High prevalence of occult thrombosis in cases of mild/moderate COVID-19

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ABSTRACT

Background and purpose: An increasing number of reports have observed thrombosis in severe cases of COVID-19. The aim of this study was to evaluate the incidence of thromboembolism in mild/moderate cases of COVID-19. All of the patients had normal coagulation tests and none had any overt thrombotic complications. Our findings indicate that it is important to screen the thrombotic status of cases with mild/moderate COVID-19.

Methods: Between 11 June and 8 July 2020, 23 patients with mild/moderate COVID-19 pneumonia consented to having computed tomography pulmonary angiography (CPTA) and computed tomography venography (CTV) scans of the lungs and extremity veins. Doppler ultrasound (DUS) was also performed in all patients for screening. The incidence, clinical manifestations, laboratory examinations, imaging features, and prognosis, of patients with venous thromboembolism (VTE) were analyzed and compared with those of patients with COVID-19 pneumonia without VTE.

Results: Nineteen patients (82.6%) had VTE, mainly distal limb thrombosis. Only one of the VTE patients was positive when screened by DUS; the other VTE patients were negative by DUS. All of the mild/moderate patients with VTE were screened by CTPA + CTV. Blood tests for inflammatory, coagulation, and biochemical, parameters were all within the normal range, except for WBC and LDH.

Conclusions: When using CTV screening for DVT, we found that the incidence of thrombosis in patients with mild/moderate COVID-19 markedly increased to 82.6% (19/23). Screening for thrombosis is therefore important in patients with COVID-19. CTV is more sensitive than DUS for the detection of thrombosis. More research is now needed to evaluate the significance of thrombosis in COVID-19 pneumonia.

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Introduction

As the number of confirmed cases of severe COVID-19 has increased, an increasing number of reports have suggested that thrombotic complications in severe to critical COVID-19 cases may represent an important risk (Helms et al., 2020). An increasing body of evidence, acquired via autopsy or imaging, also supports the existence of thrombo-embolism in severe cases of COVID-19 (James et al., 2020; Maximilian et al., 2020). However, very little is known with regards to the specific characteristics of thromboembolic complications in cases of mild/moderate COVID-19.

Thrombotic complications include pulmonary thromboembolism (PE) and venous thromboembolism (VTE). Most previous reports have focused on PE but have rarely considered venous clots, especially sacral thrombosis (Jean-Marie et al., 2020). Coagulopathy is known to contribute to the severity of COVID-19 infection; this is associated with an excess of venous, arterial, or microvascular-associated events.

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The activated coagulation pathway and endothelial dysfunction are the leading factors associated with the development of thrombosis (Ning et al., 2020). The combination of thrombocytopenia, prolonged prothrombin time, and increased levels of D-dimer, are all known markers of thrombosis (Marcel et al., 2020). The measurement of D-dimer levels in the plasma is emerging as a direct prognostic marker for patientsd with COVID-19. However, most previous reports concerned patients with severe COVID-19. In the present study, we showed that thrombotic complications also occurred in mild to moderately ill patients with COVID-19; most of these patients had normal D-dimer levels and prothrombin time.

Doppler ultrasound (DUS) is the method that is normally used to screen for thrombosis in patients with COVID-19 (Anna Maria, 2020). A previous study, involving patients in the Intensive Care Unit (ICU), reported that the incidence of VTE ranged from 9% to 65% when screened by routine ultrasound (Fatimah et al., 2020). However, another study failed to identify any patients with DVT after undergoing routine lower extremity ultrasound screening (Marco et al., 2020). CT venography (CTV) is another method that can be used to screen for thrombosis. In this study, we compared different screening methods for thrombosis in patients with COVID-19.

Methods

Patients

Consecutive patients with confirmed COVID-19 were enrolled in Beijing Ditan Hospital, the designated hospital for COVID-19 in Beijing. COVID-19 was formally diagnosed according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) (Zhou et al., 2020). This study was approved by the Ethics Committee of Beijing Ditan Hospital (Beijing, China).

We recruited patients with mild and moderate COVID-19 who were diagnosed during their hospital stay; 23 patients were enrolled between 11 June and 8 July 2020. All patients had consented to undergo computed tomography pulmonary angiography (CPTA) and computed tomography venography (CTV) scans of the lungs and extremity veins. Doppler ultrasound (DUS) was also used to screen for thrombosis in the same patients. For each

Table 1
Demographic and clinical characteristics of 23 patients with COVID-19.

Variable	Total (N = 23)	VTE (n = 19)	Non-VTE (n = 4)	P value
Male, n (%)	14 (60.1)	12 (63.2)	2 (50.0)	1.000
Age (years)	42.7 ± 12.0	43.2 ± 12.1	40.8 ± 13.5	0.725
BMI	23.6 ± 2.8	23.3 ± 2.4	25.1 ± 4.4	0.260
Onset of symptoms				
Fever, n (%)	15 (65.2)	12 (63.2)	3 (75.0)	1.000
Cough, n (%)	12 (52.2)	10 (52.6)	2 (50.0)	1.000
Sputum, n(%)	3 (13.0)	3 (15.8)	0 (0.0)	1.000
Fatigue, n (%)	6 (26.1)	5 (26.3)	1 (25.0)	1.000
Dyspnea, n (%)	1 (4.3)	0 (0.0)	1 (25.0)	0.174
Diarrhea, n (%)	5 (21.7)	4 (21.1)	1 (25.0)	1.000
Sore throat, n (%)	4 (17.4)	3 (15.8)	1 (25.0)	1.000
Anosmia, n(%)	4 (17.4)	3 (15.8)	1 (25.0)	1.000
Vital signs				
Temperature (℃)	37.7 ± 0.7	37.7 ± 0.8	37.8 ± 0.8	0.798
Respiratory rate (breaths per min)	19.4 ± 1.0	19.4 ± 1.0	19.0 ± 1.2	0.466
Heart rate (beats per min)	86.4 ± 10.6	84.8 ± 9.6	93.8 ± 13.4	0.128
SBP (mmHg)	125.7 ± 16.7	125.3 ± 17.0	127.5 ± 17.5	0.826
DBP (mmHg)	80.3 ± 10.8	79.7 ± 10.9	83.3 ± 11.2	0.560
Padua prediction score	1 (1, 4)	1 (1, 4)	1	0.794
Hematological and infection-related indices				
White blood cells ($\times 10^9$/L)	6.7 ± 1.7	7.1 ± 1.6	5.1 ± 1.3	0.042
Lymphocytes ($\times 10^9$/L)	2.3 ± 0.7	2.4 ± 0.7	1.8 ± 0.4	0.115
Neutrophil ($\times 10^9$/L)	4.1 ± 1.5	4.4 ± 1.4	2.8 ± 1.1	0.056
Neutrophils/lymphocytes	2.5 ± 1.1	2.5 ± 1.1	2.1	0.458
Platelets ($\times 10^9$/L)	187.3 ± 61.8	182.2 ± 61.0	211.4 ± 68.9	0.404
Hemoglobin (g/L)	134.8 ± 20.0	136.6 ± 18.2	126.5 ± 29.1	0.374
Coagulation function index				
D-dimer (μg/mL)	3.3 ± 13.2	0.5 ± 0.5	0.4 ± 0.3	0.441
PT (seconds)	12.0 ± 0.8	12.0 ± 0.9	12.0 ± 0.6	0.982
APTT (seconds)	35.0 ± 10.7	35.6 ± 11.6	31.8 ± 2.7	0.239
Liver function index				
Aspartate aminotransferase (U/L)	32.5 ± 16.0	32.4 ± 15.7	32.7 ± 20.2	0.981
Alanine aminotransferase (U/L)	43.7 ± 35.8	44.3 ± 37.8	40.9 ± 28.0	0.866
Total bilirubin (μmol/L)	11.0 ± 3.4	10.9 ± 3.3	11.6 ± 4.3	0.703
Direct bilirubin (μmol/L)	3.7 ± 1.3	3.6 ± 1.2	3.9 ± 1.8	0.691
Lactic dehydrogenase (U/L)	241.1 ± 72.0	254.6 ± 71.6	177.1 ± 25.0	0.048
Kidney function index				
Blood urea nitrogen (mmol/L)	5.1 ± 1.0	5.1 ± 1.0	5.0 ± 1.6	0.885
Serum creatinine(μmol/L)	70.6 ± 12.8	70.9 ± 12.9	69.2 ± 14.0	0.821
K+ (mmol/L)	3.2 ± 0.3	3.2 ± 0.3	3.2 ± 0.2	0.953
Na+ (mmol/L)	141.9 ± 1.3	141.9 ± 1.2	141.8 ± 1.8	0.828
CRP (mg/L)	16.2 ± 25.0	14.7 ± 21.2	23.3 ± 42.5	0.465
SAA(mg/L)	63.2 ± 93.1	67.4 ± 98.4	42.8 ± 69.6	0.641
Pneumonia index	136.7 ± 166.6	145.8 ± 174.9	93.5 ± 130.5	0.581

BMI: body mass index; COVID-19: coronavirus disease 2019; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; VTE: venous thromboembolism; PT:Prothrombin time; APTT:Activated partial thromboplastin time; CRP: C-reactive protein; SAA: serum amyloid A.
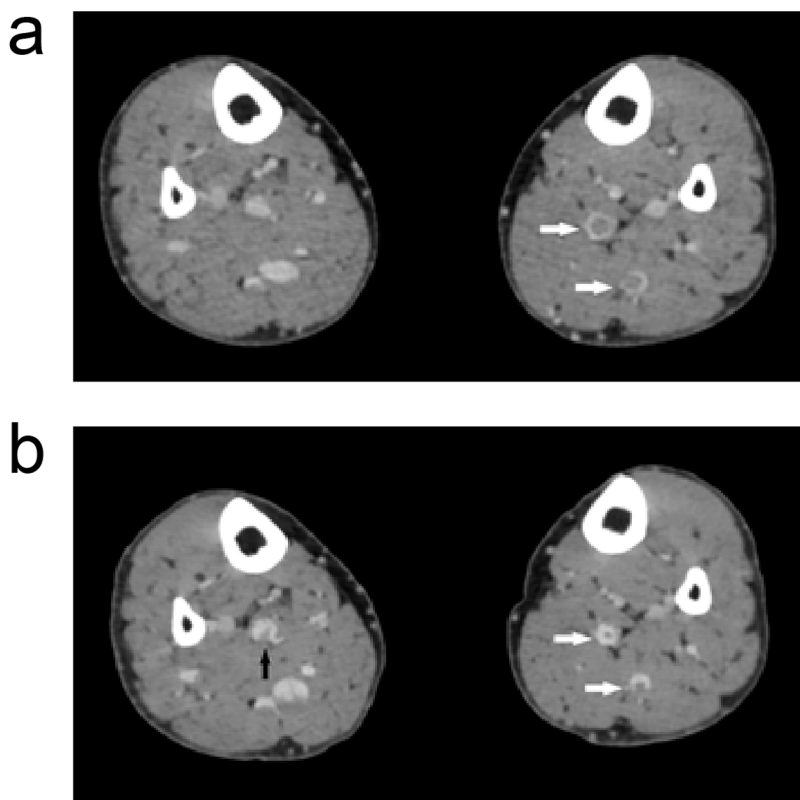
Figure 1. An image of patient 8 before and after LMWH treatment. (a) Before LMWH treatment showing thrombosis in the left plexus venosus leg muscle (arrow). (b) After LMWH treatment. The thrombosis in the left plexus venosus leg muscle (white arrow) had reduced and a thrombosis in the right plexus venosus leg muscle (black arrow) had emerged.

patient, we collated a range of clinical data, including demographic information, comorbidities, symptoms on admission, blood test results, lower limb venous ultrasound Doppler, time between admission and CT scan diagnosis, and patient outcome.

Procedures

CT scans were performed on a 256-slice spiral CT system (Philips, iCT, Netherlands). CT images were independently reviewed by two experienced thoracic radiologists (CBD and XRM). Disagreements were resolved by consensus. The radiologists

assessed both lung and lower veins and were blinded to all clinical data. All images were examined *via* dedicated windows. We also used by artificial intelligence (AI) technology to evaluate inflammation caused by pneumonia.

Statistical analysis

Data are given as mean $\pm$ standard deviation, median (interquartile range), or numbers (percentages), where appropriate. $P < 0.05$ was considered to be statistically significant. Data were analyzed using SPSS 21.0 for Windows (SPSS Inc.).

Table 2
The characteristics of thromboembolism complications.

No.	Sex	Age (year)	Plt	PT	APTT	D-D	Padua	CRP	Pneumonia index	Site of DVT
1	M	37	283	11.2	33.8	0.51	1	0.7	0.7	PTV (L,R); FV (L,R)
2	M	49	273	12.3	83	0.18	1	3.1	139.9	FV (L,R); DFV
3	M	29	298	11.2	31.9	0.11	1	4.1	210.2	ATV (R)
4	M	36	227	11.5	33.8	0.24	1	0.3	3.5	PTV (R,L)
5	M	45	224	10.2	30.1	0.27	1	3.5	3.6	ATV (L,R), PTV (L,R)
6	M	52	208	11.2	32.5	0.19	1	2.9	456.9	ATV (L,R), PTV (L,R), FV (R)
7	F	55	257	12.6	35	0.43	1	3.8	84.3	ATV (L)
8	F	64	166	10.9	30.9	0.12	2	5.2	439.1	ATV (L), PTV (L), FV (L,R)
9	F	34	441	10.4	29.1	0.18	4	1.3	0.4	PTV (L), FV (L,R), DFV
10	M	30	339	11	31.9	0.08	1	6.7	97.49	PTV (L), FV (L,R)
11	F	43	286	10.9	29.7	0.1	1	0.6	6.9	ATV (R)
12	F	65	389	11.7	33.6	0.17	2	53	336.7	ATV (L)
13	F	29	124	13.9	26.8	0.13	1	0.8	90.9	PTV (R)
14	M	58	143	11.5	34.1	0.3	1	9.6	102.3	PV
15	M	36	298	12.3	30	0.35	1	0.8	3.9	Prostatic venous
16	M	39	301	10	30.5	0.14	1	2.8	159.6	ATV (L), FV (R)
17	F	50	314	11.3	34.1	0.31	1	0.5	60.3	ATV (R), PTV (R), FV (R)
18	M	24	252	12.6	32.1	0.36	1	7.7	15.5	PTV (R)
19	M	45	249	12.4	32.4	0.24	1	8.9	557.3	ATV (R), PTV (R)

right: R; left: L; posterior tibial vein: PTV; fibular veins: FV; deep femoral vein: DFV; anterior tibial veins: ATV; popliteal vein: P.

Results

Patient population and clinical characteristics

We recruited 23 patients (14 males and 9 females); each patient had a complete set of clinical information and laboratory data. Table 1 shows the baseline patient characteristics for the VTE and non-VTE groups. The mean age was 42.7 ± 12.0 years. We performed CTPA + CTV all patients 10–14 days after admission.

The initial symptoms of our patient group included fever, cough, fatigue, and other non-specific symptoms. Only three patients had a significant past medical history; one had hypertension, one had pulmonay fibrosis (case 10), and the third

had breast cancer (case 12). All of these conditions were stable at the time of admission.

All 23 patients had pneumonia when they were enrolled, as determined by according to CT scan. Table 1 shows AI scores for pulmonary pathology, as determined from CT characterization data. The mean inflammation value, as determined by AI, was 136.7 ± 166.6.

Thrombotic events and the incidence of such events

In total, 82.6% (19/23) of the patients had deep venous thrombosis (DVT), as determined by radiographic scans; none of these patients had any related symtoms. Padua prediction scores for embolism were normal in all patients. Blood tests for
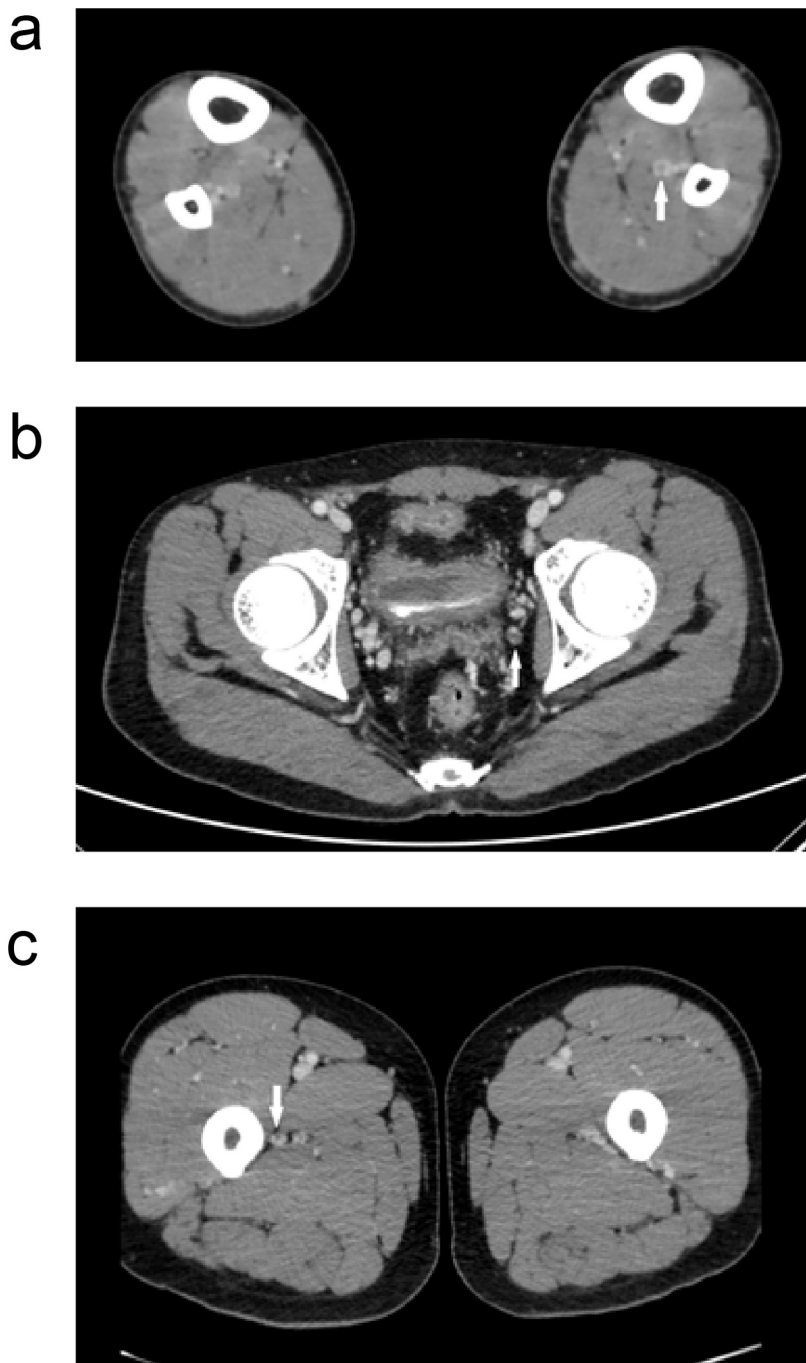
Figure 2. Embolism in different veins. (a) Posterior tibial vein thrombosis (arrow), (b) prostatic venous thrombosis (arrow), and (c) fibular vein thrombosis (arrow).

inflammation, coagulation, and biochemistry, were not statistically significant when compared between the DVT and the non-DVT group, other than plasma LDH and total WBC. Analysis showed that LDH and WBC were significantly higher in VTE group than in the non-VTE group. We also performed univariable and multivariable OR; however, only univariable analysis showed that LDH and WBC were significant risk factors for VTE.

In the radiographically-confirmed VTE patients, only one patient (patient 8) showed VTE when screened by ultrasound; this patient had the most severe VTE of all patients. Patient 8 was a 64 year old female who had a history of pulmonary fibrosis. Her pulmonary fibrosis was mild and she did not require need oxygen support prior to hospitalisation. Following CTPA + CTV, we identified thrombosis in the anterior tibial, posterior tibial, and fibular veins (Figure 1a). Subsequently, she received low molecular weight heparin (LMWH) at therapeutic doses. After two weeks of treatment, we repeated the CTV; her thrombosis had resolved or improved (Figure 1b).

Thrombosis characteristics

We found that the 19 VTEs were distributed in different veins (Table 2). Most cases had a distal DVT (18/19). Onne patient had thrombosis in the prostatic venous plexus and one other patient had a proximal DVT (Figure 2). Other than patient 8, none of the other patients received anti-coagulation treatment.

All of these patients were discharged according to our clinical guidelines. None of the patients became severe or critical. None of the patients developed sequelae related to thrombosis.

Discussion

The most important and simple way to diagnose COVID-19 is by chest CT scan without the administration of contrast agent (Fang et al., 2020). Research has shown that the incidence of PE in patients with COVID-19 ranges from 20.4% to 28% (Julien et al., 2020). However, this data is potentially biased because the number of CTPAs performed is lower in patients with COVID-19.

In the present study, we performed a prospective cross-sectional study and investigated 19 patients with mild to moderate COVID-19 who had experienced thrombotic events. The proportion of patients with VTE, as detected by CT, was as high as 82.6%. We found that radiographic examination resulted in far more thromboembolic diagnoses (19/23) than duplex ultrasound (1/23). None of these patients had any evidence of VTE on routine blood counts or by clinical symptoms or signs. Higher WBC and LDH levels might be associated with thrombosis; these were significantly higher in the VTE group than in the non-VTE group, but only in our univariate analysis. In contrast to severe cases (Fontana et al., 2020), patients with mild/moderate disease in both the VTE and non-VTE groups, showed no specific blood test results that were indicative of infection, immunology, viral load, or coagulation.

Thrombosis is an important part of the clinical picture of in COVID-19 that needs to be taken into consideration. Ultrasound is one of the most common methods used by clinicians to detect thrombosis. Some cases of thrombosis in COVID-19 were detected by CTPA or at autopsy (Barnes et al., 2020; Kosior et al., 2020; Moores et al., 2020; Spyropoulos et al., 2020). Almost all of the existing reports in this field have focused on severe or critically ill patients; very little attention has been paid to those with mild to moderate COVID-19 (Chen et al., 2020).

In the present study, we found that thrombosis was much more common in case of mild disease (82.6%) than in patients with severe disease (49%) (Linnemann et al., 2020). In the current study, we used CTPA + CVT; this increased the sensitivity of clot detection, particularly in the distal veins. None of our patients had any risk

factors for thrombosis in their medical history and their Padua scores were all within the normal range. Although we did not treat most of these patients with anticoagulant therapy, this study highlights the need for us to pay more attention to the risk of thromboembolism in patients with COVID-19. The mechanism involved may be a direct effect of SARS-CoV-2 or some indirect effects related to vascular endothelial cells (Varga et al., 2020). We might speculate that some of this occult thrombosis could be associated with some of the post-COVID-19 syndromes that have been described (Danying et al., 2020). In our report, it is evident that the use of routine tests and clinical evaluations, such as the Padua score (Chen et al., 2020; Demelo-Rodriguez et al., 2020), are associated with certain limitations when sued toevaluate the risk of thrombosis. The accuracy of the diagnosis of thrombosis in CTV is more sensitive than by DUS. Surveillance for thrombosis may therefore be important when evaluating patients with COVID-19 (Hanny et al., 2020; Zadow et al., 2020).

Our study has certain limitations that need to be considered. For example, this is a relatively small, single-center study. We do not have long term follow-up of these cases to determine whether these thromboses were associated with sequelae. Furthermore, this was a cross sectional study. We need to obtain more serial data to evaluate the value of early surveillance for thrombosis in the vessels of patients with COVID-19.

Ethical approval

This study was approved by the Ethics Committee of Beijing Ditan Hospital. Informed consent was obtained from each patient prior to the study.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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