Original Article

Pulmonary embolism in coronavirus disease 2019: the silent killer

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ABSTRACT

Background: Pulmonary embolism (PE) has been identified as one of the deadliest complications of coronavirus disease 2019 (COVID-19), especially in patients admitted to the intensive care unit (ICU). Western literature reminds us of the high prevalence of PE in COVID. Here, we report a series of 13 cases of PE diagnosed and managed at our hospital.

Methods: Retrospective analysis of medical records of 13 cases of PE admitted at our hospital from February 1, 2020, to September 31, 2020, were done. Their clinical, laboratory, and radiologic data were assessed in detail.

Results: Computed tomography pulmonary arteriography was used to make the diagnosis in eight patients (61.53%), and clinical findings with corroborative ultrasound and laboratory parameters were used to label PE in five patients (38.46%). Five patients were hemodynamically unstable, requiring thrombolysis with recombinant tissue plasminogen activator, and four patients (30.76%) suffered a fatal outcome.

Conclusion: COVID-19 is a highly prothrombotic state, and all physicians should keep a high vigilance for PE. All hospitalized patients with COVID-19, especially those admitted in ICU, should be on prophylactic anticoagulation and, if there is any worsening, should be started...
Coronavirus disease 2019 (COVID-19) has spread like wildfire since the beginning of 2020 and has also made its way into our country, affecting all our lives and proving fatal to quite a few. Declared as a pandemic in March 2020 by World Health Organization (WHO), understanding of the disease has been evolving. COVID-19 is caused by a beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and has a multitude of clinical manifestations. Apart from COVID-19 pneumonia and acute respiratory distress syndrome, thrombotic complication such as pulmonary embolism (PE) has been identified as a prime cause of morbidity and mortality. The gold standard for the detection of PE is computed tomographic pulmonary angiography (CTPA). Incidence of PE ranges from 1.9% to 8.9% in all patients hospitalized with COVID-19 and acute respiratory distress syndrome, and can complicate the stay of up to 50% of patients admitted to intensive care unit (ICU). However, the actual prevalence is much higher, as most patients admitted with COVID-19 generally are not subjected to definitive tests for PE either because of the inability to shift them to a radiology center or because of the lack of availability of these tests. Studies have also shown that prophylactic anticoagulation can lead to decreased mortality rates. Pulmonary thromboembolism is known to occur in patients, despite the standard use of prophylactic anticoagulation in COVID-19. Herein, we present our experience of management of PE in COVID-19 patients who either presented with PE or developed it during their hospital stay. Our literature review could identify many case reports of PE in COVID-19; this is the largest series of PE in COVID-19 to the best of our knowledge from our country.

Material and methods

The study was conducted in our hospital from February 2020 to September 2020. A retrospective review of the medical documents of COVID-19 patients diagnosed with PE during this period was carried out. Approval from institutional ethical committee was obtained before the study.

Demographic profile of each patient was collected from the medical documents. The clinical symptoms, signs, and comorbidities were identified and noted from the medical records. Electrocardiography (ECG) findings were also documented for each patient.

The diagnosis of COVID-19 was made either through a reverse transcriptase polymerase chain reaction or a rapid antigen test performed on a nasopharyngeal or throat swab. The severity of the disease was defined as per the WHO clinical management protocol. PE was diagnosed either clinically or through CTPA, which is considered as the gold standard. Evaluation was initiated on clinical suspicion of PE if a patient had acute onset breathlessness with tachycardia. A clinical diagnosis of PE was established if patient had high probability Wells’ score with corroborating findings suggestive of PE on ECG and echocardiography. Compression ultrasonography (CUS) with Doppler of the lower limb vessels was also performed in patients unfit to undergo CTPA to look for any evidence of deep vein thrombosis. Lack of compressibility using an ultrasound probe of the proximal veins was taken as a sign of deep vein thrombosis, and color flow Doppler was used concurrently to confirm the diagnosis. CTPA was performed using a 256-slice CT scanner (Brilliance ICT, 256 slice; Philips) in those patients who could be shifted to the radiology suite. CTPA was performed using bolus tracking method in caudocranial direction with region of interest placed over the main pulmonary artery. Scanning was performed in inspiration, image acquisition initiated using predetermined threshold (120HU), and intravenous nonionic contrast administered at 4.5 mL/s followed by saline chaser at the same rate. The images were reviewed by both the radiologist and pulmonologist, and they consented on the diagnosis of PE. In bolus tracking method, multiple dynamic images are obtained in the same position after injection of contrast material. When a predetermined threshold was met (e.g., 120 HU in our study), scanning was initiated, typically with a preset delay to allow maximum opacification. Typically, 60–150 mL of intravenous contrast followed by saline chaser ensured adequate contrast material in the lower pulmonary vessels and minimized streak artifact from contrast material in the superior vena cava or brachiocephalic vein.

Bedside plain radiograph of the chest was also performed in all patients. It was used to identify the pulmonary parenchymal opacities, and no comments were made on the pulmonary vasculature or the cardiac shadow because they were taken in anteroposterior projection rather than posteroanterior.

Routine hematological and biochemical tests were carried out on each patient. These consisted of hemoglobin, total leucocyte count, differential leucocyte count, platelets, coagulation profile, renal function tests, liver function tests, and serum electrolytes (sodium and potassium). C-reactive protein (CRP), ferritin, D-dimer, and lactate dehydrogenase (LDH) were also done in every patient. Other laboratory investigations were performed as per the clinical requirements arising out of the management of the disease and its complications.
Results

A total of 1840 patients with COVID-19 were admitted to our center during the study period, of which 300 had moderate to severe disease. A total of 13 patients were identified to have developed clinically significant PE. The demographic characteristics of the patients included in our study have been summarized in Table 1. The mean age of patients who developed PE was 48.58 years (standard deviation of 11.45 years, age range 34–70 years). Only one female, who was also the youngest of our sample population (34 years), was diagnosed with PE. At presentation, severe COVID was observed in seven patients (53.83%), and the remaining six patients (41.6%) had moderate disease.

Comorbidities noted were diabetes mellitus in three patients (23.07%), primary hypertension in two patients (15.38%), obesity in four patients (30.76%), and two patients (15.38%) were found to have bronchial asthma.

The frequency of symptoms has been listed in Table 1. Dyspnea was the predominant symptom in our study population, which was seen in 10 patients (76.90%). Cough and fever were seen in nine patients (69.23%). One patient had hemoptysis, and none presented with expectoration or chest pain. Irritation of throat or sore throat was seen in five patients (38.4%), and nasal congestion or nose block was also a complaint in four patients (30.76%) who developed PE. Other symptoms documented among the sample population were generalized fatigue or malaise seen in eight patients (66.67%) and diarrhea (one patient).

Chest radiograph and CTPA findings have been elaborated in Table 2. CTPA diagnosis of PE was made in eight patients (61.53%). Clinical, CUS, and other supporting tests (ECG and color flow Doppler) were used to identify PE in the remaining five patients as they were unfit to be shifted.

The mean hemoglobin at presentation was 12.54 g/dL. These levels were higher in patients with moderate disease compared with those requiring ventilation.

Radiological diagnosis of PE was made through CTPA in all patients with moderate disease and could be shifted to the radiology suite. Fig. 1 shows the various findings observed on CTPA. In 50% of patients (four patients) who underwent CTPA, subsegmental PE was observed, whereas in the remaining patients (four patients), segmental defect suggestive of PE was seen.

Clinical diagnosis of PE was made in five patients who had progressed to severe disease and had high oxygen requirements warranting noninvasive/invasive ventilation.

Elevated CRP levels were also noticed in these patients, with mean levels of 88.3 mg/L. D-dimer, ferritin, and LDH were also measured, and the mean levels of 6.01 mg/dL, 615 ng/L, and 800 IU/L were noted, respectively. These markers were also comparatively elevated in patients requiring ventilation. Table 3 summarizes all the laboratory parameters in our patient.

Continuous positive pressure ventilation was instituted in seven patients (53.84%), of whom five patients (38.46%) worsened, requiring invasive mechanical ventilation (IMV). Oxygen was the main modality of management in the remaining six patients (46.15%). All patients were also administered therapeutic anticoagulation with alteplase.
Of five patients who required IMV, four patients (30.76%) died.

Discussion

PE has gained importance and popularity in the COVID-19 era, as it is known to be the cause of death in more than one-third of all COVID-19-related deaths.9 The prevalence of any form of thrombosis was found to be 16% in hospitalized COVID-19 patients in a study conducted by Bilaloglu et al,10 and a recent literature review identified a pooled prevalence of PE in COVID-19 to be 15.8%.11 Previous research has linked deranged coagulopathy with increased mortality and is also the likely cause for the increased prevalence of PE.8,12 Apart from this, the prothrombotic state has been attributed to multiple factors such as angiotensin-converting enzyme 2 activation, hypoxia, decreased mobility, and endothelial damage.12–14

Studies also emphasize that a high index of suspicion is to be maintained among COVID-19 patients for PE.5,15,16 In our study, patients suspected to have PE either on clinical or laboratory evaluation were subjected to CTPA. Of a total of 1500 patients treated at our center, 53 patients were subjected to CTPA, of which eight (15%) were identified to have PE. Five patients were given a clinical diagnosis of PE, as they were either hemodynamically unstable or had high oxygen requirement warranting mechanical or nonmechanical ventilation, and shifting them were not possible. In a study conducted by Grillet et al5 to establish the prevalence of PE in COVID-19, CTPA performed on 100 patients of COVID-19 with respiratory failure revealed PE in 23 (23%), of which 15 patients warranted mechanical ventilation.

Comorbidities have been known to complicate the disease. Callender et al had analyzed the impact of comorbidities in COVID-19. Diabetes, primary hypertension, and cardiovascular disease were the most prevalent. However, their effect on the disease per se was not clear in view of their association with each other as well as because of the multiple drugs that each of those patients were on.17 Obesity was the most prevalent, followed by diabetes mellitus and hypertension.

Apart from one patient, all others were male. Studies have also identified males to be having more severe disease and a higher mortality due to exaggerated immune response.18,19 Increased inflammation, in turn, can lead to damage of the pulmonary endothelial cells12 and hence an increased incidence of PE. With our small study population, it is difficult to confirm whether males have a higher predisposition for the

| Patient | D-dimer (mg/ml) | Wells score | Chest X-ray | Mode of diagnosis/if CTPA done, then site of PE | RV/LV ratio | ECG       |
|---------|----------------|-------------|-------------|-----------------------------------------------|-------------|-----------|
| 1       | 2.12           | 6           | Multifocal peripheral opacities, predominantly in upper lobes, mild (left) pleural effusion | Segmental PE both upper lobes (left > right) | 0.7         | Sinus tachycardia |
| 2       | 3.20           | 7.5         | Multifocal peripheral consolidation (basal > apical) | Segmental PE right lower lobe and left upper lobe | 0.7         | Sinus tachycardia |
| 3       | 0.29           | 6           | Minimal ground glass opacities and consolidation in subpleural region of both lower lobes (basal region) | Segmental PE in both upper lobe and right middle lobe | 0.5         | Sinus tachycardia |
| 4       | 0.51           | 6           | Minimal subsegmental peripheral ground glass opacities in left upper lobe | Subsegmental PE in both lower lobes | 0.8         | NSR       |
| 5       | 2.08           | 6           | Widespread multifocal consolidation in all lobes of both lungs, more in lower lobes | Subsegmental PE in both upper lobes, right middle lobe, and right lower lobe | 0.6         | Sinus tachycardia |
| 6       | 0.37           | 6           | Minimal ground glass opacities peripherally in both lower lobes | Subsegmental PE in the right lower and upper lobe | 0.6         | NSR       |
| 7       | 4.1            | 6           | Bilateral nonhomogenous air opacities in middle and lower zones | Clinical diagnosis | S1Q3T3, RA, RV strain |
| 8       | 7.00           | 6           | Bilateral nonhomogenous air opacities in middle and lower zones | Clinical diagnosis | S1Q3T3, RA, RV strain |
| 9       | 13.59          | 9           | Bilateral nonhomogenous air opacities in middle and lower zones | Clinical diagnosis | Sinus tachycardia RA, RV strain |
| 10      | >20            | 7           | Multifocal peripheral atelectasis all lobes, more in basal segments | Segmental PE left lower lobe | 0.7         | Sinus tachycardia |
| 11      | 1.45           | 10          | Bilateral nonhomogenous air opacities in middle and lower zones | Clinical diagnosis | Sinus tachycardia RA, RV strain |
| 12      | 6.01           | 6           | Bilateral nonhomogenous air opacities in middle and lower zones | Clinical diagnosis | S1Q3T3, RA, RV strain |
| 13      | 1.51           | 6           | Predominantly peripheral multifocal ground glass opacities and basal region consolidation | Subsegmental PE in both upper and lower lobes | 0.9         | Sinus tachycardia |

CTPA, computed tomographic pulmonary angiography; ECG, electrocardiography; LV, left ventricle; PE, pulmonary embolism; RA, right atrium; RV, right ventricle.
development of PE, and more studies are required to validate this finding.

The clinical manifestation of PE varies from no symptoms to shock. Dyspnea was the predominant symptom among our study population, followed by cough and fever. One of our patients also presented only with hemoptyysis. These symptoms, however, are not specific to PE, and all physicians should keep a differential diagnosis of PE in such patients and should carry out extensive evaluation to rule out PE, as has been mentioned by Chen et al.

### Table 3 – Laboratory features.

| Patient | C-reactive protein (mg/L) | Ferritin (ng/L) | LDH (IU/L) | Hemoglobin (gm/dL) | Total leucocyte count (cells/μL) | Neutrophil/lymphocyte | Platelets (cells/μL) | PT (sec) | PTTK (sec) | INR | Urea (mg/dL) | Creatinine (mg/dL) | Na/K (mEq/L) |
|---------|------------------------|----------------|----------|-------------------|-------------------------------|---------------------|---------------------|---------|-----------|-----|--------------|------------------|-------------|
| 1       | Positive               | 352            | 438      | 11.3              | 11,500                        | 91/05               | 330,000             | 13.8    | 25.4      | 0.98| 56          | 0.8               | 143/3.8     |
| 2       | Negative               | 196            | 256      | 16.1              | 6600                          | 85/13               | 163,000             | 13.7    | 31.1      | 0.96| 29          | 0.9               | 135/4.9     |
| 3       | Positive               | 216            | 250      | 15.3              | 3500                          | 46/42               | 152,000             | 20.1    | 36.8      | 1.45| 36          | 1.4               | 139/5.3     |
| 4       | Positive               | 207.6          | 307      | 14.9              | 6100                          | 55/23               | 256,000             | 16.1    | 33        | 1.18| 25          | 0.8               | 137/4.4     |
| 5       | Positive               | 416            | 515      | 12.1              | 6500                          | 80/10               | 377,000             | 14.7    | 35.1      | 1.05| 52          | 1.1               | 137/4.5     |
| 6       | Positive               | 356            | 342      | 11.3              | 3200                          | 69/25               | 270,000             | 13.1    | 32.4      | 0.93| 31          | 0.94              | 146/4.2     |
| 7       | Positive               | 402            | 365      | 9.8               | 15,800                        | 88/06               | 301,000             | 23.9    | 44        | 1.25| 96          | 1.5               | 157/4.0     |
| 8       | Positive               | 515            | 1074     | 10.2              | 8700                          | 84/10               | 319,000             | 16.2    | 32.8      | 1.16| 104         | 1.2               | 139/4.8     |
| 9       | Positive               | 421            | 646      | 12.7              | 6100                          | 91/05               | 220,000             | 17      | 35.8      | 1.22| 75          | 1.1               | 151/3.6     |
| 10      | Positive               | 748            | 1045     | 13.3              | 4400                          | 70/18               | 167,000             | 16      | 37.6      | 1.15| 52          | 0.8               | 139/4.9     |
| 11      | Positive               | 182            | 159      | 13.2              | 9900                          | 64/26               | 199,000             | 16.1    | 31.5      | 1.16| 28          | 1                 | 139/4.0     |
| 12      | Positive               | 615            | 800      | 10.3              | 5300                          | 87/07               | 253,000             | 15.1    | 32        | 1.08| 18          | 0.6               | 139/4.7     |
| 13      | Positive               | 457            | 538      | 13.4              | 9300                          | 80/09               | 250,000             | 14.1    | 39.4      | 1.01| 44          | 0.8               | 138/4.5     |

INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTTK, partial thromboplastin time with kaolin.
CTPA is the gold standard for the diagnosis of PE. If there is a history of contrast allergy or renal dysfunction or any other contraindication for CTPA, then ventilation–perfusion (V/Q) scan is indicated. Of all the patients who were fit to undergo CTPA in our study, four each had segmental and subsegmental PE. Central PE was not seen in any of the individuals; however, the patients who had a clinical diagnosis in view of their hypotension and concomitant severe pneumonia were likely to have central PE. This was also suggested by the bedside two-dimensional echo study, which revealed right heart strain in all patients who could not undergo CTPA.

Laboratory profile has been elaborated in Table 3. Lymphopenia was observed in two of our patients, and thrombocytopenia, which was seen in more than 50% of patients with severe disease, was not seen in any of our patients. D-dimer levels were low in four patients, and all had moderate disease and was managed with oxygen only. Except for two patients with a high D-dimer value who had moderate disease, the rest all required noninvasive ventilation, with five progressing to IMV. D-dimer levels have been corroborated with disease severity in a previous study by Yao et al, and the same was found in our cohort of patients. CRP, ferritin, and LDH were also raised in most patients, indicating a proinflammatory state.

Except for one, all patients were on low molecular weight heparin, three being on prophylactic and nine on therapeutic doses. All patients with PE had oxygen requirement, with nine requiring management in critical care unit. Of these nine patients, a 39-year-old male was diagnosed with PE on admission and was also thrombolysed with recombinant tissue plasminogen activator (Alteplase). Including this patient, a total of five patients had refractory hypoxia along with hemodynamic instability and had to be thrombolysed. Fatal outcome was seen in four patients (30.76%), which was much higher than what was seen in other studies, as most patients in our study cohort (53%) suffered from severe disease.

All patients at the time of discharge were switched to novel oral anticoagulants and were advised to continue the same for a minimum period of 6 months. The actual duration of anticoagulation required after COVID-19 is a subject, which requires more research. None of the patients required domiciliary oxygen at the time of discharge.

One of the major limitations of our study was the small sample size. Also, some patients could not be followed up, as most were hesitant on reporting back to the hospital in view of the increasing number of COVID-19 patients in our country. As these patients were mostly managed in ICU, witnessing multiple deaths around them could also have contributed to the same.

Conclusion

PE has proven itself as one of the deadliest complications of COVID-19. Our study shows that when COVID-19 is complicated with pulmonary embolism, it is associated with high mortality. Every physician should keep an increased vigilance for PE to enable early detection and to prevent its development. It is also to be emphasized that all suspected patients should be subjected to CTPA, and if not possible, all other investigations should be carried out to exclude the diagnosis. In addition, all proven cases should be continued on oral anticoagulants for at least 6 months as per the latest European Society of Cardiology guidelines.

Disclosure of competing interest

All authors have none to declare.

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