CLINICAL RESEARCH

Analysis of Risk Factors for Thromboembolic Events in 88 Patients with COVID-19 Pneumonia in Wuhan, China: A Retrospective Descriptive Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDE 1 **Wenyu Wang**
CDF 2 **Qingfeng Sun**
BC 1 **Yongxia Bao**
BC 3 **Ming Liang**
BC 4 **Qingwei Meng**
BC 1 **Hong Chen**
BC 1 **Jianing Li**
BC 5 **Hongliang Wang**
BC 6 **Huiqing Li**
BC 7 **Ying Shi**
BF 1 **Zhaoguo Li**
F 1 **Xinyan Wang**
F 1 **Shuai Zhao**
F 1 **Hongwei Wang**
F 1 **Jinling Xiao**
F 3 **Liyan Chen**
F 8 **Yan Zheng**
F 8 **Di Wang**
AEG 1 **Kaiyu Han**

1 Department of Respiratory and Critical Medicine, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China
2 Department of Vascular Interventional Surgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China
3 Department of Infection, Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China
4 Department of Oncology, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, P.R. China
5 Department of Critical Care Medicine, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China
6 Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China
7 Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China
8 Department of Respiratory Medicine, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China

Corresponding Author: Kaiyu Han, e-mail: hankaiyu2002@163.com

Background: Since the outbreak of COVID-19 in December 2019, there have been 96 623 laboratory-confirmed cases and 4784 deaths by December 29 in China. We aimed to analyze the risk factors and the incidence of thrombosis from patients with confirmed COVID-19 pneumonia.

Material/Methods: Eighty-eight inpatients with confirmed COVID-19 pneumonia were reported (31 critical cases, 33 severe cases, and 24 common cases). The thrombosis risk factor assessment, laboratory results, ultrasonographic findings, and prognoses of these patients were analyzed, and compared among groups with different severity.

Results: Nineteen of the 88 cases developed DVT (12 critical cases, 7 severe cases, and no common cases). In addition, among the 18 patients who died, 5 were diagnosed with DVT. Positive correlations were observed between the increase in D-dimer level (≥5 μg/mL) and the severity of COVID-19 pneumonia (r=0.679, *P*<0.01), and between the high Padua score (≥4) and the severity (r=0.799, *P*<0.01). In addition, the CRP and LDH levels on admission had positive correlations with the severity of illness (CRP: r=0.522, *P*<0.01; LDH: r=0.600, *P*<0.01). A negative correlation was observed between the lymphocyte count on admission and the severity of illness (r=-0.523, *P*<0.01). There was also a negative correlation between the lymphocyte count on admission and mortality in critical patients (r=-0.499, *P*<0.01). Univariable logistic regression analysis showed that the occurrence of DVT was positively correlated with disease severity (crude odds ratio: 3.643, 95% CI: 1.218-10.896, *P*<0.05).

Conclusions: Our report illustrates that critically or severely ill patients have an associated high D-dimer value and high Padua score, and illustrates that a low threshold to screen for DVT may help improve detection of thromboembolism in these groups of patients, especially in asymptomatic patients. Our results suggest that early administration of prophylactic anticoagulant would benefit the prognosis of critical patients with COVID-19 pneumonia and would likely reduce thromboembolic rates.

Keywords: COVID-19 • Embolism and Thrombosis • Pneumonia

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/929708

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Background

Since the outbreak of COVID-19 in December 2019, there have been 96 623 laboratory-confirmed cases and 4784 deaths by December 29 in China [1]. Over 70 million people were diagnosed with COVID-19 globally. Over 1.6 million people died directly because of the COVID-19 [2]. It was identified that the initial symptoms of COVID-19 pneumonia are usually fever, dry cough, and fatigue, dyspnea, and/or hypoxemia and these often occur in severe patients 1 week after onset. Serious cases can rapidly progress to acute respiratory distress syndrome, coagulation dysfunction, and disseminated intravascular coagulation (DIC). Rapid deterioration and sudden death occurring in critical patients highlight the high risk of thrombosis [3]. Clinical observations have observed a hypercoagulable state in severely and critically ill patients with COVID-19 pneumonia [4-6], and the diagnostic rate of ultrasound was 22.7% for deep vein thrombosis (DVT) [7].

Several hypotheses have been proposed for the incidence of thrombosis among patients infected by COVID-19. First, inflammatory mediators, respiratory failure, and local hypoxia by venous stasis may lead to vascular endothelial activation and consequent endothelial injury [8]. Subsequently, a dysfunctional endothelium can initiate thrombosis and promote atherosclerosis [9]. Second, the massive release of inflammatory mediators in patients with severe or critical COVID-19 pneumonia, and the application of glucocorticoids in patients with excessively activated inflammatory responses, can contribute to hypercoagulability [10]. Water loss caused by sweating during fever, body fluid loss caused by vomiting, and/or diarrhea can also lead to hemoconcentration and exacerbate the hypercoagulable state. The immune mechanism also can contribute to pulmonary intravascular coagulopathy [11]. Third, most patients presented with fatigue and dyspnea [12]. Critical patients who depend on a ventilator and patients in the intensive care unit are bedridden during hospitalization, which may cause venous blood flow stasis. Additionally, metabolic abnormalities, obesity, and other underlying diseases are more common in older people. Moreover, thrombosis developed not only in the lower-extremity deep veins but also in small pulmonary vessels [13]. In summary, the endothelial injury, hypercoagulable state, and venous stasis contribute to thrombosis in COVID-19 pneumonia patients. Nevertheless, the risk factors for COVID-19 pneumonia-induced DVT remain to be further explored.

Previously, due to a lack of specific antiviral medicines, treatment strategies have focused on anti-inflammation and anti-respiratory failure treatments. After experience with our previous DVT case in the clinical work in Wuhan, we began to pay attention to the relationship between DVT and prognosis in COVID pneumonia patients. In our study, all critical patients had a risk of developing thrombosis. Among the critical patients, the rate of DVT complications was 38.7% (12/31). The present retrospective study describes the occurrence of DVT in 88 patients with COVID-19 pneumonia and the relationship between thrombosis and prognosis. With the number of cases increasing globally, it will be important to prevent and diagnose DVT in patients with severe and critical COVID-19 pneumonia.

Material and Methods

Data Sources

We conducted a retrospective study focusing on the thrombotic risks of confirmed cases of COVID-19 pneumonia at Wuhan Union Hospital (Wuhan, China). This study was approved by the Institutional Research Ethics Boards of the Union Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan. Data were collected from 88 patients with COVID-19 pneumonia (confirmed by positive polymerase chain reaction test results on nasopharyngeal swab specimens) admitted to the hospital between 29 January 2020 and 29 February 2020. Information was collected on dates of illness onset and hospital admission. Only patients (both sexes, and age range 19-79 years) who tested positive in a nucleic acid test for SARS-CoV-2, with typical radiological findings of pneumonia, and negative results for other pathogen tests (influenza A and B, parainfluenza, respiratory syncytial virus, rhinovirus, adenovirus, and mycoplasma), and onset in Wuhan were included in this study. Patients with a history of underlying respiratory diseases, heart failure, hepatic insufficiency, or renal insufficiency before COVID-19 pneumonia onset, and patients with active malignancy, were excluded from the present study. The objective of the exclusion was to reduce the clinical effect of other severe disease on the prognosis of patients with COVID-19 pneumonia.

Clinical Classification

Classification as mild, common, severe, and critical was carried out according to the diagnosis and treatment program of novel coronavirus pneumonia (Trial Seventh Edition) issued by the National Health Commission. The diagnosis of critical COVID-19 pneumonia was based on the fulfillment of 1 out of 3 of the following criteria: 1) developed respiratory failure requiring mechanical ventilation, 2) developed shock, and 3) combined with other organ failure requiring intensive care treatment. Severe patients fulfilled 1 out of 3 of the following criteria: 1) respiratory frequency ≥30 breaths/min; 2) blood oxygen saturation ≤93% at rest; and 3) blood oxygen saturation (PaO_2)/inspired oxygen fraction (FiO_2) ≤300 mmHg.

Laboratory Results, Examination Results, and Treatment

The D-dimer value was measured by STAGO-R (Succeeder, Beijing, China). The data were reported in FEU. The absolute measurement unit was ug/mL and the cut-off value was 0.5 ug/mL. Lymphocyte count, hemoglobin, C reactive protein (CRP), lactate dehydrogenase (LDH), and serum calcium assays were performed using conventional methods. The blood samples for these laboratory assays were collected on the day of admission and were reviewed every 3-5 days, as needed. DVT was evaluated using Doppler ultrasound. The Doppler ultrasound examination was performed both on patients with symptomatic DVT and on asymptomatic patients with a D-dimer value increase. Computed tomographic pulmonary angiography was the method of choice for imaging the pulmonary vasculature in patients with suspected pulmonary thromboembolism (PTE) [14]. Patients received anticoagulants and prophylaxis therapy according to the guidelines of the Padua risk assessment scale (medical patients' venous thromboembolism risk assessment recommended by guidelines from the American College of Chest Physicians) [15]. In the Padua scale, the high risk of thrombosis was defined by a cumulative score ≥4 points. Each of the following 6 risk factors: elderly (≥70 years), heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity (BMI ≥30) and ongoing hormonal treatment, was scored with 1 point. The risk factor recent (≤1 month) trauma and/or surgery increased the score by 2 points. Each of 4 risk factors – active cancer, previous venous thromboembolism (VTE), reduced mobility (bed rest ≥3 days), and already known thrombophilia – added 3 points [16].

Statistical Analysis

All analyses were performed using SPSS software (version 19.0; IBM Corp.). Continuous and categorical variables are presented as median (interquartile range) and n (%), respectively. We used the Mann-Whitney U test, χ^2 test, or Fisher's exact test to compare differences between critical and severe groups, as appropriate. Spearman's correlation analysis was conducted to evaluate the correlation between variables. The multivariable adjustment was performed using linear regression for continuous data and logistic regression for dichotomous data.

Results

Clinical Characteristics of Patients with COVID-19 Pneumonia

A total of 88 patients with confirmed COVID-19 pneumonia treated between 29 January 2020 and 17 March 2020 (**Table 1**) were reviewed in this report. Up to the time of submission of this article for publication, 19 patients (12 critical cases and 7 severe cases) developed DVT during hospitalization. Among the 18 patients who died, 5 were diagnosed with DVT. All 31 patients with critical COVID-19 pneumonia exhibited a Padua score increase (≥4), and 27 of them also exhibited a D-dimer value increase (≥5 μg/mL). Because the common group generally had a low score of Padua without any thrombotic events, they were not included in the comparison. The results indicated a positive correlation between the increase in D-dimer value (≥5 μg/mL) and the severity of COVID-19 pneumonia (r=0.679, P<0.01) and between the high Padua score (≥4) and the severity (r=0.799, P<0.01). In addition, the CRP and LDH levels on admission had positive correlations with the severity of illness (CRP: r=0.522, P<0.01; LDH: r=0.600, P<0.01). A negative correlation was observed between the lymphocyte count on admission and the severity of illness (r=-0.523, P<0.01). There was also a negative correlation between the lymphocyte count on admission and mortality in critical patients (r=-0.499, P<0.01). A weak correlation was also noticed between sex and illness severity (r=0.254, P<0.05). Moreover, univariable logistic regression analysis showed that the occurrence of DVT was positively correlated with disease severity (crude odds ratio: 3.643, 95% CI: 1.218-10.896, P<0.05). Based on the Padua score (≥4), a total of 38 patients received anticoagulants or prophylaxis therapy; 17 of these patients had a diagnosis of DVT during hospital, but there were also 2 other patients with confirmed DVT who had not received prophylaxis therapy.

Clinical Characteristics of Thrombotic Complications in 19 Patients with COVID-19 Pneumonia and DVT

The clinical characteristics of the 19 patients exhibiting complications in the form of DVT are shown in **Table 2**. Except for one 38-year-old female patient who reported pain and swelling in her right lower limb, DVT was identified in all cases by ultrasound screening following an increase in the D-dimer value. All these patients had no previous history of DVT. Most of these patients had no complaint of lower limb discomfort. One patient was finally diagnosed with PTE (case 5). The most common risk factors observed in the present study were bed rest and infection. The average hospitalization period was 6.7 days prior to the discovery of a marked D-dimer value increase (≥5 μg/mL) in the patients who were eventually diagnosed with DVT. Univariable logistic regression analysis showed an increased odd of DVT with D-dimer levels greater than or equal to 5 μg/mL (crude odds ratio: 4.539, 95% CI: 1.289-15.991, P<0.05). Twelve of the 19 patients with DVT received prophylaxis after the discovery of D-dimer value increasing to above the normal range; 6 of them received antithrombotic therapy after the diagnosis of DVT, and 1 79-year-old patient received antithrombotic therapy after the diagnosis of DVT. For patients with confirmed DVT, anticoagulant therapy was provided according to antithrombotic therapy for VTE disease

Table 1. Demographics and clinical characteristics of patients with COVID-19.

	All patients (n=88)	Disease severity			
		Critical patients (n=31)	Severe patients (n=33)	*P* value*	Common patients (n=24)
Age -median (IQR)	61.5 (55.0-68.8)	66.5 (61.0-71.0)	61.0 (53.0-66.0)	0.11	56.0 (42.5-66.5)
Sex -n (%)				<0.05	
Female	39 (44.3)	10 (32.3)	19 (57.6)	**	10 (41.7)
Male	49 (55.7)	21 (67.7)	14 (42.4)	**	14 (58.3)
Padua score -n (%)				<0.001	
<4	50 (56.8)	0 (0.0)	26 (78.8)	**	24 (100.0)
≥4	38 (43.2)	31 (100.0)	7 (21.2)	**	0 (0.0)
D-dimer top-value – n (%) (normal range 0-0.5)				<0.001	
<5 ug/mL	54 (61.4)	4 (12.9)	26 (78.8)	**	24 (100.0)
≥5 ug/mL	34 (38.6)	27 (87.1)	7 (21.2)	**	0 (0.0)
DVT -n(%)	19 (21.6)	12 (38.7)	7 (21.2)	0.169	0
Female	10 (52.6)	4 (33.3)	6 (85.7)	**	0
Male	9 (47.4)	8 (66.7)	1 (14.3)	**	0
Death – n (%)	18 (20.5)	18 (58.1)	0	<0.001	0
DVT	5 (27.8)	5 (27.8)	0	**	0
Padua score ≥4	18 (100.0)	18 (100.0)	0	**	0
D-dimer value ≥ 5ug/mL	17 (94.4)	17 (94.4)	0	**	0
Lymphocyte count -median (IQR) (normal range 1.1-3.2×10^9/L)	1.01 (0.60-1.35)	0.55 (0.41-0.83)	1.08 (0.74-1.46)	<0.001	1.29 (1.05-1.76)
LDH – median (IQR) (normal range 109-245 U/L)	250.0 (178.5-485.8)	543.0 (392.5-608.0)	236.0 (179.0-324.5)	<0.001	174.0 (139.5-229.5)
CRP – median (IQR) (normal range 0-8 mg/L)	32.33 (3.61-77.64)	85.48 (53.14-114.31)	19.62 (4.34-63.06)	<0.001	3.09 (0.10-18.00)

	Critical patients (n=31)			Critical and severe patients (n=64)		
	Non-survivor (n=18)	Survivor (n=13)	*P* value	Non-DVT (n=45)	DVT (n=19)	*P* value
Age – median (IQR)	67 (60-70)	66 (61-74)	0.553	62 (55.3-67.8)	64 (56-71)	0.36
Sex – n (%)			0.704			0.421
Female	6 (33.3)	4 (30.8)	**	19 (42.2)	10 (52.6)	**
Male	12 (66.7)	9 (69.2)	**	26 (57.8)	9 (47.4)	**
Padua score – n (%)			**			<0.05
<4	0 (0.0)	0 (0.0)	**	24 (53.3)	2 (10.5)	**
≥4	18 (100.0)	13 (100.0)	**	21 (46.7)	17 (89.5)	**

Table 1 continued. Demographics and clinical characteristics of patients with COVID-19.

	Critical patients (n=31)			Critical and severe patients (n=64)		
	Non-survivor (n=18)	Survivor (n=13)	*P* value	Non-DVT (n=45)	DVT (n=19)	*P* value
D-dimer top-value – n (%) (normal range 0-0.5)			0.548			<0.05
<5 ug/mL	1 (5.6)	3 (23.1)	**	26 (57.8)	4 (21.1)	**
≥5 ug/mL	17 (94.4)	10 (76.9)	**	19 (42.2)	15 (78.9)	**
DVT -n(%)	5 (27.8)	7 (53.8)		0 (0.0)	19 (100.0)	**
Female	**	**	**	**	**	**
Male	**	**	**	**	**	**
Death – n (%)	18 (100.0)	0 (0.0)	**			**
DVT	**	**	**	**	**	**
Padua score ≥4	**	**	**	**	**	**
D-dimer value ≥5 ug/mL	**	**	**	**	**	**
Lymphocyte count – median (IQR) (normal range 1.1-3.2×10⁹/L)	0.47 (0.27-0.62)	0.76 (0.57-0.89)	<0.05	0.89 (0.49-1.30)	0.75 (0.52-0.98)	0.142
LDH – median (IQR) (normal range 109-245 U/L)	564.5 (465.3-677.5)	451.5 (289.5-550.5)	0.078	294.0 (184.3-556.8)	461.0 (348.0-564.0)	0.123
CRP – median (IQR) (normal range 0-8 mg/L)	89.4 (56.7-120.3)	65.2 (35.7-108.8)	0.203	47.6 (7.4-84.5)	72.4 (52.3-120.8)	0.29

IQR – interquartile range; CRP – C-reactive protein; LDH – lactate dehydrogenase. * P values were calculated between critical and severe groups by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.

guidelines (Tenth Edition) issued by the American College of Chest Physicians [12]. The adjuvant treatment included physical therapy and reduced activity. Six patients were discharged successfully with further oral rivaroxaban medication (cases 1, 2, 5, 6, 7, and 17).

Thrombosis Risk in 18 Patients with COVID-19 Pneumonia Who Died

Among the 31 patients with confirmed critical COVID-19 pneumonia, 18 eventually died (**Table 3**). We observed that they may all have suffered from coagulation dysfunction with a marked increase in D-dimer levels before death. We also identified 6 deaths suspected to be associated with thrombosis (cases 4, 5, 6, 10, 13, and 14). One patient suspected of having PTE developed acute respiratory failure before death and exhibited continuously rising D-dimer and troponin levels without any myocardial infarction change (case 6). The other 13 critical patients' Padua scores were generally high, and 7 were diagnosed with DVT. The decrease in the D-dimer level and no signs of thrombosis indicated that they might benefit from anticoagulation therapy. Non-critical patients without DVT were also scored to assess whether anticoagulation should be administered for prevention.

Discussion

Since the outbreak of COVID-19 in December 2019, this pandemic continues to evolve worldwide. To date, there are still no sufficient and totally effective vaccines or effective antiviral agents available anywhere in the world. Moreover, considering the potential virus variation and the vaccine acceptance rates in normal healthy people, the effects of current vaccines still need to be observed. The virus continues to cause a large number of deaths. We performed a single-center study of patients with COVID-19 pneumonia. This study found high mortality in critical COVID-19 pneumonia patients. We also reported the factors that affect disease severity and the association between the possible methods (like early ultrasound screening and/or prophylactic anticoagulant) and the improvement of the prognosis.

In the present study, we observed that the mortality rate of critically ill patients was 58.1%. According to previous reports, the mortality rate of hospitalized COVID-19 patients ranged from 1.4 to 25.7% [17-19], and the rate was significantly higher (39.3-61.5%) in patients with severe hypoxemia and who required mechanical ventilation [20-22].

Table 2. Thrombotic complications in 19 patients with COVID-19.

Case	Age (years)	Sex (M/F)	Diagnosis of COVID-19	Risk factors	Symptoms of DVT	Days A*	D-dimer top-value (ug/mL)	Days B**	Deep vein ultrasound found DVT
1	38	F	Severe	Bed rest infection obesity	Pain swelling	5	7.04	5	Right fibular vein right gastrocnemius intermuscular vein
2	68	F	Severe	Bed rest infection	–	15	>8	16	Right popliteal vein both fibular vein both posterior tibial vein both gastrocnemius intermuscular vein
3	64	F	Severe	Bed rest infection hypertension DM history of PCI	–	6	>8	12	Both gastrocnemius intermuscular vein
4	56	F	Severe	Bed rest infection	–	1	>8	16	Both gastrocnemius intermuscular vein
5	64	F	Severe	Bed rest infection	–	12	4.08	19	Both gastrocnemius intermuscular vein
6	66	F	Severe	Bed rest infection	–	2	3.95	9	Left gastrocnemius intermuscular vein
7	62	M	Severe	Infection	–	1	1.38	8	Left gastrocnemius intermuscular vein
8	70	F	Critical	Bed rest infection advanced age history of pulmonary malignant	–	1	>8 (found on day 16)	16	Both gastrocnemius intermuscular vein
9	61	M	Critical	Bed Rest Infection Obesity Hypertension	–	7	>8	7	Right fibular vein
10	77	M	Critical	Bed Rest Infection Advanced Age	–	9	5.42	20	Both fibular vein both posterior tibial vein both gastrocnemius intermuscular vein
11	71	F	Critical	Bed rest infection obesity DM	–	5	>8	8	Not performed***
12	55	M	Critical	Bed rest infection	–	5	>8 (found on day 14)	19	Both gastrocnemius intermuscular vein
13	61	F	Critical	Bed rest infection	–	2	>8	12	Both gastrocnemius intermuscular vein
14	61	M	Critical	Bed rest infection hypertension	–	2	>8	6	Left popliteal vein left fibular vein left posterior tibial vein both gastrocnemius intermuscular vein
15	79	M	Critical	Bed rest infection advanced age hypertension history of DVT history of PCI history of cerebral infarctioon	–	1	>8	1	Left popliteal vein left fibular vein left gastrocnemius intermuscular vein

Table 2 continued. Thrombotic complications in 19 patients with COVID-19.

Case	Age (years)	Sex (M/F)	Diagnosis of COVID-19	Risk factors	Symptoms of DVT	Days A*	D-dimer top-value (ug/mL)	Days B**	Deep vein ultrasound found DVT
16	75	M	Critical	Bed rest infection advanced age hypertension history of cerebral hemorrhage	–	2	4.16	4	Right posterior tibial vein right gastrocnemius intermuscular vein
17	70	M	Critical	Bed rest infection advanced age hypertension	–	1	>8 (found on day 12)	8	Both gastrocnemius intermuscular vein
18	72	F	Critical	Bed rest infection advanced age DM hypertension cerebral infarctioon (acute phase)	–	2	>8	7	Right gastrocnemius intermuscular vein
19	55	M	Critical	Bed rest infection hypertension	–	9	>8	10	Left posterior tibial vein both gastrocnemius intermuscular vein

Case	Therapeutic LMWH	Echocardiographic evaluation	CTPA (Y/N)	Outcomes
1	q12h	No pulmonary hypertension	Not performed	Discharged home after 21-day hospitalization
2	q12h	No pulmonary hypertension	Not performed	Discharged home after 26-day hospitalization
3	qd (from dayA to dayB) q12h (after dayB)	No pulmonary hypertension	Not performed	Discharged home after 50-day hospitalization
4	q12h (after dayA)	Not performed	N	Discharged home after 51-day hospitalization
5	q12h (after dayB)	Not performed	Y	Discharged home after 35-day hospitalization
6	qd (from dayA to dayB) q12h (after dayB)	Not performed	Not performed	Discharged home after 35-day hospitalization
7	qd (from dayA to dayB) q12h (after dayB)	Not performed	Not performed	Discharged home after 17-day hospitalization
8	qd (from dayA to dayB) (discontinued for bleeding and decrease of D-Dimer value from 1.28 to 0.67) (after dayB)	Mild pulmonary hypertension (found on day 21)	Not performed	Disease progress after 16-day hospitalization died after 15-day in ICU
9	q12h (discontinue after 9 days for gastrointestinal bleeding)	No pulmonary hypertension	Not performed	Died after 24-day hospitalization
10	qd (increase the dose after DVT were found)	No pulmonary hypertension	Not performed	Discharged home after65-day hospitalization
11	q12h (after dayB)	Not performed	Not performed	Died after 9-day hospitalization
12	qd (after day14)	Not performed	Not performed	Died after 19-day hospitalization
13	qd (after dayA)	Not performed	Not performed	Died after 16-day hospitalization
14	qd (from dayA to dayB) q12h (after dayB)	not performed	not performed	Discharged home after 48-day hospitalization

Table 2 continued. Thrombotic complications in 19 patients with COVID-19.

Case	Therapeutic LMWH	Echocardiographic evaluation	CTPA (Y/N)	Outcomes
15	qd (after day 8)	No pulmonary hypertension	Not performed	Discharged home after55-day hospitalization
16	qd (from dayA to dayB) q12h (after dayB)	Not performed	Not performed	Discharged home after 40-day hospitalization
17	qd (from dayB to day12) q12h (after day12)	Not performed	Not performed	Discharged home after 23-day hospitalization
18	qd (after dayA)	Not performed	Not performed	Discharged home after 44-day hospitalization
19	q12h (after dayB)	No pulmonary hypertension	Not performed	Discharged home after 54-day hospitalization

* Days of hospitalization before the discovery of D-dimer value increase than normal range; ** Days of hospitalization before thrombosis were found; *** Thrombosis were found in femoral vein during femoral vein catheterization. DM – diabetes mellitus; PCI – percutaneous coronary intervention; DVT – deep vein thrombosis; ICU – Intensive Care Unit; CTPA – computed tomographic pulmonary.

Several reasons probably explain the high mortality rate. First, older people with complications are more susceptible to COVID-19 infection [23]. The average age of the critically ill and common groups was 65.9 and 48.5 years, respectively. Second, an objective reason was that the medical institutions lacked sufficient medical resources at that time. The critical group had an average of 11.7 days of symptoms at home before admission, which caused the continuous progression of the disease without systematic intervention. Furthermore, not every inpatient could receive invasive mechanical ventilation therapy at the early stage of the COVID-19 pandemic. Third, one main reason was that the critical patients were commonly had multiple complications and organ failure, which predicts a higher risk of poor outcomes. Recent evidence [24,25] indicates that coagulation dysfunction and thrombosis-related diseases, including DVT, PTE, and DIC, were present in the majority of deceased patients. The clinically determined causes of death seemed to correspond to the autopsy results. An autopsy study [26] of 12 deceased patients reported that 33.3% were diagnosed with pulmonary embolism as a direct cause of death, and 58.3% of the patients were confirmed to have DVT. In another autopsy study [27], involving 80 deceased patients, the incidence rates of PTE and DVT complications were 10% and 40%, respectively.

We found that 12 of the 31 (38.7%) critical patients and 7 of the 33 (21.2%) severe patients developed isolated distal deep vein thrombosis (IDDVT). The univariate analysis showed an association between IDDVT and disease severity (odds ratio=3.643 *P*<0.05). IDDVT is a common type that tends to spread out toward the proximal vein and tends to develop into PTE [15]. PTE is a common cause of respiratory failure or sudden death [14]. Unfortunately, IDDVT is easily missed by physicians because of the lack of clinical symptoms. Only 5.3% (1/19) of patients complained of pain or swelling of the lower extremities. Moreover, the COVID-19 pneumonia patients undoubtedly suffered more from dyspnea and fever than from lower limb symptoms. Considering the high rate of thrombosis in hospitalized covid-19 patients [28,29], it is necessary to pay attention to thrombosis during clinical treatment. A timely DVT ultrasound screening in COVID inpatients could be helpful for early diagnosis.

Therefore, it is crucial to use appropriate methods for early judgment of DVT occurrence. The Padua prediction score contains 11 common VTE risk factors, including age over 70 years, overweight, bed rest over 3 days, acute infection and/or rheumatic diseases, respiratory and/or heart failure, acute myocardial infarction and/or ischemic stroke, receiving hormone therapy, history of venous thromboembolism, history of operation or trauma within the past month, active tumors, and has disease with thrombotic tendency. This score can be easily evaluated and applied by clinicians. In addition, the increase in D-dimer level generally reminds us of thrombotic events. Our results showed that 78.9% (15/19) of the patients with DVT had a high Padua score (>4) and a high D-dimer level (≥5 µg/mL). Meanwhile, the 18 dead critical cases exhibited a Padua score increase (>4), and 94.4% (17/18) of them also showed a D-dimer value increase (≥5 µg/mL) before death. Eventually, the univariate analysis confirmed that the 2 factors were positively associated with disease severity. This result indirectly confirms the viewpoint of McFadyen et al. [30], who wrote that the increase in plasma D-dimer levels has emerged as a prognostic marker in COVID-19 pneumonia. D-dimer value is easy to access, and it can be helpful to perform a lower limb venous ultrasound screening subsequently both on asymptomatic and symptomatic patients.

Table 3. Padua score of 18 deceased cases.

Case	Sex (M/F)	Age (years)	D-dimer top-value (ug/mL)	Obesity BMI ≥30 kg/m² (Y/N)	Underlying disease	Bed rest (more than 3 days) (Y/N)	Acute infection and (or) rheumatic disease (Y/N)	Glucocorticoid treatment (Y/N)	Respiratory failure (Y/N)	Others* (Y/N)	The Padua score	Deep vein thrombosis (DVT) (Y/N)
1	M	57	>8	Y	–	Y	Y	Y	Y	N	7	Not performed
2	M	71	>8	N	–	Y	Y	Y	Y	N	7	Not performed
3	M	67	>8	Y	Hypertension; DM	Y	Y	Y	Y	N	7	Not performed
4	F	71	>8	Y	DM	Y	Y	Y	Y	N	8	Y
5	F	70	>8	N	History of pulmonary malignant	Y	Y	Y	Y	N	7	Y
6	M	70	6.2	N	Hypertension; history of PCI; DM; coronary heartdisease	Y	Y	Y	Y	N	7	Not performed
7	M	56	3.97	Y	Hypertension	Y	Y	Y	Y	N	7	Not performed
8	M	61	7.56	N	–	Y	Y	Y	Y	N	6	Not performed
9	M	74	6.79	N	History of prostate cancer	Y	Y	Y	Y	N	7	Not performed
10	M	61	>8	Y	Hypertension	Y	Y	Y	Y	N	7	Y
11	M	69	>8	N	Hypertension	Y	Y	N	Y	N	5	Not performed
12	F	65	5.12	Y	DM	Y	Y	Y	Y	N	7	Not performed
13	M	67	>8	N	Hypertension	Y	Y	Y	N	N	5	Not performed
14	M	55	>8	N	–	Y	Y	Y	Y	N	6	Y
15	F	61	>8	N	–	Y	Y	Y	Y	N	6	Y
16	M	74	>8	N	Hypertension	Y	Y	N	Y	N	6	Not performed
17	F	54	>8	N	DM	Y	Y	N	Y	N	6	Not performed
18	F	68	>8	N	Hypertension; DM	Y	Y	Y	Y	N	6	Not performed

* Including acute infarction, history of venous thromboembolism, thrombophilia and history of operation or trauma within the past month. BMI – body mass index; DM – diabetes mellitus; PCI – percutaneous coronary intervention.

Low-molecular-weight heparin (LMWH) was administered to the patients according to their risk of thrombosis, as evaluated by the Padua score and D-dimer level. We noticed that no further deterioration had occurred and no DVT had developed in patients who had a moderate increase in D-dimer level (1-5 µg/mL) and a high Padua score (>4), receiving prophylactic anticoagulant. Additionally, the disease state was stable in the severe patients treated for DVT with LMWH (**Table 2**, cases 1-7). However, anticoagulation did not result in disease reversal in patients who subsequently died. We think that the

disease progression was not only promoted by the coagulation disorder, but also by the inflammatory storm, acute organ failure, and so on. An early appropriate anticoagulation treatment probably assists in improving the outcome of COVID-19 pneumonia patients with a high Padua score and an elevated D-dimer value. Considering the limited sample size of the present study, the effect of the prophylactic anticoagulant in the critical patients warrants further investigation.

In summary, to improve the outcome of the critical patients with COVID-19 pneumonia, it is helpful to evaluate risk factors for DVT as early as possible. This report highlights the advantage of performing D-dimer and lower-extremity vascular ultrasound screening. It is possible that a D-dimer level-guided positive thrombosis prophylaxis in COVID-19 pneumonia patients, especially in asymptomatic patients, will help decrease the potential for VTE and mortality. Moreover, rehabilitation treatment, graded compression stockings, and intermittent pneumatic compression should be used as soon as possible, especially for the critical and bedridden patients whose Padua scores are high [31]. The present research was a retrospective descriptive study in a single center, and the small sample size might have affected the accuracy of risk factors assessment and the prognosis analysis. A multi-center, prospective study is needed to further clarify the value of early diagnosis and treatment of DVT in critically ill COVID-19 pneumonia patients.

Conclusions

Our report illustrates that critically or severely ill patients have an associated high D-dimer value and high Padua scores, and suggests that a low threshold to screen for DVT may help improve detection of thromboembolism in these groups of patients, especially in asymptomatic patients. Our results suggest that early administration of prophylactic anticoagulant would benefit the prognosis of critical patients with COVID-19 pneumonia and would likely reduce thromboembolic rates.

Data Availability

Data used to support the findings of this study are available from the corresponding author upon request.

Conflict of Interest

The authors declare no conflicts of interest with this study.

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