induce an antimicrobial state to limit viral

replication at an early stage [84]. However, a delayed IFN response was a characteristic of the immunosenescence. Therefore, the virus could escape from the immune response in the early phase of infection and patients were at a high risk of severe infection [85]. In addition, insufficient activation of cells or responses involved in the innate immunity leads to a low adaptive immune response, which was already impaired resulting from immunosenescence. All of this could delay viral clearance and result in a dysregulated immune response in which cytokines were released extensively, leading to a cytokine storm and severe condition in older patients [86]. Inflammaging defined as a low-grade persistent increase in inflammatory mediators [87], is another well-recognized feature of aging immunity involved in the age-based exponential increase in fatality rate. As age advances, chronic low-grade inflammation exists as a protective mechanism. However, dysfunctional regulation by anti-inflammatory molecules in some older adults results in excessive inflammatory response [88]. What's more, chronic comorbidities are more prevalent among older adults and these chronic diseases are already in a proinflammatory state [89]. Hence, immunosenescence and inflammaging were estimated to lead to severe outcomes in older COVID-19 patients, which was consistent with the results that elevated levels of cytokines and inflammatory indices, such as CRP, interleukin (IL)-6, and tumor necrosis factor, were observed in severely ill COVID-19 patients [90-92].

Recently, cytokines and inflammatory have been recognized as various risk factors triggering VTE formation. Previous studies have shown that higher baseline CRP levels are associated with a higher risk of arterial thrombosis [93]. The positive association between the neutrophil-to-lymphocyte ratio and the VTE risk has also been confirmed [94]. Interestingly, it has been reported that this association was only present in patients experiencing VTE within the first year after baseline and was not significant after a long follow-up time [94, 95], highlighting the possibility that acute inflammation was associated with the risk of thromboembolism. In the present meta-analysis, higher CRP levels, which are expected in acute infections, were commonly observed in COVID-19 patients who developed thromboembolic events, which was consistent with previous conclusions. In terms of the main mechanism of inflammation-induced coagulation, TF-mediated thrombin generation plays a central role during the initiation of the coagulation process. Under normal conditions, cells expressing TF are found in tissues and are not in direct contact with blood. It is reasonable to hypothesize that vessel wall damage and higher TF expression on various cells would be observed in COVID-19 patients because of viral infection of endothelial cells, which is mediated by ACE2 receptor and the inflammatory response [96, 97], leading to initial activation of

coagulation and resulting in thromboembolism. During the process, inflammation of vessel wall is the key event in the initiation of thrombus formation. Pro-inflammatory cytokines promote a procoagulant state by inducing the expression of tissue factor to play a role in VTE formation. In addition, immune system components participate in the underlying inflammatory process of VTE [98, 99]. In our analysis, older COVID-19 patients were more likely to occur venous thromboembolic events, which could be supported by the concept of immunosenescence and inflammaging.

The pooled results indicated elevated D-dimer levels were positively related to the prevalence of thromboembolic events in patients with COVID-19. Elevated D-dimer levels can indicate the probability of VTE formation, including DVT and PE, which might be used to evaluate cardiovascular and hematological diseases [100-102]. A gradual increase in D-dimer levels during disease course was particularly associated with disease worsening, and elevated D-dimer levels are commonly found in patients with severe and critical COVID-19 [32, 103]. In the present meta-analysis, D-dimer was much higher in patients with thromboembolic events, suggesting elevated D-dimer levels are a predictor and can be used in the prognosis of COVID-19 patients. Moreover, the results showed a positive association between venous thromboembolic events and the APTT. The APTT is an index for evaluating the function of the endogenous coagulation pathway, which participates in both thrombosis and hemorrhage. It was found that APTT was significantly high on extracorporeal membrane oxygenation predicted VTE [104]. Patients with proximal venous thrombosis whose APTT was longer than 1.5 times that of controls tended to suffer a high risk (25%) of recurrent VTE [105]. Hence, prolonged APTT might be a good marker for thromboembolic events in COVID-19. The APTT has also been used to measure the anticoagulant effects of heparin and to adjust the dose to maintain levels in the target therapeutic range [106]. Fibrinogen is a plasma glycoprotein comprised of 2A $\alpha$ , 2B $\beta$ , and 2 $\gamma$  polypeptide chains and circulates at 2-5 mg/mL. When coagulation is activated, fibrinogen is converted into fibrin and formed an insoluble network by thrombin-mediated cleavage [107]. It has been demonstrated elevated fibrinogen level could independently promote thrombosis by multiple mechanisms, such as promoting faster formation and higher density of fibrin network, increasing thrombus fibrin content, enhancing clot strength and stability, and increasing resistance of thrombus to lysis [108]. Several studies have indicated that elevated plasma fibrinogen levels were associated with increased risk of VTE [109-111]. Dose effect of plasma fibrinogen on venous thrombosis has also been detected. Person with 4.0-4.9 mg/mL fibrinogen (compared with person with < 3mg/mL) had a 1.6-fold higher thrombotic risk, while person with elevated fibrinogen level ( $\geq$  5mg/mL) had an adjusted OR for venous

thrombosis of 4 [111]. In addition, Rosendaal et al analyzed the relationship between increased level of fibrinogen and the risk of venous thrombosis, stratified by sex. The result showed elevated fibrinogen level was closely associated with the risk of venous thrombosis mainly in older individuals [112]. Together, these findings were consistent with our pooled result and strongly suggest that fibrinogen contributed to the pathophysiology of VTE and may be applied to identify patients at higher risk for venous thrombosis.

Considering the hypercoagulable state and the frequency of thromboembolic events, it seems reasonable to initiate treatment with anticoagulants. It has been reported that dipyridamole treatment significantly decreases D-dimer levels compared with control patients, and it was associated with significant clinical cure [113]. Low molecular weight heparin (LMWH) also improved the coagulation function of COVID-19 patients by modulating the levels of D-dimer and fibrinogen degradation products. In addition, LMWH significantly increased lymphocyte and reduced IL-6 levels [114]. Importantly, it has been shown that LMWH appears to decrease mortality in severe COVID-19 patients with coagulopathy [115]. It is recommended that all hospitalized COVID-19 patients be treated with pharmacologic VTE prophylaxis [116]. However, Llitjos et al. found controversial results, pointing out that prophylactic and therapeutic anticoagulation could not reduce the incidence of thromboembolic events [117], highlighting the hypercoagulative status of COVID-19 patients. Strong clinical evidence of the effects of anticoagulants on the incidence of thromboembolism among COVID-19 patients remains limited, and future studies are needed to validate the preliminary conclusions. Moreover, clinicians should carefully assess the coagulation profile of COVID-19 patients. It is clear that patients with comorbidities are vulnerable to developing severe COVID-19, which will affect the effectiveness and safety of anticoagulants [33]. Chronic liver diseases may significantly reduce the ability of hepatic clearance, increasing the risk of hemorrhage. Therefore, it is reasonable to carefully determine the timing and dosage of anticoagulants for COVID-19 patients with thromboembolism to minimize the risk–benefit ratio.

There have been several studies to analyze the relationship between COVID-19 and venous thromboembolic events. Current meta-analysis mostly focused on the incidence of venous or arterial thromboembolic events [118-121]. Incidence of VTE and PE in severe COVID-19 patients varied in different studies because of different included trials. However, all these studies supported that thromboembolism is a common complication in severe COVID-19 patients, which was consistent with our result. A study also revealed that mortality rate of COVID-19 patients with PE was 45.1%, suggesting the importance

of preventing the occurrence of venous thromboembolic events [122]. Chi *et al.* also demonstrated that a higher level of D-dimer was observed in COVID-19 patients with VTE [123]. In our pooled results, age and gender were associated with the incidence of VTE, which were different with previous studies [121, 124]. Compared with previous studies, we specified the characteristics of patients with VTE and focused on factors linked to the risk of VTE. Furthermore, our analysis included more trials and pooled results showed little publication bias and low heterogeneity ( $I^2 < 50\%$ ).

### **Limitations**

Our meta-analysis had several limitations. First, most of the included studies were retrospective studies with a low level of evidence. However, the quality of the majority of studies included in the meta-analysis was moderate or high. Second, due to the limited number of studies, we didn't compare mortality rate of patients with and without VTE and evaluate the effectiveness of anticoagulants for patients developing VTE.

### **Conclusion**

In the present study we successfully and systematically evaluated the incidence and risk factors of VTE in patients with COVID-19. Thromboembolism is a common complication in severe COVID-19 patients. The inflammatory response may be involved in the occurrence of venous thromboembolic events. Elevated D-dimer and fibrinogen levels, and longer APTT can serve as significant predictors of venous thromboembolic events in patients with COVID-19. Thromboembolic events are also associated with adverse outcomes. Clinicians must pay much attention to thromboembolic events and assess coagulation profiles according to the levels of coagulation factors and individual conditions of COVID-19 patients. Early prevention and intervention of thromboembolism will significantly improve the prognosis of COVID-19 patients.

Table 1 Study characteristics of included studies

First Author	Country	Events/Total (N)	Male (%)	Age (years) Min. Mean. Max	Subtypes (N)	Research Type	Quality
<i>Grillet et al</i> <sup>39</sup>	France	23/100	70	66	PE (23)	Retrospective study	Moderate
<i>Leonard-lorant et al</i> <sup>41</sup>	France	32/106	66	63.5	PE (23)	Prospective study	High
<i>Llitjos et al</i> <sup>44</sup>	France	18/26	77	68	VTE (18) PE (6)	Retrospective study	High
<i>Klok FA et al</i> <sup>47</sup>	Netherlands	57/184	76	64	VTE (57) PE (25)	Prospective study	Moderate
<i>Cui et al</i> <sup>50</sup>	China	20/81	46	59.9	VTE (20)	Retrospective study	Moderate
<i>Zhang et al</i> <sup>51</sup>	China	66/143	51.7	63	DVT (66)	Retrospective study	High
<i>Middeldorp et al</i> <sup>54</sup>	Netherlands	39/198	66	61	VTE (39)	Retrospective study	Moderate
<i>Li et al</i> <sup>45</sup>	China	11/24	63.6	36, 63, 76	PE (11)	Retrospective study	High
<i>Ren et al</i> <sup>59</sup>	China	41/48	54.2	70	DVT (41)	Prospective study	Moderate
<i>Stoneham et al</i> <sup>61</sup>	UK	21/274			VTE (21)	Retrospective study	High
<i>Helms et al</i> <sup>64</sup>	France	64/150	81.3	63	PE (25) DVT (3)	Prospective study	High
<i>Beun et al</i> <sup>70</sup>	Netherlands	25/75	50	53, 60.5, 68	PE (20) DVT (3)	Retrospective study	Moderate
<i>Manjunath et al</i> <sup>76</sup>	USA	7/23	65.2	46, 67.8, 81	PE (7)	Retrospective study	Moderate
<i>Demelo-Rodríguez et al</i> <sup>63</sup>	Spain	23/156	65.4	68.1	DVT (23)	Prospective study	High
<i>Gervaise et al</i> <sup>40</sup>	France	13/72	75	22, 62.3, 92	PE (13)	Retrospective study	Moderate
<i>Bompard et al</i> <sup>42</sup>	France	32/135	70	64	PE (32)	Retrospective study	Moderate
<i>Artifoni et al</i> <sup>43</sup>	France	16/71	60.6	64	DVT (15) PE (7)	Retrospective study	Moderate
<i>Chen et al</i> <sup>46</sup>	China	10/25	60	65	PE (10)	Retrospective study	High
<i>Koleilat et al</i> <sup>48</sup>	USA	18/135	53.3	63.3	DVT (18)	Retrospective study	High
<i>Chen S et al</i> <sup>49</sup>	China	40/88	61	63	DVT (40)	Retrospective study	High
<i>Soumagne et al</i> <sup>52</sup>	France	55/375	76.8	63.5	DVT (11) PE (55)	Retrospective study	Moderate
<i>Poissy et al</i> <sup>53</sup>	France	22/107			PE (22)	Retrospective study	Moderate

					DVT (5)		
<i>Poyiadji et al</i> <sup>55</sup>	USA	72/328	45.7	61.3	PE (72)	Retrospective study	Moderate
<i>Alonso-Fernández et al</i> <sup>56</sup>	Spain	15/30	63.3	64.5	PE (15)	Prospective study	High
<i>Whyte et al</i> <sup>57</sup>	UK	80/214	60.3	61.1	PE (80)	Retrospective study	Moderate
<i>Xu et al</i> <sup>58</sup>	USA	101/101	73	62	PE (101)	Retrospective study	Moderate
<i>Contou et al</i> <sup>60</sup>	Spain	16/26	84.6	63	PE (16)	Retrospective study	Moderate
<i>Le Jeune et al</i> <sup>62</sup>	France	8/24	54.8	64.6	DVT (8)	Retrospective study	High
<i>Yu et al</i> <sup>65</sup>	China	50/142	57.1	61.9	DVT (50)	Retrospective study	Moderate
<i>Nahum et al</i> <sup>66</sup>	France	27/34	78	62.2	DVT (27)	Prospective study	Moderate
<i>Desborough</i> <sup>67</sup>	UK	10/66	73	22, 59, 83	DVT (6) PE (5)	Retrospective study	High
<i>Maatman et al</i> <sup>68</sup>	USA	31/109	57	18, 61, 95	DVT (30) PE (5)	Retrospective study	High
<i>Grandmaison et al</i> <sup>69</sup>	Switzerland	17/29	62.1	37, 64.3, 79	DVT (15) PE (2)	Retrospective study	Moderate
<i>Fang et al</i> <sup>71</sup>	UK	41/93	64.5	59.2	PE (41)	Retrospective study	High
<i>Kerbikov et al</i> <sup>72</sup>	Russia	15/75	48	27, 63.4, 92	DVT (15)	Retrospective study	Moderate
<i>Hékimian et al</i> <sup>73</sup>	France	8/51	50	56.8	PE (8)	Retrospective study	Moderate
<i>Longchamp et al</i> <sup>77</sup>	Switzerland	8/25	64	49, 68, 82	DVT (6) PE (2)	Prospective study	High
<i>Al-Samkari et al</i> <sup>74</sup>	USA	19/400	57	23, 61.8, 99	DVT (7) PE (10)	Retrospective study	High
<i>Voicu et al</i> <sup>75</sup>	France	26/56	75		DVT (26)	Prospective study	Moderate

Abbreviation: DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism; UK: The United Kingdom; USA: The United States of America;

Table 2 Incidence and Clinical features of COVID-19 patients who developed venous thromboembolic event

	Overall (95%CI)		Overall (95%CI)
PE, %	17(13-21)	Hemoglobin, g/L	120.14(112.11-128.16)
VTE, %	42(25-60)	Platelet, 10 <sup>9</sup> /L	241.16(218.05-264.27)
Age, years	64.50(63.23-65.76)	D-dimer, ug/mL	7.47(6.34-8.60)
BMI, kg/m <sup>2</sup>	27.22(25.70-28.75)	Fibrinogen, g/L	6.01(5.29-6.72)
Male, %	69(61-77)	APTT, s	38.06(36.33-39.79)
WBC, 10 <sup>9</sup> /L	9.05(8.42-9.68)	CRP, mg/L	136.99 (103.60-170.37)
Neutrophils, 10 <sup>9</sup> /L	7.62(6.57-8.68)	Severe condition, %	45 (24-67)
Lymphocyte, 10 <sup>9</sup> /L	0.77(0.70-0.84)		

Abbreviation: APTT: Activated partial thromboplastin time; BMI: Body mass index; CRP: C-response protein; PE: Pulmonary embolism; VTE: Venous thromboembolism; WBC: White blood cell;



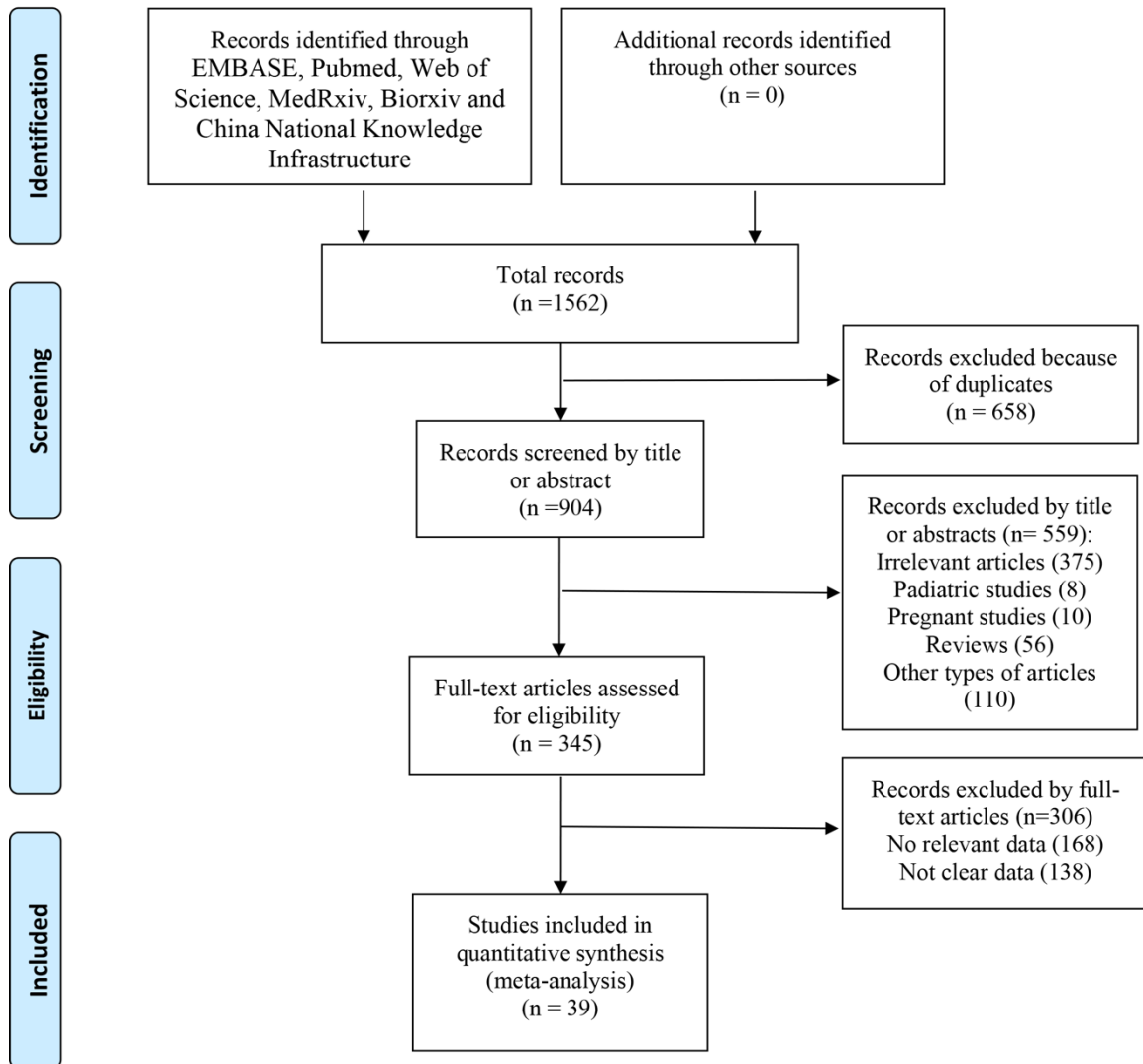
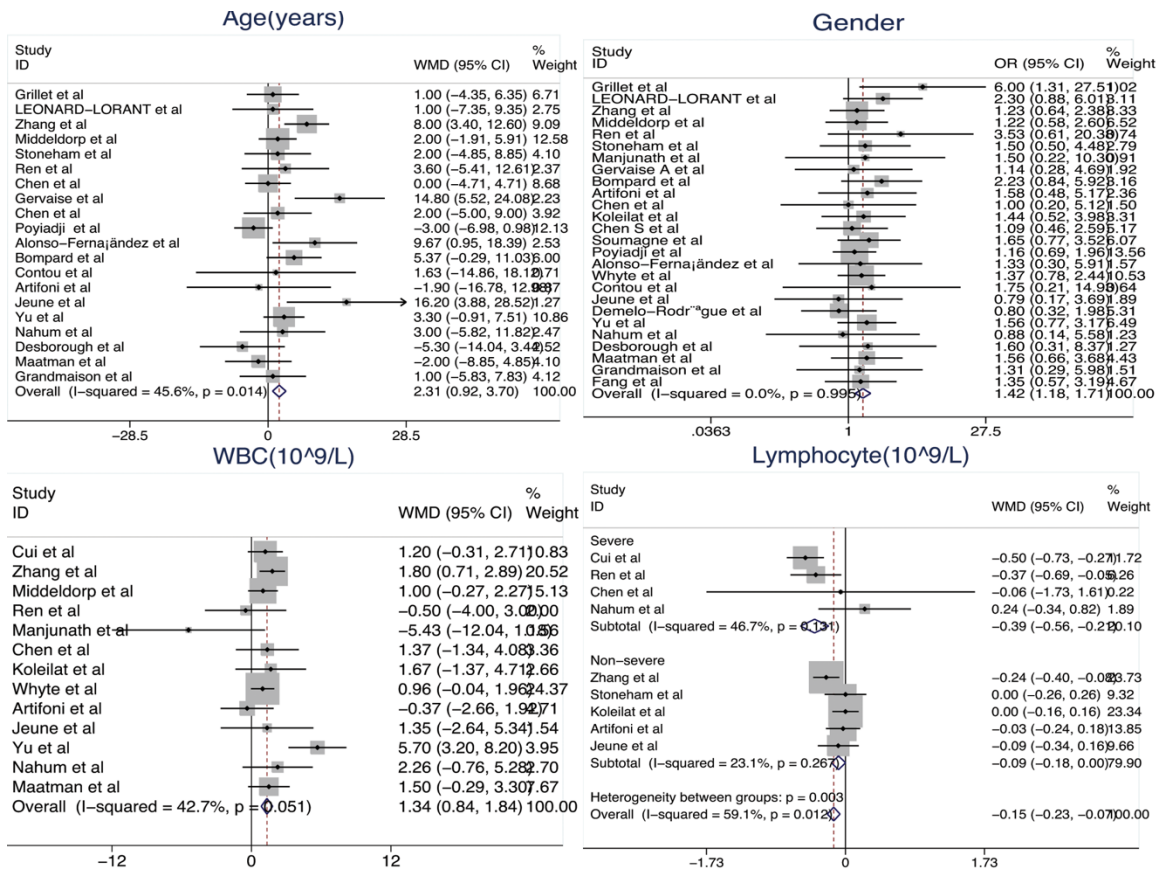
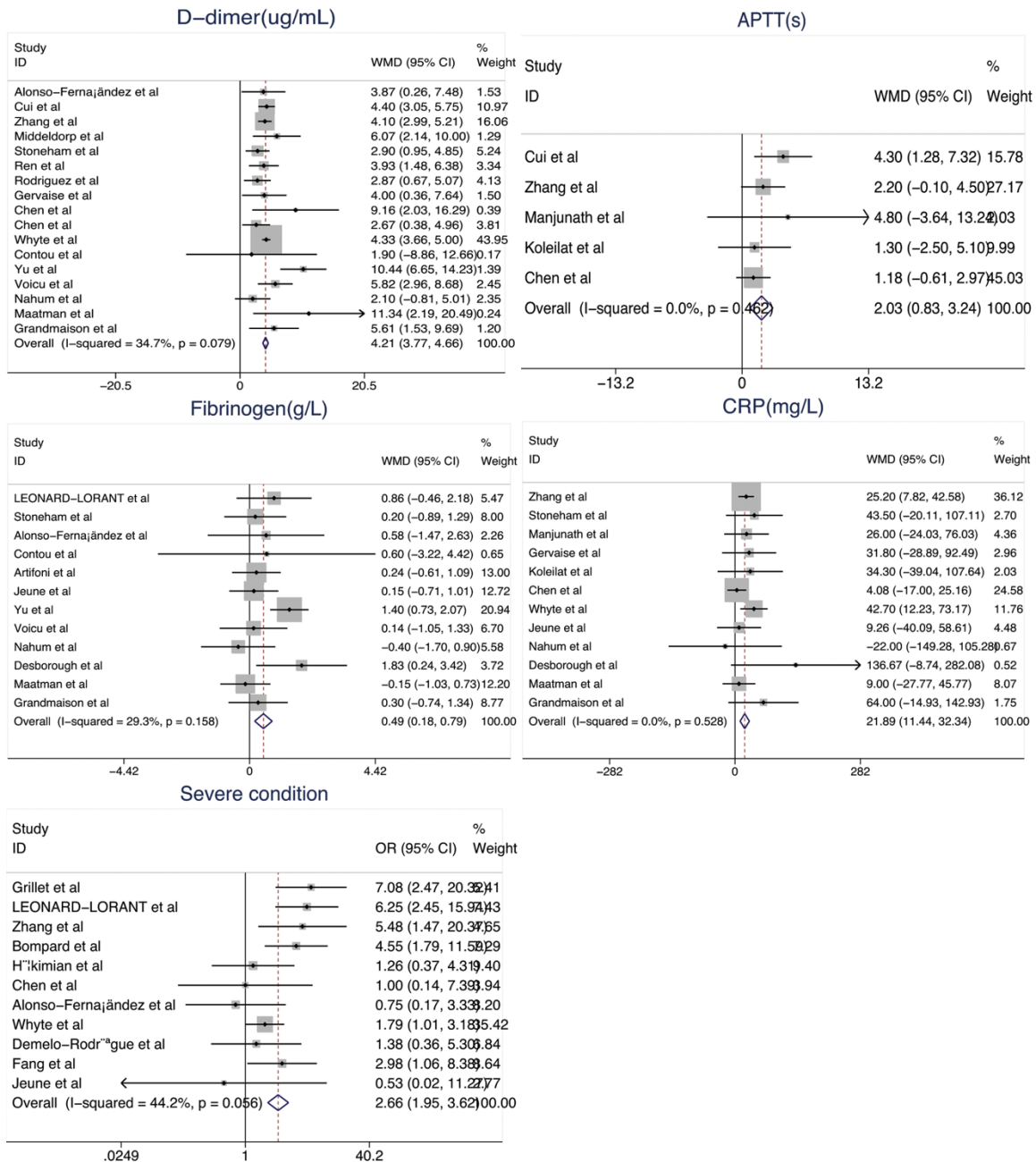


Figure 1 PRISMA Diagram of Study Selection



**Figure 2** Meta-analysis of factors (Age, Gender, WBC, Lymphocyte) associated with prevalence of venous thromboembolic event. We did subgroup analysis according to disease severity of patients in included trials to figure out the source of heterogeneity.



**Figure 3** Meta-analysis of factors (D-dimer, APTT, fibrinogen, CRP, severe condition) associated with prevalence of venous thromboembolic event.

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Please note that a full list of 124 references can be found in Appendix 5.

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