

# Clinical Features of COVID-19 Patients With Venous Thromboembolism

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## Abstract

This study aimed to assess the clinical features of coronavirus disease 2019 (COVID-19) patients with VTE, to help develop preventive measures for venous thromboembolism (VTE in COVID-19) cases. COVID-19 patients admitted to Henan Provincial People's Hospital were retrospectively analyzed, including 23, 4 and 8 cases with mild to moderate, severe and critical symptoms, respectively. VTE incidence, age at onset, relevant laboratory parameters and prognosis were analyzed. Overall, VTE incidence in the 35 patients was 20.0%, occurring in severe ( $n = 1$ ) and critical ( $n = 6$ ) cases. D-dimer showed statistical significance in laboratory examination, representing except a diagnostic index and especial can be a prognostic factor in VTE among COVID-19 patients. Severe and critical COVID-19 cases had significantly reduced platelet counts, with a risk of hemorrhage. During treatment, the risk of both hemorrhage and thrombosis should be considered. VTE occurs in COVID-19 cases, affecting individuals with severe and critical symptoms. Significant D-dimer increase is of great significance in the risk assessment of death in critical cases of COVID-19. Appropriate measures should be taken to prevent VTE during treatment.

## Keywords

venous thromboembolism, COVID-19, pneumonia, incidence

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## Introduction

The 2019 novel coronavirus (2019-nCoV), also termed severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) (its current designation) and originally detected in Wuhan City (Hubei Province, China), is spreading to the world at an alarming rate.<sup>1,2</sup> Indeed, COVID-19 disease is now considered a high-risk pandemic.<sup>3-5</sup> The range of COVID-19 encompasses asymptomatic or paucisymptomatic forms, clinical conditions featuring respiratory failure and requiring mechanical ventilation, and multi-organ and systemic signs such as sepsis, septic shock, and multiple organ dysfunction syndrome (MODS).<sup>6,7</sup> These clinical manifestations have been grouped by the Chinese Center for Disease Control and Prevention into mild to moderate, severe and critical disease types.<sup>8</sup>

Multiple observational studies have revealed that venous thromboembolism (VTE) is very common in COVID-19 patients, even on standard or higher intensity pharmacologic VTE prophylaxis.<sup>9,10</sup> In addition, elevated D-dimer amounts could predict VTE occurrence in case of no suitable diagnostic testing.<sup>9,11</sup> However, further investigation is needed to comprehensively assess COVID-19 patients with VTE. Therefore, this

study aimed to assess the clinical features, laboratory test results and treatment experiences of COVID-19 patients with VTE, to help further develop preventive and rescue measures for VTE in COVID-19 cases. Our findings provide a reference for improving the treatment of COVID-19.

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## Patients and Methods

### Patients

Patients with COVID-19 admitted to Henan Provincial People's Hospital from January 24, 2020 to February 19 2020 were retrospectively evaluated. Inclusion criteria were: 1) COVID-19 diagnosis based on viral nucleic acid detection by RT-PCR and computed tomography findings;<sup>12</sup> 2) age between 20 and 90 years. Disease classification was based on the rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia.<sup>13</sup>

The patients were classified as follows: 1) mild to moderate (clinically mild symptoms with imaging examinations showing no signs of pneumonia or fever and respiratory symptoms and imaging examinations showing signs of pneumonia); 2) severe (cases with 1 or more of items including a) shortness of breath and respiratory rate [RR]  $\geq 30$  times/min, b) finger oxygen saturation  $\leq 93\%$  in the resting state, and c) arterial partial pressure of oxygen [PaO<sub>2</sub>]/concentration of oxygen inhalation [FiO<sub>2</sub>]  $\leq 300$  mmHg [altitude > 1000 m], or pulmonary imaging showing lesion progression beyond 50% within 24-48 h); and 3) critical (patients meeting 1 or more of items comprising a) respiratory failure requiring mechanical ventilation, b) shock, and c) failure of other organs and intensive care unit (ICU) support requirement).

The study was approved by the ethics committee of Henan Provincial People's Hospital. The requirement for informed consent was waived due to its retrospective nature.

### Preventive anticoagulation for risk assessment and diagnosis of VTE.

All patients with COVID-19 were assessed for VTE by calculating individual Caprini scores.<sup>14</sup> Patients at high risk of VTE ( $\geq 4$  points) were administered mechanical prophylaxis and low molecular weight heparin for preventive anticoagulation treatment. Bedside lower extremity venous Doppler ultrasound was performed routinely for each patient which aim to diagnosed and evaluated daily.<sup>15</sup>

### Data Collection

Clinicopathological data, including age, gender, continuous renal replacement therapy (CRRT) application, extracorporeal membrane oxygenation (ECMO), in bed sedation, ventilator use, anticoagulant measures (prevention/treatment), and a history of hypertension, coronary disease, cerebral infarction, emphysema, or chronic obstructive pulmonary disease (COPD), were recorded.

Laboratory data including C-reactive protein(CRP), platelet indexes, D-dimer and Fibrinogen value were collected. CRP and platelet count was measured on a XN2000 Automatic Blood Analyzer with 5 classifications (Sysmex, Japan). While D-dimer and Fibrinogen were measured on a STAGO Automatic Hemagglutination Analyzer (France). Normal index values were: 1) CRP levels, 0-10mg/L; 2) platelet count,  $125-350 \times 10^9/L$ ; 3) D-dimer levels, 0-0.5 $\mu$ g/ml; 4) Fibrinogen levels, 2-4 g/L.

**Table 1.** Clinicopathological Data of Patients With Novel Coronavirus Pneumonia (COVID-19).

Patients With COVID-19	Common Case (n = 23)	Severe Case (n = 4)	Critically Severe Case (n = 8)
Number of cases with VTE	0	1 (25.0%)	6 (75.0%)
Caprini scores( $\geq 4$ points)	10	4	8
Caprini mean scores	3	4.75	5
Age (years old)	20-58	42-58	32-90
Male	16 (69.6%)	3 (75.0%)	5 (62.5%)
Female	7 (30.4%)	1 (25.0%)	3 (37.5%)
Application of CRRT	0	1 (25.0%)	7 (87.5%)
Application of ECMO	0	0	2 (25.0%)
Sedation in bed	0	2 (50.0%)	8 (100.0%)
Application of ventilator	0	1 (25.0%)	8 (100.0%)
Hypertension	8 (34.8%)	1 (25.0%)	5 (62.5%)
Coronary disease	2 (8.7%)	0	2 (25.0%)
cerebral infarction	1 (4.3%)	0	2 (25.0%)
Emphysema, chronic obstructive pulmonary disease	2 (8.7%)	0	3 (37.5%)
Anticoagulant measures (prevention / treatment)	15 (65.2%)	2 (50.0%)	8 (100.0%)

### Statistical Analysis

The SPSS18.0 statistical software (SPSS Inc., Chicago, USA) was used for data analysis. All analysis were descriptive statistics.

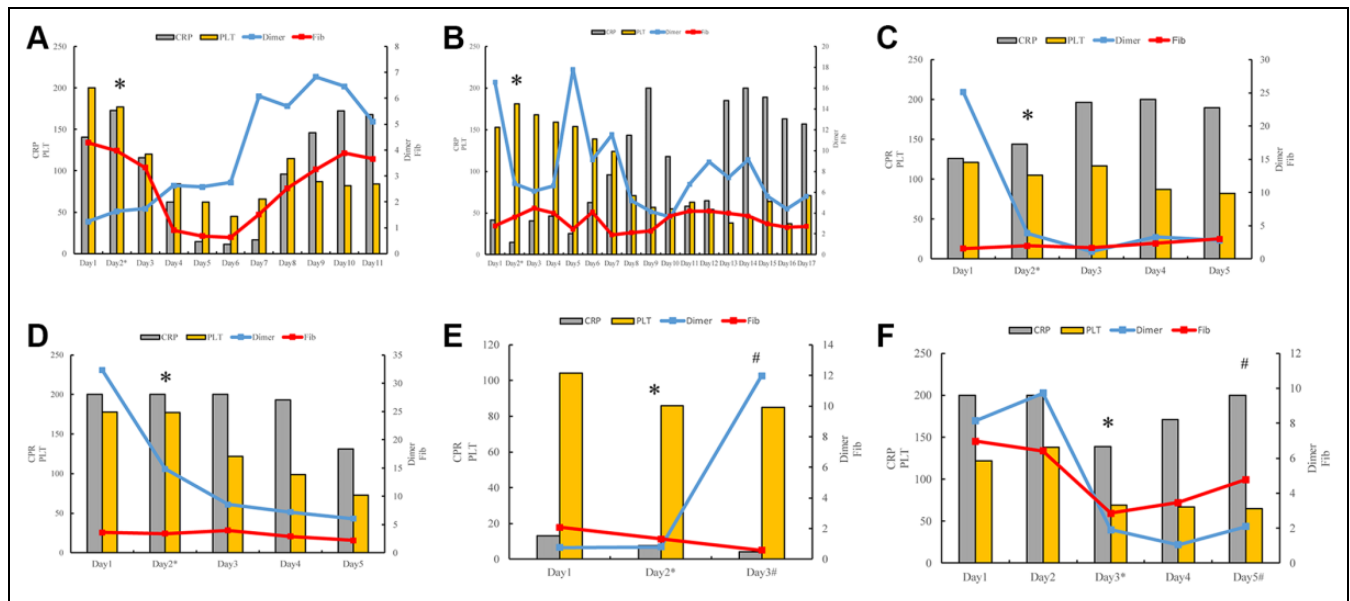
## Results

### Patient Characteristics

A total of 35 patients with COVID-19 were assessed, including 23, 4 and 8 cases with mild to moderate, severe and critical symptoms, respectively. There were 18 males and 17 females, aged 20-90 years. The detailed clinicopathological data are shown in Table 1.

### VTE Prediction and Incidence

All the 35 patients with COVID-19 included in this study were assessed for VTE risk on admission. Bedside lower extremity venous Doppler ultrasound was performed daily for each patient. Patients diagnosed with VTE or Caprini scores  $\geq 4$  (considered to be at high risk of VTE) underwent preventive anticoagulation treatment and clinical monitoring of D-dimer. One critical case of COVID-19 was not anticoagulated because of gastrointestinal bleeding, and other patients were treated with anticoagulants (low molecular weight heparin treatment). After evaluation and preventive anticoagulation treatment, VTE incidence in all 35 patients with COVID-19 was 20%. There was no VTE occurrence in mild to moderate cases, while 1 of the 4 severe cases developed VTE, indicating an incidence of 25% in this subgroup. Anticoagulant treatment was carried out in 7 of the 8 critical cases, excluding 1 who had severe coagulation dysfunction. VTE occurred in 6 critical cases, including 4 simple DVT cases and 2 DVT cases accompanied



**Figure 1.** Laboratory data analysis in 6 critical patients with COVID-19. Data of D-dimer, fibrinogen, C-reactive protein and platelet in 6 critical patients during hospitalization. A, D-dimer values of case 1 had increase at beginning time, and tendency of values gradually continued to rise in the later stage of the treatment; Fibrinogen value was slightly higher than the normal range, but fluctuated greatly during hospitalization; C-reactive protein (CRP) value was significantly higher than the normal value, also the fluctuation was obvious during the whole hospitalization period; There was a downward trend of the platelet value in cases 1 and the trend accelerated with the progress of the disease in the later period. B, D-dimer values of case 2 was higher than the normal range at beginning time, but it showed a slight declined tendency in the later stage of the treatment; The fibrinogen value was basically in the normal range although slightly higher than the normal value; C-reactive protein (CRP) value was abnormal in case 2 and the value fluctuated greatly during the whole hospitalization period; Platelet count values showed a downward trend during the whole treatment period. C, D-dimer values of case 3 was abnormal greatly at beginning time, but there was a obviously downward trend in the later stage of the treatment; The fibrinogen value was basically in the normal range; C-reactive protein (CRP) value of case 3 was significantly higher than the normal value and the overall value did not fluctuate obviously during the whole hospitalization period; Platelet count values was abnormal, but the overall trend was only slightly lower than the normal level. D, D-dimer values of case 4 still was abnormal greatly at beginning time, but the tendency of value showed a significant decrease in the later stage of the treatment; The fibrinogen value was basically in the normal range in whole treatment period; C-reactive protein (CRP) value was significantly abnormal during the whole hospitalization period; There was a downward trend of the platelet value in cases 4 in the whole period. E, D-dimer values of case 5 was increased by 15 times (0.77-11.97 mg/L) from beginning to death; Fibrinogen value was slightly higher than the normal range and the tendency decreased in the whole treatment period; C-reactive protein (CRP) value of case 5 was slightly abnormal during the whole hospitalization period; Platelet count values was slightly lower than the normal level. F, D-dimer values of case 6 was abnormal greatly at beginning time, but there was a obviously downward trend till to death suddenly; Fibrinogen value was higher than the normal range and fluctuated greatly during hospitalization; C-reactive protein (CRP) value was significantly abnormal during the whole hospitalization period; There was a downward trend of the platelet value in cases 6 during the whole hospitalization period. Note: A-F represents critical COVID-19 case 1-6 with VTE respective, \* represents diagnosis time of VTE, # represents death event.

with PE. The incidence of VTE in the critical group was 75%; 1 case in this group died of PE.

### Laboratory Data Analysis in 6 Critical Patients With COVID-19

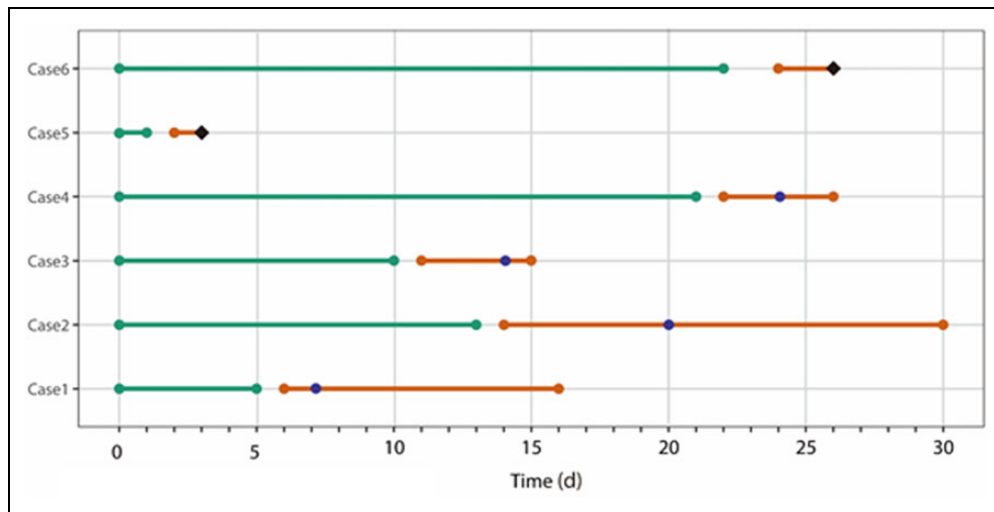
**C-reactive protein (CRP) values:** the CRP values of 6 critical patients were significantly higher than the normal value, and the fluctuation range of case 1 and 2 was significant. Although the values of case 3-6 were higher than the normal value, the overall value did not fluctuate obviously during the whole hospitalization period.

**Platelet count values:** Of the 6 patients, there was a downward trend of the platelet value in 5 cases (1,2,4,5,6). Although blood products were supplemented during the treatment, the downward trend accelerated with the progress of the disease, especially in case 1, 2, 4 and 6.

**D-dimer values:** D-dimer value of 6 critical cases had obvious increase at beginning time. After the diagnosis of VTE, with the improvement of treatment, the values of 4 patients (Case 2, 3, 4, 6) showed a downward trend. On the contrary, in case 1, D-dimer gradually increased due to the progress of the disease. Among the 2 death case, case 6 died of acute myocardial infarction due to old age and previous coronary heart disease, but the early D-dimer value tendency still decreased accompanied by the improvement of treatment. Interestingly, case 5 died of PE whose D-dimer was increased by 15 times (0.77-11.97 mg/L).

**Fibrinogen value:** The fibrinogen values of 6 patients were slightly higher than the normal range, and the value of case 1 and 6 fluctuated greatly during hospitalization, The fibrinogen value of case 2-5 were basically in the normal range.

Laboratory data analysis in 6 critical patients with COVID-19 are showed in Figure 1.



**Figure 2.** Timelines of COVID-19 and VTE in 6 cases. A total of 4 cases underwent CRRT/ECMO during the VTE timeline. Green line, time from COVID-19 infection to admission to the ICU; Orange line, time from diagnosis to the end of follow-up; blue dot, time to using CRRT/ECMO; black dot, time to death. VTE indicates venous thromboembolism; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

### Analysis of COVID-19 Cases Diagnosed With VTE

All the 7 patients diagnosed with VTE occurred in severe or critical cases. Of the 7 cases diagnosed with VTE, 2 (28.57%), 2 (28.57%) and 3 (42.86%) were 40-60, 60-80 and >80 years old, respectively. One case accompanied by coronary heart disease had received coronary artery bypass grafting (via the great saphenous vein), 3 had hypertension, 1 had cerebral infarction, and 2 had pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and emphysema. All 7 patients underwent deep venous catheterization. Among them, 5 cases were treated with CRRT to eliminate inflammatory factors, 1 was administered CRRT as emergency rescue, and 2 were administered ECMO due to severe respiratory and circulatory disorders (1 case each via the VA and VV modes). However, in 6 critical cases, VTE occurred before CRRT/ECMO through analysis of the time line of VTE, Case 5 died of PE and case 6 died of acute myocardial infarction on the second and third day of ICU admission, respectively.

COVID-19 and VTE timelines in 6 patients are displayed in Figure 2.

### Discussion

This study demonstrated that VTE occurs in patients with COVID-19, particularly in individuals with severe and critical symptoms. In addition, from the laboratory data analysis, it can be observed that the D-dimer value showed a downward trend when the treatment for COVID-19 turns for the better, but if the disease worsens, D-dimer value had significant increase contrarily. We demonstrated that D-dimer value tendency is of great significance in the risk assessment of prognosis in critical cases of COVID-19.

The high mortality of COVID-19 has attracted worldwide attention.<sup>3-5</sup> It has been reported that almost all severe and

critical cases have coagulation disorders,<sup>16</sup> which eventually activate coagulation cascade reactions and inhibit the fibrinolytic process, further promoting thrombosis. Once VTE occurs, it greatly increases the difficulty of treatment and further elevates the risk of death.<sup>17,18</sup>

A previous study reported that advanced age is a high risk factor for VTE in in-hospital patients.<sup>19</sup> As shown above, VTE occurred in 7 patients, including 5 who were over 60 years old. Among these 7 cases, 3 were over 80 years old (42.86%). As a high risk factor for VTE, advanced age should be paid special attention to in the treatment of severe and critical cases of COVID-19, for 2 main reasons. On the one hand, critical COVID-19 cases are mainly elderly patients. On the other hand, advanced age itself is an independent risk factor for VTE, and many elderly patients have underlying diseases such as diabetes, hypertension and chronic obstructive pulmonary disease, which also increase the risk of VTE.<sup>20</sup> However, VTE also occurred in 2 patients with COVID-19 aged 40-60 years. This might be related to the effects of acute inflammatory response on coagulation and fibrinolytic function after acute infection through a variety of pathways, including decreased levels of protein C and antithrombin III, which affect the coagulation system.<sup>21</sup> Therefore, it is necessary to pay special attention to VTE occurrence in elderly patients with critical COVID-19 while also preventing and screening VTE in young individuals with critical COVID-19.

In the 35 patients with COVID-19 assessed, platelet counts in severe and critical cases showed a downward trend during the treatment period, especially with disease progression. Platelet counts in patients administered CRRT/ECMO decrease due to blood system destruction, and the downward trend was less significant than observed in this study.<sup>22</sup> This analysis showed that such decrease might be related to platelet consumption following venous thrombosis. The severely damaged

coagulation system of COVID-19 patients<sup>23</sup> and decreased platelet count could both significantly increase the risk of hemorrhage.

In this study, 1 critical COVID-19 case died of severe PE. The patient had a high risk of VTE, including advanced age, comorbidities and a Caprini score of 9. However, no preventive anticoagulation treatment was carried out due to severe gastrointestinal hemorrhage. Nevertheless, VTE could be avoided if intensive analysis of the coagulation function and early intervention according to condition evolution were carried out. This suggests higher requirements for the current procedures for rescuing critically ill patients, which should take into account the risk of hemorrhage as well as the high mortality of VTE.

Based on recommendations by experts in related academic groups of the Chinese Medical Association and the experiences of our center, suggestions for the diagnosis and treatment of VTE in patients with COVID-19 are as follows: 1) VTE risk scores should be assessed routinely in all patients with COVID-19, with effective intervention carried out according to results; 2) in severe and critical cases of COVID-19, mechanical prophylaxis and anticoagulant treatment should be actively performed to prevent VTE in those with low hemorrhage risk; 3) in patients with current VTE, anticoagulant treatment should be standardized on the basis of a comprehensive assessment of disease condition; 4) in patients with high risk of recurrent pulmonary embolism, inferior vena cava filter placement should be performed to prevent further pulmonary embolism. Considering the transfer risk of critical cases as well as epidemic prevention and isolation,<sup>24</sup> it is suggested to conduct inferior vena cava filter placement under the guidance of bedside ultrasound.

This study had several limitations. First, this was a single center study, and selection bias could not be ruled out. In addition, the sample size was relatively small. Furthermore, it was a retrospective study, with inherent shortcomings. Moreover, although inflammation may play a role in VTE, classic molecular markers of inflammation, including cytokines, were not assessed. Therefore, large well-designed studies performed in multiple centers are required to confirm the present findings.

## Conclusion

COVID-19-associated pneumonia develops rapidly and causes high mortality. During the treatment process, besides the attention paid to organ function and targeted treatment, the high risk of concurrent VTE should also be addressed clinically. Advanced age and significantly D-dimer tendency are important risk assessment indexes for VTE occurrence as well as treatment evaluation in severe and critical COVID-19 cases. VTE occurrence in critical cases of COVID-19 greatly increases the difficulty of treatment as well as the risk of death. During clinical treatment, active and effective measures should be taken to prevent and treat VTE in order to further reduce the risk of VTE in patients with COVID-19.

## Author Contribution

Kai Liang and Ying Fu contributed equally to this work.


## 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.

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