

BRIEF REPORT

Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia

Songping Cui¹ | Shuo Chen¹ | Xiunan Li¹ | Shi Liu² | Feng Wang^{3,4,5,6}

¹Department of Thoracic Surgery, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

²Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

³Department of Respiratory and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

⁴Beijing Institute of Respiratory Medicine, Beijing, China

⁵Beijing Engineering Research Center for Diagnosis and Treatment of Respiratory and Critical Care Medicine (Beijing Chao-Yang Hospital), Beijing, China

⁶Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing, China

Correspondence

Feng Wang, Department of Respiratory and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020 China.
Email: tad2008@hotmail.com

Abstract

Background: Three months ago, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan, China, and spread rapidly around the world. Severe novel coronavirus pneumonia (NCP) patients have abnormal blood coagulation function, but their venous thromboembolism (VTE) prevalence is still rarely mentioned.

Objectives: To determine the incidence of VTE in patients with severe NCP.

Methods: In this study, 81 severe NCP patients in the intensive care unit (ICU) of Union Hospital (Wuhan, China) were enrolled. The results of conventional coagulation parameters and lower limb vein ultrasonography of these patients were retrospectively collected and analyzed.

Results: The incidence of VTE in these patients was 25% (20/81), of which 8 patients with VTE events died. The VTE group was different from the non-VTE group in age, lymphocyte counts, activated partial thromboplastin time (APTT), D-dimer, etc. If 1.5 µg/mL was used as the D-dimer cut-off value to predicting VTE, the sensitivity was 85.0%, the specificity was 88.5%, and the negative predictive value (NPV) was 94.7%.

Conclusions: The incidence of VTE in patients with severe NCP is 25% (20/81), which may be related to poor prognosis. The significant increase of D-dimer in severe NCP patients is a good index for identifying high-risk groups of VTE.

KEYWORDS

blood coagulation, coagulation parameter, D-dimer, novel coronavirus pneumonia, venous thromboembolism

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of respiratory transmitted virus. By mid-March 2020, it had sickened more than 80 000 people and killed more than 3000 in China, triggering a global pandemic. A number of studies have shown

that coagulation dysfunction exists in patients with severe novel coronavirus pneumonia (NCP),¹⁻⁴ which is clearly correlated with poor prognosis.³ The conventional coagulation parameters of intensive care unit (ICU) patients were significantly higher than those of non-ICU patients.² However, the prevalence of venous thromboembolism (VTE) in ICU patients with severe NCP is unknown. Therefore, the purpose of this study was to explore the incidence of VTE in such patients and to investigate the differences between VTE patients and non-VTE patients.

Songping Cui and Shuo Chen contributed equally to this work.

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2 | METHODS

A total of 81 patients diagnosed with NCP in the ICU of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 30 to March 22, 2020, were included. All the patients were diagnosed according to the World Health Organization guidelines.⁵ The severity of NCP was judged according to the Fifth Revised Trial Version of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance.⁶ The patients were subjected to a series of investigations, including clinical examinations, laboratory tests, chest computed tomography (CT), lower limb venous doppler ultrasound, and real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for SARS-CoV-2. All the patients received antiviral and supportive treatment after diagnosis, and no preventive anticoagulant was administered. The study was approved by the Ethics Committee of Union Hospital (Wuhan, China).

Conventional coagulation tests, which included prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR), fibrinogen (FIB), and D-dimer were performed using a Succeder SF8200 automatic coagulation analyzer (China). Clinical and laboratory information was also collected.

Data are presented as means \pm standard deviation (SD) or number (percentage) where appropriate. *T* test or Mann-Whitney *U* test were used to analyze the differences between the two groups. $P < .05$ was defined as statistically significant. Statistical analysis was conducted using SPSS software version 21.0 (IBM).

3 | RESULTS AND DISCUSSION

A total of 81 patients with severe NCP were enrolled in this study, with the mean age of 59.9 years (range, 32-91 years), including 44 females (54%). Thirty-three (41%) patients had chronic medical illness, including hypertension, diabetes, and coronary heart disease; 35 (43%) patients had a history of smoking. As of 22 March, 64 (79%) patients had been discharged from hospital, 8 (10%) had died, and the rest (9; 11%) remained hospitalized (Table 1).

A total of 20 (25%) patients with severe NCP developed lower extremity venous thrombosis, of which 8 patients died. The VTE group had older age (68.4 ± 9.1 versus 57.1 ± 14.3 years, $P < .001$), lower lymphocyte counts (0.8 ± 0.4 versus $1.3 \pm 0.6 \times 10^9/L$, $P < .001$), longer APTT (39.9 ± 6.4 versus 35.6 ± 4.5 seconds, $P = .001$), and higher D-dimer (5.2 ± 3.0 versus $0.8 \pm 1.2 \mu\text{g/mL}$, $P < .001$). Moreover, the D-dimer of the two groups was not within the normal range (Table 2).

Table 3 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different D-dimer levels in predicting VTE in patients with severe NCP. If $1.5 \mu\text{g/mL}$ was used as the cut-off value for D-dimer to predict VTE, the sensitivity, specificity, PPV, and NPV were 85.0%, 88.5%, 70.8%, and 94.7%, respectively (Table 3).

In this study, the decrease of lymphocytes was common in patients with NCP, especially in patients with VTE. Other studies have

Essentials

- The prevalence of venous thromboembolism (VTE) in patients with severe novel coronavirus pneumonia (NCP) is still unknown.
- Conventional coagulation parameters and ultrasound results of lower extremity veins in patients with severe NCP were retrospectively analyzed.
- The incidence of VTE in the intensive care unit of patients with severe NCP is 25% (20/81), which may be related to poor prognosis.
- The level of D-dimer was a good index for predicting VTE in patients with severe NCP.

also observed that infection with SARS-CoV-2 leads to lymphocytopenia.^{2,7,8} In the analysis of lymphocyte subset, T cells were more susceptible to SARS-CoV-2, because T cell count was almost half of the lower reference limit, and the severe NCP patients were more likely to be hampered.⁸ Moreover, abnormal expression of T cell associated mRNA can lead to VTE.⁹ This meant that older patients with more underlying diseases were more likely to develop immune dysfunction and have a higher risk of VTE because of their poor immunity.

Severe SARS-CoV-2 infection in NCP patients can lead to sepsis, which can also lead to the release of inflammatory cytokines

TABLE 1 Baseline characteristics of NCP patients (n = 81)

Characteristic	Number (%) or mean (SD)
Age, years	59.9 (14.1)
Range	32-91
≤39	11 (14%)
40-49	11 (14%)
50-59	13 (16%)
60-69	28 (35%)
≥70	18 (22%)
Sex	
Male	37 (46%)
Female	44 (54%)
Chronic medical illness	
Hypertention	20 (25%)
Diabetes	8 (10%)
Coronary heart disease	10 (12%)
Smoking	35 (43%)
Clinical outcome	
Remained in hospital	9 (11%)
Discharged	64 (79%)
Died	8 (10%)

Abbreviation: NCP, novel coronavirus pneumonia; SD, standard deviation.

TABLE 2 Characteristics between the VTE and non-VTE groups (n = 81)

Characteristics	Normal range	VTE (n = 20)	Non-VTE (n = 61)	P-value
Age (years)	-	68.4 ± 9.1	57.1 ± 14.3	<.001
Leucocytes (×10 ⁹ /L)	3.5-9.5	7.8 ± 3.1	6.6 ± 2.6	.120
Lymphocytes (×10 ⁹ /L)	1.1-3.2	0.8 ± 0.4	1.3 ± 0.6	<.001
Platelets (×10 ⁹ /L)	125.0-350.0	246.6 ± 110.6	248.8 ± 111.7	.938
Haemoglobin (g/L)	115.0-150.0	123.2 ± 16.5	125.3 ± 16.7	.633
APTT (s)	27.0-45.0	39.9 ± 6.4	35.6 ± 4.5	.001
Prothrombin time (s)	11.0-16.0	15.4 ± 1.0	15.6 ± 1.0	.465
D-dimer (μg/mL)	0.0-0.5	5.2 ± 3.0	0.8 ± 1.2	<.001

Abbreviation: APTT, activated partial thromboplastin time; VTE, venous thromboembolism.

TABLE 3 Sensitivity, specificity, PPV, and NPV of different D-dimer cut-off levels for predicting VTE in NCP patients

Cut-off (μg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1.0	85.0	77.0	54.8	94.0
1.5	85.0	88.5	70.8	94.7
2.0	80.0	90.2	72.7	93.2
2.5	70.0	93.4	77.8	90.5
3.0	70.0	96.7	87.5	90.8
3.5	65.0	96.7	86.7	89.4

Abbreviation: NCP, novel coronavirus pneumonia; NPV, negative predictive value; PPV, positive predictive value; VTE, venous thromboembolism.

such as IL-6, IL-8, TNF- α , etc.,⁸ similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).^{10,11} Inflammatory cytokines can promote the activation of blood coagulation in many ways, and then promote the occurrence of VTE.¹²⁻¹⁴ Sepsis is also a common cause of disseminated intravascular coagulation (DIC)¹⁵ and the incidence of DIC in dead NCP patients was 71.4%.³ This suggests that abnormal blood coagulation and thrombosis are associated with poor prognosis in patients with NCP.

Elevated D-dimer level is a sign of excessive coagulation activation and hyperfibrinolysis. Therefore, D-dimer is often used to detect active thrombus with high sensitivity but low specificity.¹⁶ But, if 3.0 μg/mL was used as the cut-off value, the sensitivity, specificity, and NPV were 76.9%, 94.9%, and 92.5%, respectively. After receiving anticoagulant therapy, the level of D-dimer decreased gradually, which means that D-dimer can not only predict thrombosis but also monitor the effectiveness of anticoagulants.

There are several limitations in our report. First, this is a retrospective, single-center, small sample study. The results may be biased and need to be confirmed by a large sample study. Second, some patients are still being treated in hospital, and the clinical outcome may change. Despite that, our study described the incidence of VTE in patients with severe NCP and demonstrated the application of D-dimer in VTE prediction. We hope that these results will contribute to the prevention, diagnosis, and treatment of VTE.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

XL and SL collected the clinical data. SPC and SC processed statistical data. SPC and SC drafted and revised the manuscript. FW designed and guided the study.

REFERENCES

- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844-847.
- Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020; Epub ahead of print. <https://doi.org/10.1515/cclm-2020-0188>
- WHO. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. 2020. <https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117>.
- The fifth revised trial version of the novel coronavirus pneumonia diagnosis and treatment guidance. <http://www.nhc.gov.cn/yzygj/s7652m/202002/41c3142b38b84ec4a748e60773cf9d4f.shtml>
- Wang D, Hu B, Hu C, et al. Novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2019;2020:e201585.
- Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020;ciaa248.
- Duan Q, Gong Z, Song H, et al. Symptomatic venous thromboembolism is a disease related to infection and immune dysfunction. *Int J Med Sci*. 2012;9:453-461.
- Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol*. 2004;136:95-103.
- Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine*. 2018;104:8-13.

12. Opal SM. Interactions between coagulation and inflammation. *Scand J Infect Dis*. 2003;35:545-554.
13. Levi M, van der Poll T, Buller HR. Bidirectional relation between inflammation and coagulation. *Circulation*. 2004;109:2698-2704.
14. van der Poll T, Levi M. Crosstalk between inflammation and coagulation: the lessons of sepsis. *Curr Vasc Pharmacol*. 2012;10:632-638.
15. Iba T, Thachil J. Present and future of anticoagulant therapy using antithrombin and thrombomodulin for sepsis-associated disseminated intravascular coagulation: a perspective from Japan. *Int J Hematol*. 2016;103:253-261.
16. Koch V, Biener M, Muller-Hennessen M, et al. Diagnostic performance of D-dimer in predicting venous thromboembolism and acute aortic dissection. *Eur Heart J Acute Cardiovasc Care*. 2020:2048872620907322.

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