Acute Pulmonary Embolism in Coronavirus Disease 2019

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Abstract

Background Pulmonary embolism is a severe condition prone to misdiagnosis given its nonspecific signs and symptoms. Previous studies on the pneumonia outbreak caused by coronavirus disease 2019 (COVID-19) showed a number of patients with elevated d-dimer, whether those patients combined with pulmonary embolism got our attention.

Methods Data on clinical manifestations, laboratory and radiological findings, treatment, and disease progression of 19 patients with laboratory-confirmed COVID-19 pneumonia,who completed computed tomographic pulmonary angiography (CTPA) during hospitalization in the Central Hospital of Wuhan from January 2 to March 26, 2020, were reviewed.

Results Of the 19 suspected pulmonary embolism and subjected to CTPA patients, six were diagnosed with pulmonary embolism. The Wells' score of the six patients with pulmonary embolism was 0–1, which suggested a low risk of pulmonary embolism. The median level of d-dimers collected at the day before or on the day of CTPA completion in the patients with pulmonary embolism was 18.36 (interquartile range [IQR]: 6.69–61.46) μg/mL, which was much higher than that in the patients without pulmonary embolism (median 9.47 [IQR: 4.22–28.02] μg/mL). Of the 6 patients diagnosed with pulmonary embolism, all patients received anticoagulant therapy, 5 of which survived and were discharged and 1 died.

Conclusion A potential causal relationship exists between COVID-19 infection and pulmonary embolism, but whether this phenomenon is common remains uncertain. The clinical manifestations of COVID-19 patients who developed pulmonary embolism are similar to those of patients with increased d-dimer alone, prompting a significant challenge on differential diagnoses.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a highly infectious type of pneumonia that has reached global pandemic status as declared by the WHO [1, 2]. Recent studies have focused on the clinical characteristics, prognostic risk factors, disease progression, and imaging features of patients with COVID-19 [3, 4]. Common symptoms of COVID-19 include fever, fatigue, dry cough, dyspnea, hemoptysis, chest pain, and diarrhea [5, 6]. Chest computed tomographic scans show bilateral patchy shadows or ground glass opacity in the lungs of all patients [7]. The potential risk factors of older age, high sequential organ failure assessment score, and d-dimer greater than 1 μg/L could help clinicians identify patients with poor prognosis at an early stage [8, 9]. Elevating d-dimer triggered by COVID-19 might shed an important indicator for clinicians to evaluate whether patients need to be screened for pulmonary embolism (PE) [10]. The symptoms of acute PE include chest pain, shortness of breath, palpitations, fainting, and signs of shock and hypotension [11], which are similar to those of COVID-19 infection. Therefore, whether the elevated d-dimers in COVID-19 patients are associated with PE needs to be identified. However, few studies have reported PE in hospitalized COVID-19 patients during the epidemic. In the present case series, we aim to report the clinical manifestations, laboratory findings, treatment, and progression of 19 laboratory-confirmed COVID-19 patients who were suspected to develop PE and underwent computed tomographic pulmonary angiography (CTPA) during hospitalization at the Central Hospital of Wuhan, Wuhan, China.

Methods

Patients

A retrospective case series was conducted on 19 COVID-19 patients with suspected PE for CTPA on the basis of clinical signs and elevated d-dimers in the Central Hospital of Wuhan from January 10 to March 26, 2020. COVID-19 was diagnosed in accordance with the interim guidance of the WHO [11]. Only patients with laboratory-confirmed SARS-CoV-2 infection from throat swab specimens were enrolled. All patients were followed up until discharge or death. The requirement for informed consent was waived due to the urgency to collect data on the emerging SARS-CoV-2. This study was approved by the Ethics Committees of the Central Hospital of Wuhan.

Data Collection

The clinical electronic medical records of 19 patients with SARS-CoV-2 infection

were reviewed by three first-line clinical physicians (Y.G, W.S, and Y.L) and

double-checked by a fourth researcher (Y.Lv.). Demographic, clinical, laboratory,

treatment, and outcome data were extracted using a standardized data collection form modified in accordance with the WHO/International Severe Acute Respiratory and

Emerging Infection Consortium case record forms.

We collected data on clinical records, laboratory findings, chest CT, and CTPA scans. Information on demographic characteristics (gender and age), comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and chronic kidney disease), clinical manifestations, treatment, and outcomes (discharge or death) were extracted from electronic medical records. Laboratory findings, including white blood cell count, neutrophil count, lymphocyte count, hemoglobin, platelet count, C-reactive protein, procalcitonin, blood urea, creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, fibrinogen, d-dimer, lactate dehydrogenase, creatine kinase, and arterial blood gases (lactate and PaO_2/FiO_2 [the ratio of partial pressure of oxygen to fraction of inspired oxygen]), were collected at admission and the day before or on the day of CTPA completion. Acute Physiology and Chronic Health Evaluation II scores (APACHE II), sequential organ failure assessment (SOFA), CURB-65 criteria and Simplified were determined within 24 h after admission. Wells' scores [12] were determined at the day before or on the day of CTPA completion. Data on all treatment measures, including antibiotic, antivirus, glucocorticoid, and intravenous immunoglobulin therapy, anticoagulation therapy, and respiratory support, were acquired during hospitalization. Throat swab samples were collected from all suspected patients, and the laboratory confirmation of SARS-CoV-2 was performed using real-time reverse transcription polymerase chain reaction in accordance with the manufacturer's protocol (Shanghai ZJ Bio-Tech Co., Ltd. Or Xi'an Tianlong Science and Technology Co., Ltd).

Definitions

PE is a form of venous thromboembolism (VTE) in which an embolus (a travelling blood clot) blocks the blood vessels of the pulmonary artery tree, which can ultimately result in sudden death [13]. Acute respiratory distress syndrome (ARDS) was determined by the consensus of two trained physician reviewers using the Berlin definition, that is, the development of acute, bilateral pulmonary infiltrates, and hypoxemia ($PaO2/FiO2 \leq 300$ mm Hg) not primarily due to heart failure or volume overload [14].

Statistical analysis

We summarized continuous variables as medians with interquartile rages (IQR) and categorical variables with n (%). Since our study is a case series study, statistical comparison is not necessary. All analyses were performed by using SPSS, version 20.0.

Results

All 19 patients with significantly elevated d-dimers were suspected with acute PE and subjected to CTPA. The clinical characteristics of all patients stratified by the result of CTPA are presented in Table 1. Six patients were diagnosed with PE by CTPA (Fig. 1). The laboratory findings were collected at the day before or on the day of CTPA completion. The age of the patients was 65 (IQR: 57–70) years, and 12 (63%) of them were male. Eight (42%) patients had chronic hypertension, and none of the patients had underlying diseases, such as diabetes, COPD, or cardiovascular disease. Sixteen (84.2%) patients had different degrees of ARDS at admission. The APACHE II score in the patients with PE was 7 (4–9) and 5 (4–6) for those without PE. The Wells' score of two patients without PE was ≥ 2. The median levels of d-dimers in the patients with PE were 18.36 (IQR: 6.69–61.46) μg/mL, which were much higher than those in the patients without PE (median 9.47 [IQR: 4.22–28.02] μg/mL). The median levels of PaO_2/FiO2 and lactate in the patients with PE were 71.0 (IQR: 58.8–95.3) mmHg and 3.3 (IQR: 2.6–4.1) mmol/L, respectively, whereas those in the patients without PE were 78.5 (IQR: 59.5–113.5) mmHg and 2.2 (IQR: 1.5–2.7) mmol/L, respectively. Among the 19 patients, 16 (84.2%) received preventive anticoagulation treatment when the levels of their d-dimers were dramatically increased. Three patients did not receive anticoagulant treatment because of the risk of bleeding or gastrointestinal bleeding. Finally, 15 (79%) of the patients were discharged, whereas 4 (21%) died.

Table 1
Clinical and laboratory characteristics of COVID-19 patients with pulmonary embolism

	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6
Sex	female	male	male	male	male	female
Age, y	57	65	70	57	80	76
Complications	Hypertension	Hypertension	Hypertension	No	No	Hypertension
Signs and symptoms on admission						
Fever	No	Yes	Yes	No	Yes	Yes
Myalgia	No	No	No	Yes	No	Yes
Fatigue	Yes	Yes	No	Yes	No	Yes
Cough	Yes	No	No	No	Yes	No
Dyspnea	Yes	No	Yes	Yes	No	No
Chest pain	No	No	No	No	No	No
Diarrhea	No	No	No	No	No	Yes
APACHEII	3	4	8	6	11	8
SOFA	3	1	6	3	4	5
CURB65 ≥ 2	No	Yes	Yes	Yes	No	No
Well scores	1	0	1	1	1	0
Laboratory characteristics at admission						
White blood cell count, × 10^9/L	8.2	6.0	9.8	11.8	3.5	5.4
Neutrophil count, × 10^9/L	6.4	2.4	8.7	8.9	3.0	4.2
Hemoglobin, g/L	124	137	146	141	126	141
Platelet count, ×10^9/L	493	115	81	235	105	113
Lymphocyte count, × 10^9/L	1.1	2.9	0.7	1.7	0.4	0.9
C-reactive protein, mg/L	0.9	7.7	5.7	0.8	8.9	5.4

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CURB65: confusion, blood urea, respiratory rate, diastolic BP and age ≥ 65 years; PaO2/FiO2: the ratio of partial pressure of oxygen to fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; CTPA, computed tomographic pulmonary angiography scans.

	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6
Procalcitonin, ng/ml	0.1	0.22	0.16	0.06	0.19	0.04
Alanine aminotransferase, U/L	92.5	50.5	26.8	31.5	33.0	24.2
Aspartate aminotransferase, U/L	51.0	68.7	25.4	35.7	65.1	34.0
Urea, mmol/L	4.8	5.4	13.9	5.6	5.9	4.1
Creatinine, μmol/L	56.3	100.2	89.9	72.6	49.9	52.4
Prothrombin time, sec	11.4	11.8	13.9	12.3	11.1	10.9
Activated partial-thromboplastin time, sec	29.0	41.0	23.2	28.0	34.9	32.4
Fibrinogen, g/L	3.2	2.8	2.0	2.2	3.0	3.1
D-dimer, μg/mL	7.72	0.72	9.36	29	3.61	1
Lactate, mmol/L	3.8	4.9	1.3	2.3	2.3	2.7
PaO2:FIO2, mmHg	192	433	193	253	170	132
ARDS	Yes	NO	Yes	Yes	Yes	Yes
Confirmatory test of SARS-CoV-2	Yes	Yes	Yes	Yes	Yes	Yes
CT evidence of pneumonia	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary scattered in patchy areas of infection	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates
Result of CTPA	Pulmonary embolism in right middle and lower pulmonary artery branches	Multiple pulmonary embolism in the pulmonary artery	Multiple pulmonary embolism in bilateral pulmonary	Multiple pulmonary embolism in bilateral pulmonary	The distal branches of the double lower pulmonary artery are not well filled	Pulmonary embolism in bilateral lower pulmonary artery branches
Treatment						

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CURB65: confusion, blood urea, respiratory rate, diastolic BP and age ≥ 65 years; PaO2/FiO2: the ratio of partial pressure of oxygen to fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; CTPA, computed tomographic pulmonary angiography scans.

	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6
Quinolones	Yes	No	Yes	Yes	Yes	Yes
Cephalosporins	Yes	No	No	No	No	Yes
Ribavirin	Yes	No	Yes	Yes	Yes	Yes
Oseltamivir	No	Yes	No	No	Yes	No
Arbidol	No	No	No	No	No	Yes
Glucocorticoid therapy	Yes	Yes	No	Yes	Yes	No
Intravenous immunoglobulin	No	No	No	No	No	Yes
anticoagulation therapy	Yes	Yes	Yes	Yes	Yes	Yes
Non-invasive ventilation	No	No	Yes	No	Yes	Yes
Clinical outcomes						
Hospital discharge	Yes	Yes	Yes	Yes	Yes	No
Death	No	No	No	No	No	Yes

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CURB65: confusion, blood urea, respiratory rate, diastolic BP and age ≥ 65 years; PaO2/FiO2: the ratio of partial pressure of oxygen to fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; CTPA, computed tomographic pulmonary angiography scans.

The clinical characteristics on admission of six COVID-19 patients who were diagnosed with PE are presented in Table 2. These patients were admitted to the hospital with flu-like symptoms, including fever ($n = 3$), myalgia ($n = 2$), fatigue ($n = 4$), cough ($n = 2$), dyspnea ($n = 3$), and only one presented with diarrhea. All patients had no leg swelling and no pain on calf palpation. Three patients (patients 2, 3, and 5) were screened for venous vessels in the lower extremities, and the presence of venous thrombosis has not been observed. Three of the six patients had lymphopenia (< 1 × 10⁹ cells per L). Four patients had increased d-dimers at admission. The Wells' score of six patients was 0–1, suggesting low risk of PE. The six patients were treated with anticoagulation (low-molecular-weight heparin [LMWH]). Patient 3 stopped anticoagulant treatment because of gastrointestinal bleeding during hospitalization, and LMWH was given after gastrointestinal bleeding stabilized. The changes in d-dimers of the six patients are presented in Fig. 2. During the treatment, the coagulation function of the six patients was within normal range, including prothrombin time, international normalized ratio, prothrombin time activity, fibrinogen, and activated partial thromboplastin time (Fig. 2). After treatment of anticoagulation, the three patients (patients 2, 3, and 4) underwent CTPA again, and the embolism of three PE patients disappeared or significantly relieved (Fig. 3). Patient 6 developed critical COVID-19 pneumonia and died on the 11th day of hospitalization.

Table 2
Characteristics of COVID-19 patients with pulmonary embolism and without pulmonary embolism

	Total (*n* = 19)	**Pulmonary embolism (n = 6)**	**Non-pulmonary embolism (*n* = 13)**
Sex (male)	12 (63.2%)	4 (66.7%)	8 (61.5%)
Age median (IQR), y	65 (57–70)	68 (57–77)	65 (55–70)
Hypertension	8 (42.1%)	4 (66.7%)	4 (30.8%)
Signs and symptoms on admission			
Fever	16 (84.2%)	4 (66.7%)	12 (92.3%)
Myalgia	6 (31.6%)	2 (33.3%)	4 (30.8%)
Fatigue	12 (63.2%)	4 (66.7%)	8 (61.5%)
Cough	12 (63.2%)	2 (33.3%)	10 (76.9%)
Dyspnea	9 (47.4%)	3 (50.0%)	6 (46.2%)
Diarrhea	2 (10.5%)	1 (16.7%)	1 (7.7%)
APACHE II	5 (4–8)	7 (4–9)	5 (4–6)
SOFA	3 (2–4)	4 (3–5)	3 (2–4)
CURB65 ≥ 2	7 (36.8%)	3 (50.0%)	4 (30.8%)
Laboratory characteristics			
PH	7.43 (7.37–7.45)	7.35 (7.33–7.44)	7.44 (7.42–7.46)
PCO_2, mmHg	39.5 (38.0-44.8)	46.0 (37.3–53.8)	38.0 (37.0-42.5)
PO_2, mmHg	73.5 (62.8–92.8)	71.0 (58.8–95.3)	78.5 (59.5-113.5)
SO_2, %	94.5 (90.0-96.7)	93.5 (87.8–96.0)	96.0 (88.5–97.8)
Blood glucose, mmol/L	5.2 (4.4–6.7)	4.4 (3.5–6.3)	5.8 (4.8–9.5)
Lactate, mmol/L	2.6 (1.9–3.3)	3.3 (2.6–4.1)	2.2 (1.5–2.7)
White blood cell count, × 10^9 cells/L	8.9 (6.5–10.8)	9.0 (7.4–12.2)	8.9 (5.1–11.0)
Hemoglobin, g/L	120 (110–141)	132 (109–148)	116 (110–140)
Platelet count, ×10^9 cells/L	247 (172–303)	219 (141–344)	247 (186–316)
HCT, %	36.3 (34.8–39.8)	36.4 (30.8–40.3)	36.3 (35.2–40.5)
Neutrophil count, × 10^9 cells/L	7.2 (5.5–9.3)	7.6 (5.7–10.5)	7.2 (3.6–9.5)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CURB65: confusion, blood urea, respiratory rate, diastolic BP and age ≥ 65 years; ARDS, acute respiratory distress syndrome; IQR, interquartile range; PaO_2, partial pressure of oxygen.

	Total (*n* = 19)	Pulmonary embolism (n = 6)	Non-pulmonary embolism (*n* = 13)
Lymphocyte count, × 10^9 cells/L	0.9 (0.7–1.3)	1.1 (0.3–3.1)	0.8 (0.7–1.2)
C-reactive protein concentration, mg/L	2.6 (0.9–5.3)	2.9 (0.7–7.1)	2.6 (0.8–5.3)
Procalcitonin, ng/ml	0.08 (0.06–0.10)	0.09 (0.08–0.15)	0.06 (0.04–0.09)
Urea, mmol/L	6.3 (4.8–8.1)	7.6 (4.6–9.6)	6.3 (4.9–7.2)
Creatinine, μmol/L	60.8 (54.6–78.9)	58.6 (54.1–76.3)	65.7 (54.7–79.1)
Total bilirubin, μmol/L	15.3 (10.1–27.4)	21.6 (13.0-34.9)	13.8 (9.3–20.1)
Direct bilirubin, μmol/L	4.2 (2.4–5.8)	5.6 (3.3–11.4)	4.1 (2.3–5.5)
Alanine aminotransferase, U/L	36.7 (20.8–64.5)	45.6 (23.5–71.5)	26.0 (16.5–73.6)
Aspartate aminotransferase, U/L	28.3 (21.3–32.5)	26.8 (21.0-35.3)	30.1 (16.3–36.3)
Albumin, g/L	33.0 (29.9–37.0)	31.8 (26.6–37.4)	33.2 (30.5–36.6)
D-dimer, μg/mL	13.7 (4.9–34.1)	18.4 (6.7–61.5)	9.5 (4.2–28.0)
Prothrombin time, sec	12.3 (11.4–12.9)	12.4 (12.1–12.8)	12 (11.3–13.4)
International normalized ratio	1.07 (0.97–1.14)	1.08 (1.05–1.11)	1.02 (0.96–1.19)
Prothrombin time activity, %	86.0 (74.3-100.5)	83.6 (75.7–93.6)	94.3 (69.3-103.5)
Fibrinogen, g/L	2.8 (2.4–3.3)	2.8 (2.2–3.2)	2.8 (2.5–3.8)
Thrombin time, sec	16.6 (15.5–18.0)	16.2 (14.4–18.0)	16.6 (15.7–18.2)
Activated partial thromboplastin time, sec	27.2 (24.5–29.1)	28.5 (25.6–31.5)	26.25 (23.4–28.9)
Lactate dehydrogenase, U/L	322.5 (215.8-435.3)	308.5 (255.5-375.8)	322.5 (195.5-467.3)
Creatine kinase, U/L	55.5 (33.3-169.9)	39.0 (32.5–44.8)	137.3 (41.3-193.9)
Creatine kinase isoenzyme, U/L	10.0 (6.5–16.3)	8.0 (5.3–12.2)	12.2 (7.0-18.5)
Troponin, ng/ml	0.030 (0.003–0.059)	0.048 (0.003–0.329)	0.03 (0.003–0.033)
Anticoagulation therapy	16 (84.2%)	6 (100%)	10 (76.9%)
Clinical outcomes			
Hospital discharge	15 (78.9%)	5 (83.3%)	10 (76.9%)
Death	4 (21.1%)	1 (16.7%)	3 (23.1%)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CURB65: confusion, blood urea, respiratory rate, diastolic BP and age ≥ 65 years; ARDS, acute respiratory distress syndrome; IQR, interquartile range; PaO_2, partial pressure of oxygen.

Discussion

COVID-19 is commonly complicated with significant abnormality of coagulation function [15, 16]. The occurrence of embolic events has aroused the attention of clinicians, such as cerebral infarctions and PE [17, 18]. A case report with a 75-year-old woman hospitalized for COVID-19 proposed a possible precipitant role of SARS-CoV-2 infection in the development of acute venous thrombo-embolism [18]. In our treatment of patients with COVID-19, we found d-dimers elevated in many patients, especially those who developed severe cases, which was similar to previous studies [5, 9]. PE is a form of VTE in which an embolus blocks the blood vessels of the pulmonary artery tree; massive PE is life threatening and can present as cardiogenic shock and cardiac arrest [11, 19]. Survivors of acute PE can develop post-PE syndrome, characterized by dyspnea and exercise intolerance, who had lower quality of life. A negative d-dimer assay allows the physician to safely rule out the diagnosis of PE. However, a positive d-dimer test is not an absolute diagnostic criterion for PE because elevated d-dimers could be observed in other clinical situations (e.g., infection, inflammation, malignancy, postsurgical status, or pregnancy) [20, 21]. Acute infections are associated with a transient increased risk of venous thromboembolic events. In our cases, the clinical characteristics of COVID-19 patients with PE were similar to those of common patients who developed COVID-19 pneumonia, which further complicates the differential diagnosis of COVID-19 from PE. CTPA is the preferred method of diagnosis [22].

In our study, 19 patients completed CTPA, of whom only six patients were diagnosed with PE. This result may be related not only to the limitation of CTPA's evaluation value for pulmonary embolus below the subsegment due to its spatial resolution but also to the characteristics of patients. The levels of d-dimers, PaO2/FiO2, lactate, and APACHE II score were much higher in the patients with PE than in those without PE. These results may provide clinicians some indications when screening patients with elevated d-dimer for CTPA. The clinical application of CTPA is also subject to certain limitations, such as the high cost, contrast agent allergy, renal insufficiency, and pregnancy, and contrast agents may cause renal injury [22]. During the outbreak of SARS-CoV-2, the transfer of patients presents with considerable difficulties and risks. For critically ill patients, bedside ultrasound may be used as an option. Echocardiographic evaluation showed a dilated and hypokinetic right ventricle with an increased mean derived pulmonary arterial pressure, which suggests PE [23].

PE is easy to be neglected in COVID-19 patients with highly elevated d-dimer because of the similar clinical symptoms between PE and severe or critical pneumonia. Especially, in these PEs are not associated with hemodynamic instability (i.e., shock or hypotension). Wells' score is often used to assess the risk of PE [24, 25]. In patients with low, moderate, and high Wells' scores, the incidence rates of PE are 6%, 23%, and 49%, respectively [26]. The Wells' score of the six PE patients in our study was 0–1, suggesting a low risk of PE for these patients. In our study, the six patients had PE but without strong predisposing risk factors for venous thrombo-embolism, such as recent surgery or immobilization, previous history of PE or deep vein thrombosis, hemoptysis, and malignancy. Therefore, the absence of major predisposing factors in those COVID-19 patients with PE seems to confirm the role of COVID-19 infection as a factor for acute PE and the causal relationship.

Parenteral anticoagulation is a common treatment for PE. LMWH carries a low risk of inducing major bleeding and heparin-induced thrombocytopenia and prefers initial anticoagulation in PE [27]. Anticoagulation should be initiated even prior to the confirmed diagnosis when the clinical suspicion of acute PE is high and the bleeding risk is low [28]. Anticoagulant therapy mainly with LMWH is associated with good prognosis in severe COVID-19 patients with markedly elevated D-dimer[16, 29]. In our study, we also recommend prophylactic anticoagulation in the absence of bleeding risk or contraindications.

Limitations

This study has several limitations. First, CTPA and vascular ultrasound of lower limb were purposefully limited during the outbreak of COVID-19 to reduce the risk of cross infection and limited medical resources. Second, this study was conducted at a single-center hospital with limited sample size. A larger cohort study of patients with COVID-19 pneumonia from Wuhan, China, other cities in China, and other countries would help define the relationship between COVID-19 infection and acute PE.

Conclusions

PE is easy to be neglected in COVID-19 patients with highly elevated d-dimer because of the similar clinical symptoms between PE and severe or critical pneumonia. COVID-19 patients with suspected pulmonary embolism with high levels of d-dimers, PaO2/FiO2, lactate, and APACHE II score may have a high possibility to be diagnosed with PE. Aside from d-dimer elevation, pulmonary embolism occurred in COVID-19 patients without other common risk factors for PE, suggesting a potential causal relationship between COVID-19 infection and pulmonary embolism, but whether this phenomenon is common is uncertain. Prophylactic anticoagulation may be considered in the absence of bleeding risk or contraindications in COVID-19 patients with elevated d-dimer.

Abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II scores
COVID-19	Coronavirus disease 2019
CTPA	Computed tomographic pulmonary angiography
LMWH	Low-molecular-weight heparin
PaO2/FiO2	The ratio of partial pressure of oxygen to fraction of inspired oxygen
PE	Pulmonary embolism
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOFA	Sequential organ failure assessment

Declarations

Ethics approval and consent to participate This study was approved by the Ethics Committees of the Central Hospital of Wuhan.

Consent for publication Not applicable

Competing interests : The authors declare that they have no competing interests

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions : Yu, Liu Z, and Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Guo, Sun, Liu Y and Lv Y contributed to the work equally and should be regarded as co–first authors.

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Figures

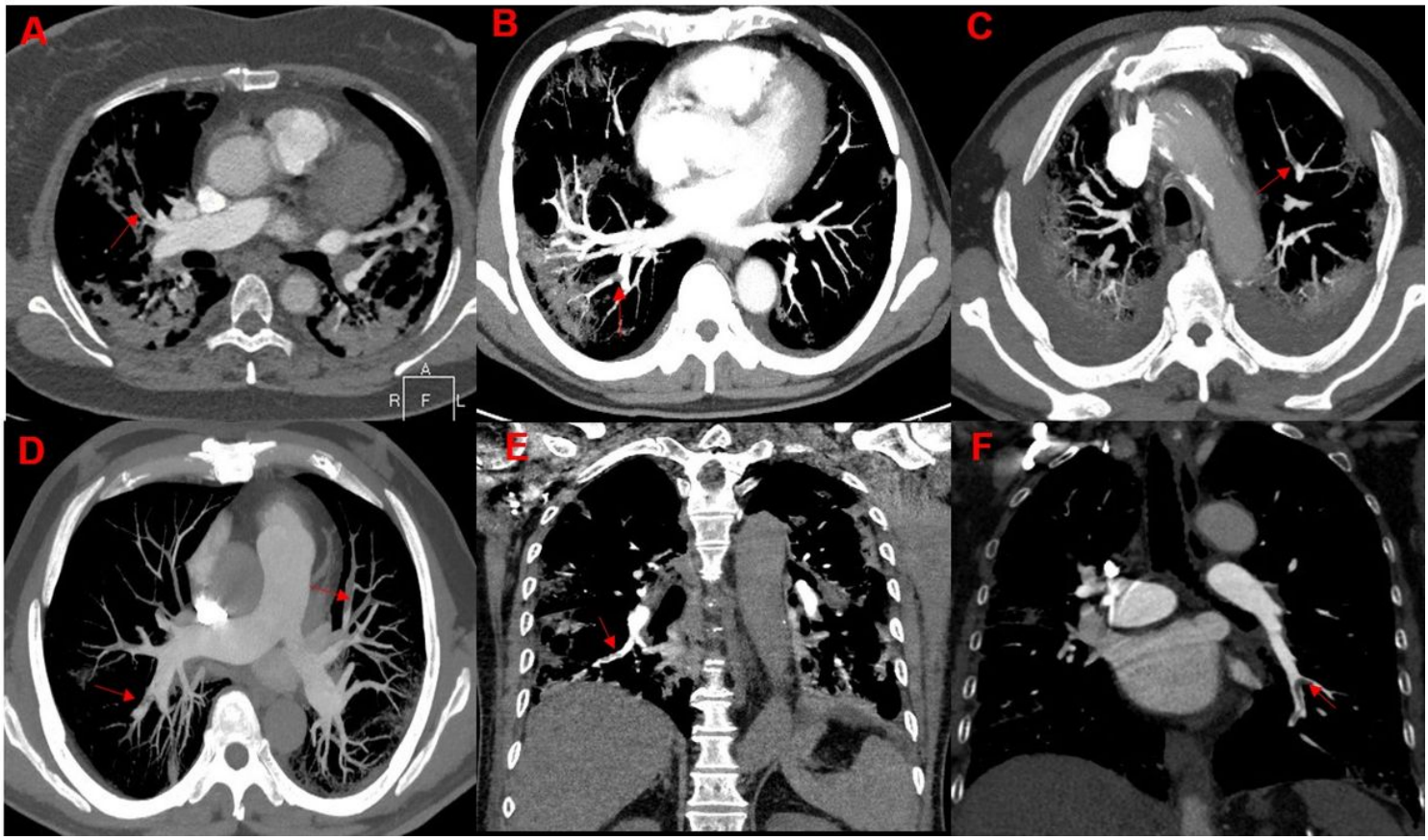

Figure 1

Computed tomographic pulmonary angiography scans (CTPA) of 6 patients with pulmonary embolism A-F was the CTPA scans of patients 1 to patients 6, respectively. The red arrows indicate the location of the pulmonary artery thrombosis.

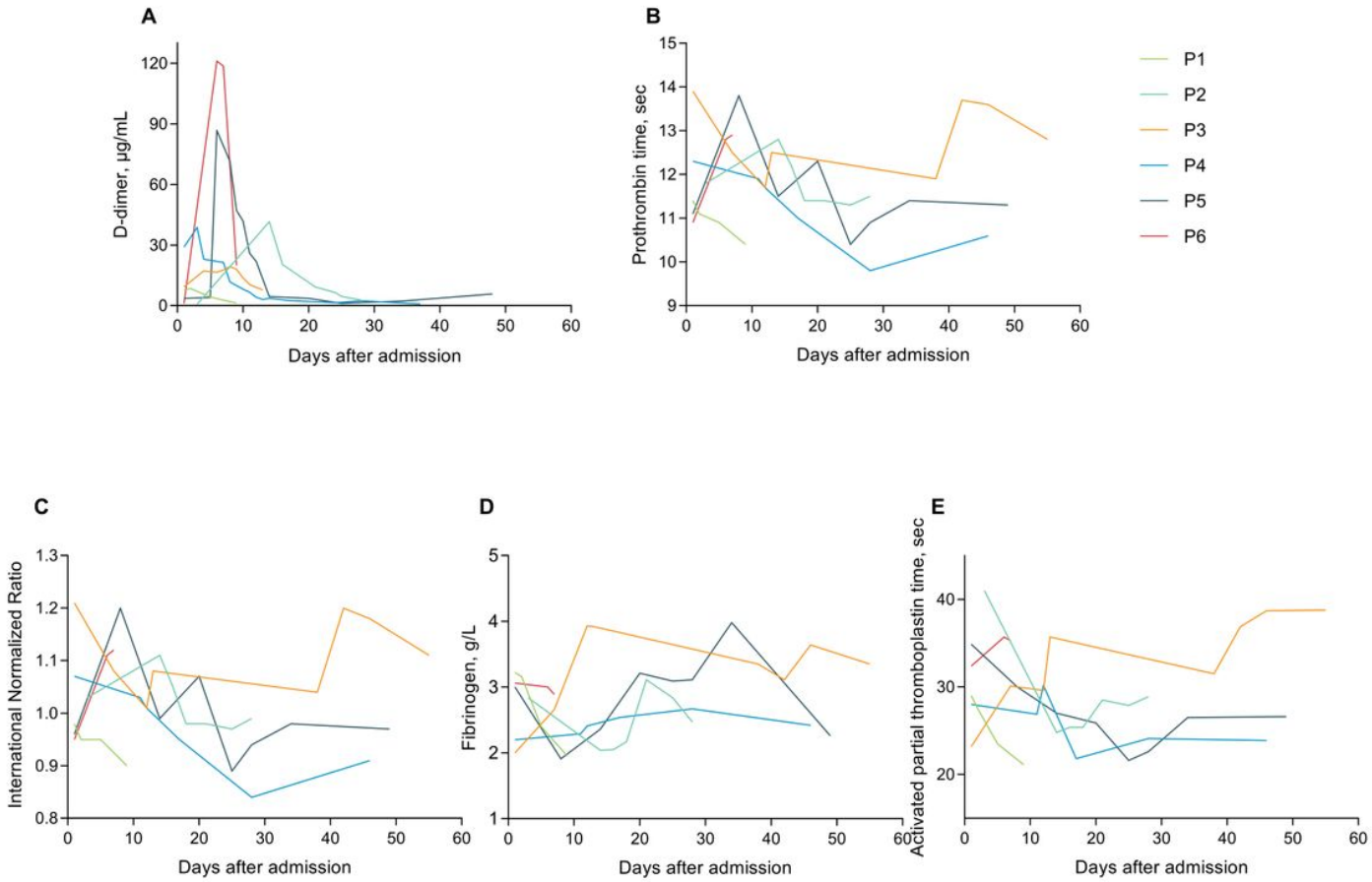

Figure 2

Changes in D-dimer levels and cogulation function in COVID-19 patients with pulmonary embolism during hospitalization. A: the d-dimer of all six pulmonary embolism patients decreased significantly after treatment. B-E: changes of coagulation function in COVID-19 patients with pulmonary embolism, including prothrombin time (PT), international normalized ratio (INR), fibrinogen (FIB) and activated partial thromboplastin time (APTT), respectively.

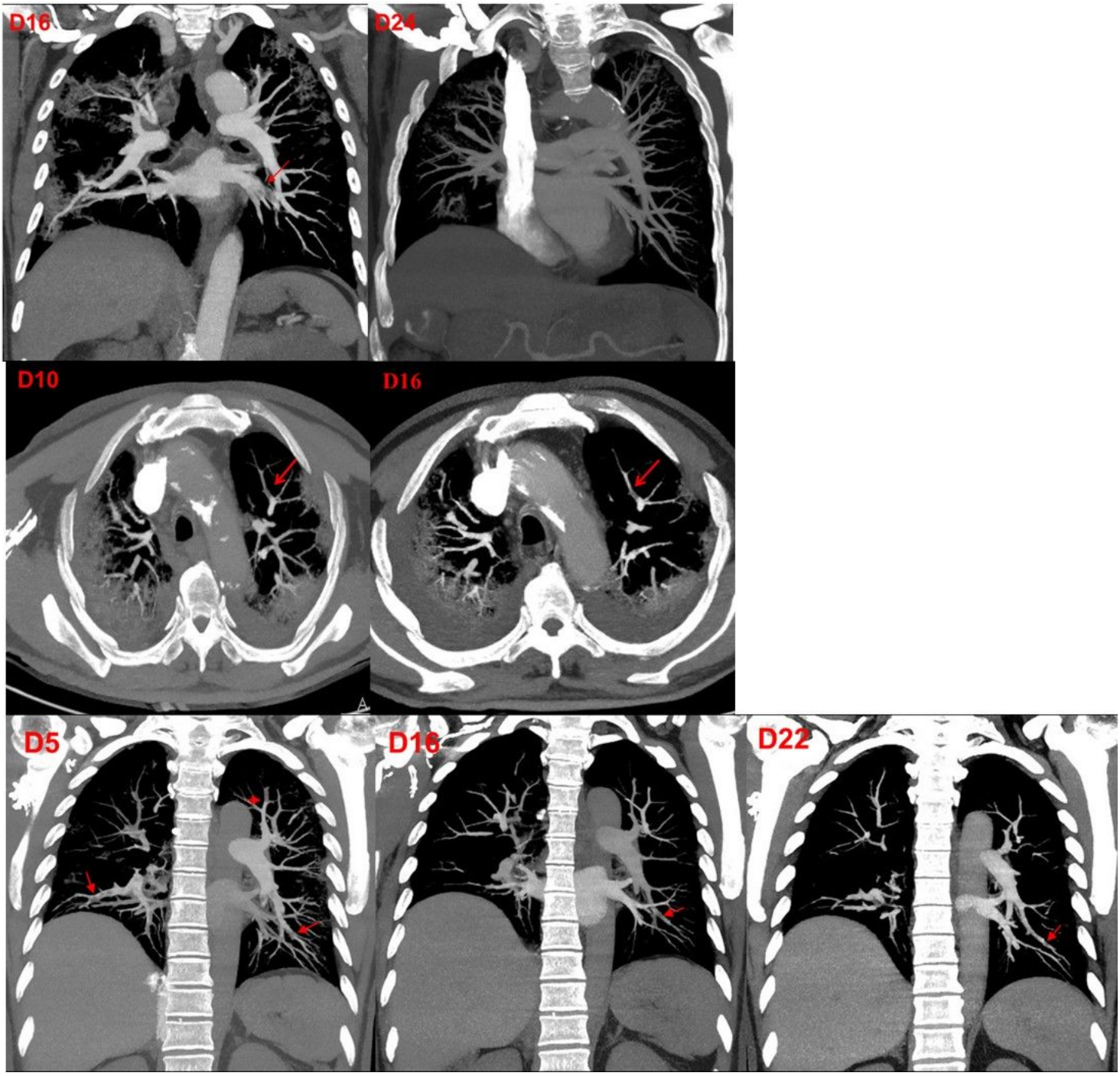

Figure 3

Online Resource 8 (Figure 3) Three of the COVID-19 patients with pulmonary embolism reviewed the CTPA. A-C are the CTPA scans of patient 2, patient 3 and patient 4, respectively. After treatment of anticoagulation, the embolism of patient 2 disappeared, which was reduced in patient 3 and patient 4. The red arrows indicate the location of the pulmonary artery thrombosis.