Original Article

Correlation between Pulmonary Thromboembolic Complications Detected by CT Pulmonary Angiography in COVID-19 Pneumonia Patients with Clinical, D-dimer Level, CTSI Score and its Prognostic Implication- A Retrospective Study

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ABSTRACT

Introduction: Pulmonary thrombosis is one of the known complications of COVID-19 infection. We aimed to assess the incidence of PE in patients with COVID-19 infection and to evaluate the relationship between the CT severity of the disease and the laboratory parameters with the incidence of PE. We also evaluate effect of PE in patients survival. This was a retrospective study conducted on 130 patients with COVID-19 pneumonia infection proved positive by RT- PCR test who underwent CT Pulmonary angiography (CTPA) with a calculation of the CT severity of COVID-19 infection. Available patient's complaint and laboratory data at the time of CTPA were correlated with presence of PE and outcome of the patients diagnosed with PE during hospital stay.

Methods: CTPA was performed on 128 slice PHILIPS CT Scanner machine on 130 patients from DECEMBER 2020 to APRIL 2021 in our SVP Hospital, NHLMMC, Ahmedabad. No age and gender bias were followed.

Results: 45 patients (34%) showed positive PE with the median time for the incidence of PE which was 12 days after onset of the disease. No significant correlation was found between the incidence of PE and the patients' age, sex and inflammatory markers. A statistically significant correlation was found between the incidence of PE and clinical findings including progressive dyspnoea and haemoptysis. Incidence of pulmonary thrombo-embolism increased with rising D-dimer level as well as the moderate to severe CTSI score. There was significant improvement in the patients who were detected early with thrombosis, received early treatment and showed increased rate of survival.

Conclusion: Increased CTSI and the rising in D-dimer level are considered the most important parameters suggesting underlying PE in patients with positive COVID-19 infection which is commonly seen during the second week of infection and mandate the use of CT pulmonary angiography to exclude or confirm PE. This may help in improving the management of COVID-19 infection and increased survival of the patients.

Key words: CT pulmonary angiography (CTPA), Pulmonary Embolism (PE), D-dimer, CRP, CBC, COVID-19.

INTRODUCTION

The corona virus infection outbreak initially began in December 2019, in Wuhan, Capital of China has rapidly emerged as a global health crisis. The outbreak of COVID-19 started in India in MARCH -2019. The current coronavirus pandemic caused by SARSCoV2 has rapidly emerged as a global health crisis. Symptoms range from asymptomatic or mild constitutional symptoms to pneumonia, sepsis and sometimes severe acute respiratory distress syndrome (ARDS) necessitating hospitalization and intensive care unit (ICU) admission.[1] The pivotal role of thrombo-inflammation and endothelial injury in the pathogenesis of the disease is being increasingly recognized. Overproduction of pro-inflammatory cytokines, including tumour necrosis factor (TNF), Interleukin (IL) -6, IL-8, and IL-1β, are believed to be the cause of what is being termed, "cytokine release syndrome" or "cytokine storm", a phenomenon which is however not unique to this disease and has been noted in sepsis and sterile inflammation as well. This exaggerated cytokine response may lead to multiorgan failure and eventually death in some patients.[2] In addition to elevations in pro-inflammatory markers, hypercoagulability has been identified to be playing a key role determining prognosis in patients with COVID-19.[3] In some observational series, thrombotic complications have been noted to be as high as 31% in patients requiring ICU admission and the risk persists even in patients on anticoagulation.[4-7]

Pathogenesis and risk factors

COVID-19 shares multiple similarities with other well defined inflammatory states such as sepsis and sterile inflammation wherein simultaneous rise in pro and anti-inflammatory cytokines are seen.[8,9] Moreover, there is evidence of complement activation in COVID-19 by direct endothelial injury which includes release of anaphylatoxin C5a.[10] Complement activation as seen in COVID-19 not only drives neutrophil dysfunction leading to susceptibility to secondary infections but also activates the coagulation system thereby propagating a prothrombotic state.

Coagulopathy associated with COVID-19 may be explained by the 'two-way activation' theory, as seen by thrombocytopenia in critically ill patients (TICP) and the encompassing inflammatory and micro-thrombogenic responses that occur when endothelial insult takes place.[11] While the inflammatory pathway releases cytokines, the activation of micro thrombotic pathway is mediated by the release of large polymers of Von Willebrand factors (VWF). Due to sepsis- induced endothelial injury, this reaction is aggravated, causing enhanced platelet activation and consumption thrombocytopenia.[12] Therefore, it seems that in keeping with Virchow's triad, thrombosis is driven both by the activation of coagulation factors and endothelium.

In addition to the factors mentioned above, these patients have additional risk factors for increased thrombosis, most among those being hypoxia, comorbidities and immobility (made worse by frequent use of prone positioning).[13-15]

The patients of COVID-19 pneumonia revealed diffuse alveolar oedema, thrombosis, formation of hyaline membrane resembling an ARDS like pattern.[15-17] The term MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) secondary to micro vascular pulmonary thrombosis has been termed to describe the pulmonary manifestations of the disease.[18] Various studies reported a wide range of thromboembolic complications including venous (PE, DVT) as well arterial thrombosis. Micro thrombosis in lungs noted as high as 80% in autopsy of fatal COVID -19.[19]

METHODS

All patients with COVID-19 infection proved positive by RT-PCR who underwent CT pulmonary angiography. No age or sex predilection. Patients with available complaints and laboratory data at the time of CTPA scanning. We excluded patients with unavailable RT- PCR results, as well as patients with no data about the clinical condition and unavailable laboratory results.

CTPA was performed on 128 slice PHILIPS CT Scanner machine on 130 patients from DECEMBER 2020 to APRIL 2021 in our SVP Hospital, NHLMMC, Ahmedabad. This was a retrospective study conducted on 130 patients with COVID-19 pneumonia infection proved positive by RT- PCR test who underwent CT Pulmonary angiography (CTPA) with a calculation of the CT severity of COVID-19 infection.

CT technique

Patients' preparation: Patients were required to fast for 4 h, and normal kidney function was needed using serum creatinine as a reference. Adequate hydration was instructed before and after the procedure. An 18–20-gauge cannula was inserted into the antecubital vein.

CT machine: 128 Slice CT machine (Phillips Ingenuity 128 CT Scanner).

The patients were scanned in a supine position with the arm above the head. A breath-hold was requested from the patients trying to avoid respiratory motion artifact. A region over interest was drawn on the main pulmonary artery. Bolus IV injection of iodinated nonionic contrast medium (Omnipaque) 1.2 ml/kg was used at rate 5 ml/s using injector pump followed by 40 ml saline at rate 4 ml/s.

CT parameters: The scan area extended from diaphragm to lung apex with scan time used = 10 s. The tube voltage was 120 KVP and tube current: 160 MAs. Rotation time was 0.4 s, 5 mm slice thickness, 0.7 reconstruction increment (mm) and 1.4 Pitch.

Image processing and interpretation: The images were transferred to the workstation where the axial cuts and multi-planar reformation were reviewed by two radiologists.They were blinded to the aim of the study and the clinical condition of the patients or the laboratory results.

The following items were fulfilled:

- Presence or absence of pulmonary embolism. If positive pulmonary embolism, site if unilateral or bilateral and extent if segmental, lobar, or main arterial.
- CT probability of COVD-19 infection according to RSNA recommendations.[7]
- CT severity score for COVID-19 infection: The lung was divided into five lobes and was visually scored on a scale of 0 to 5. Score 0 : if no CT evidence of pulmonary involvement; score 1 if the pulmonary involvement was less than 5%; score 2 if 5–25%; score 3 if 26–49%; score 4 if 50–75%; and score 5 if more than 75%. The highest total CT score was 25.

The patients were divided according to the CTPA results into two groups: a group with positive PE and a group with negative PE.

The clinical and laboratory data included the following: The timing of the CTPA after the onset of the symptoms, the main complaint at the time of CTPA scanning, The laboratory results including the WBC count, D-dimer , ferritin and CRP levels. All laboratory results included must be within 24 h from the time of CTPA.

RESULTS

The study included hospitalized 130 patients proved by RT-PCR to have COVID-19 infection. 45 patients representing 34 % of the patients showed positive PE. The mean age of the patients was 61.5±15 years with age range 21-88. 100 patients were males while the rest 30 patients were female.

Out of 100 patients, 39 (87%) male patients were positive for pulmonary thromboembolism, while 6(13%) females were positive for pulmonary thromboembolism.

The main complaint at the time of CTPA was progressive dyspnoea detected in 115 patients (88.4%) which shows a significant relationship with the incidence of PE. However, haemoptysis showed a statistically significant relationship with the incidence of PE being significantly higher between patients with positive PE (Table 1)

Regarding the laboratory data, patients with positive PE showed higher D-dimer and CRP levels. However, no significant relation was found between the level of the ferritin, CRP, WBC count and the incidence of PE (Table 1). However, incidence of PE increased with rising in the D-dimer level with a sensitivity of 91 %. (Table 1)

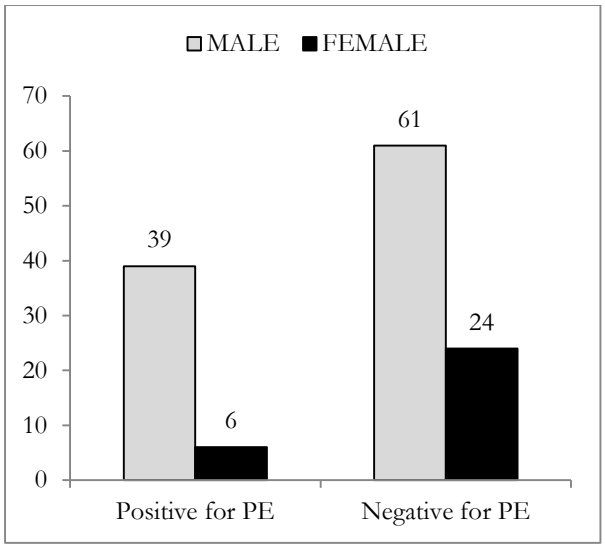

Figure 1: Positivity for Pulmonary Embolism

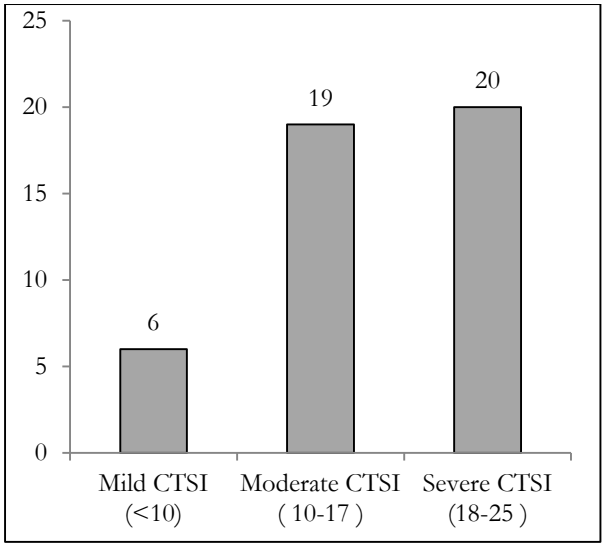

Figure 2: Relationship between positive pulmonary embolism and CT severity index

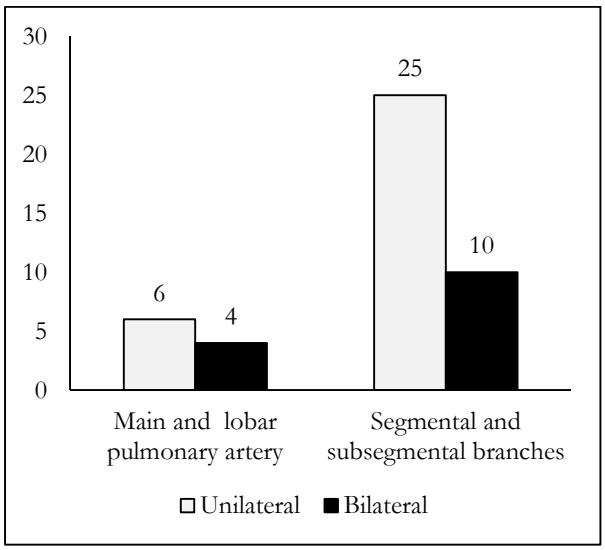

Figure 3: Extent of pulmonary embolism

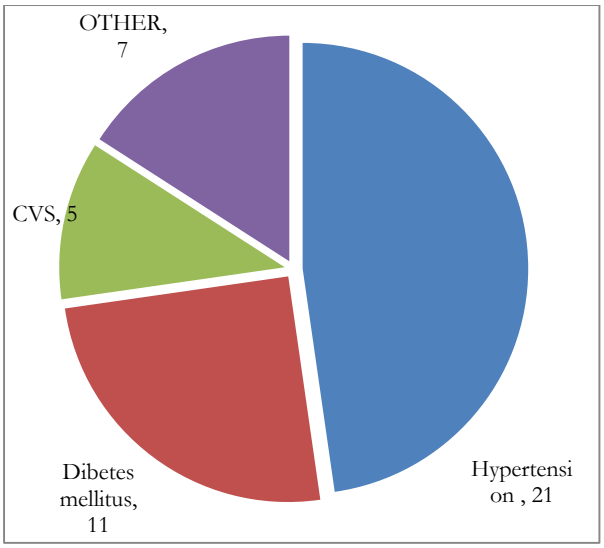

Figure 4: Incidence of pulmonary embolism with comorbidities

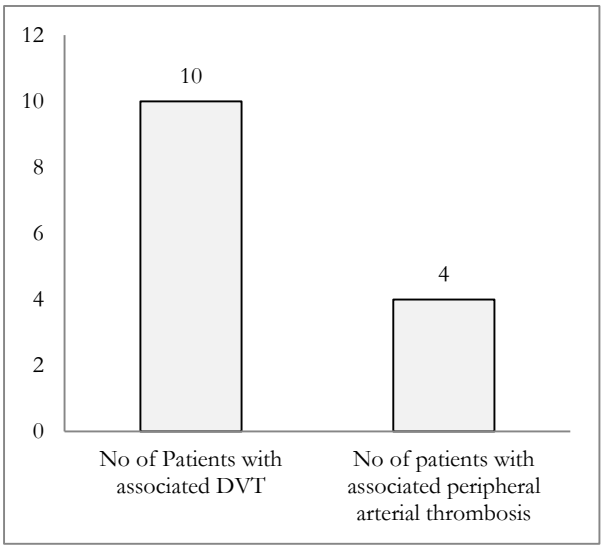

Figure 5: No of patients positive for thrombus on CTPA with associated peripheral thrombotic complication

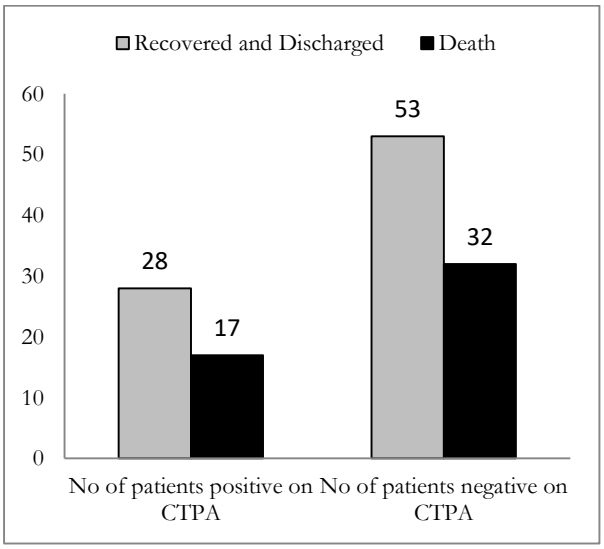

Figure 6: Overall outcome of COVID 19 patients undergoing CTPA

Table 1: Illustrate the relationship between main complainants at the time of the CTPA, inflammatory marker levels and care status of the patients

Characteristics	CT pulmonary angiography		Total	P Value
	Negative	Positive		
The main complaints at the time of CTPA				
Desaturation	45 (52.9%)	30 (66.6 %)	75 (57.6%)	0.63
Haemoptysis	5 (5.8%)	10 (22.2%)	15 (11.5%)	0.017
Progressive dyspnoea	80 (94.1%)	35 (77.7%)	115 (88.4%)	0.041
Tachycardia	17 (20%)	8 (17.7%)	25 (19.2%)	0.54
Chest pain	40 (47.5%)	30 (66.6%)	70 (53.8%)	0.30
Laboratory Parameters				
D-Dimer Level	67 (78.8%)	41(91.1%)	108 (88.3%)	0.25
CRP	74 (87.1%)	36 (80 %)	110 (84.6%)	0.84
WBC	68 (80%)	32 (71.1 %)	100 (76.9%)	0.71
Ferritin	75 (88.2%)	34 (75.5 %)	109 (83.8%)	0.55
Care Status				
Conventional	58 (68.2%)	26 (57.7%)	84 (64.6%)	0.23
Critical	27 (31.7%)	19 (42.2 %)	46 (35.3%)	

A p value of <0.05 is considered significant.

Regarding the CT, the median time for CTPA was 9 days for patients with negative PE and 12 days for patients with positive PE with no significant relationship found between the timing of CTPA and incidence of PE.

Figure 2 suggests most patients with positive pulmonary embolism show moderate to severe CT severity index.

In patients with positive PE according to CTPA Thirty-one Patients representing 68.8 % showed unilateral PE while the remaining 14 (31.3%) of the patients showed bilateral PE. Also, 35 patients (77.7%) showed PE involving the segmental and subsegmental branches while the rest 10 (22%) showed main and lobar branches involvement. Positive RV strain was noted only in 2 cases.

There is evidence of higher incidence of pulmonary embolism in patients with comorbidities specially hypertension in 21 patients (47%).

Out of 45, in 37 patients we have performed peripheral arterial and venous doppler, deep vein thrombosis is seen in 10 patients while 4 peripheral arterial thrombosis was seen in 4 patients, so, in a patients with pulmonary thrombosis there is increased incidence of deep vein thrombosis and peripheral arterial thrombotic complication.

In COVID 19 positive patients with pulmonary artery thrombosis 21(67%) patients were recovered and discharged while 17 (38%) patients were died due to complicated course during hospital stay. So, with early diagnosis of thrombotic complications we can improve the survival of the patients.

DISCUSSION

The current study focused on highlighting the relationship between the incidence of pulmonary embolism, COVID-19 disease severity either laboratory or by the CT severity score, trying to help in early diagnosis and treatment of complicated COVID-19 infection cases. The study included 130 patients with COVID-19 infection suspected to have PE, out of which 45 were positive; representing 34% of patients with suspected PE. The most common symptom was worsening dyspnoea with an incidence of 88.4 % in this study population, which is statistically significant. Another statistically significant symptom was haemoptysis.

We studied the relationship between the D-dimer, ferritin, CRP, WBC count and the incidence of PE which were found insignificant although patients with positive PE showed higher levels of D-dimer. This mandates incorporation of the follow-up of D-dimer in the management of patients.

Patients with high levels of D-dimer have a higher probability of developing PE. The patients with high D-dimer and high CRP were more susceptible to develop PE. The median time to develop PE was found to be 12 days. The Duration of illness in our opinion could raise a need for continuous follow-up of other alarming symptoms and serial measures of D-dimer. In our study patients with moderate to severe CTSI scores had a higher incidence of developing pulmonary thrombosis. Again, the follow-up of critically ill patients is considered the key to early diagnosis and life-saving for those critically ill patients. The incidence of segmental and sub segmental PE was higher among our study population with only 2 cases among the positive cases developed RV strain.

Limitations

Our study has few limitations; first, a retrospective study was done in one centre and larger multicentric studies are needed to further understand the nature of this novel complex illness. We did not include patients treated with anticoagulants in our study.

CONCLUSION

We conclude from our study that incidence of PE to occur during COVID-19 infection is high with clinical findings like haemoptysis and progressive dyspnoea . Rising D-dimer during the second week of disease is sensitive laboratory finding which will alert to do CT pulmonary angiography to exclude or confirm PE. This also raises the utmost need for anticoagulation prophylactically and improves overall survival of the patients.

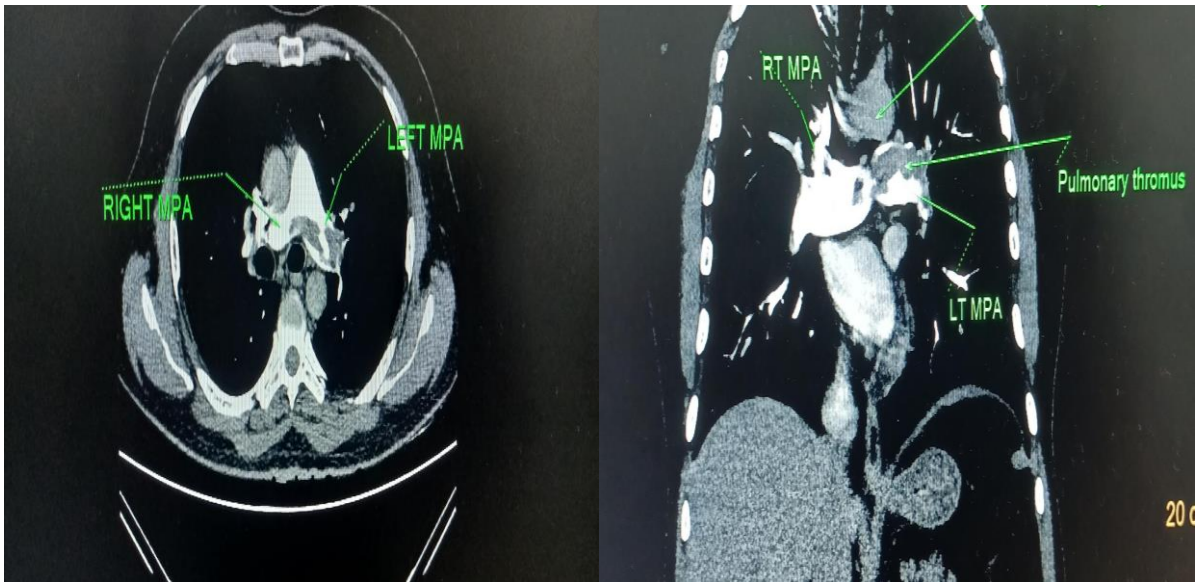

Image 1-2 (Thrombus within lumen of right and left main pulmonary artery)

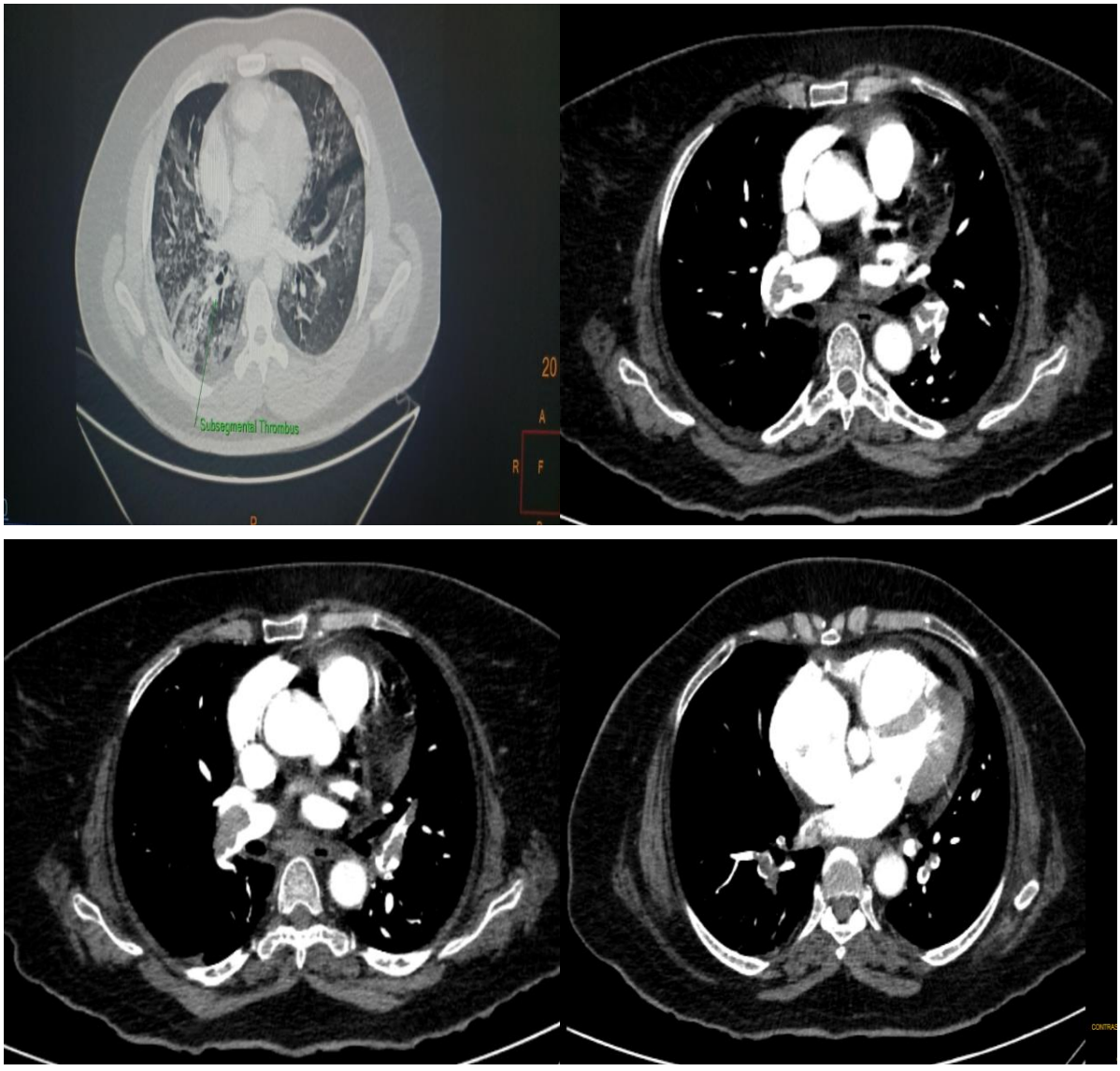

Image 3-6 (Wedge shaped ground glass opacity with Partial thrombo-embolism in right main pulmonary artery, left main pulmonary artery ,inferior interlobar artery extending to segmental and sub segmental branches supplying right middle lobe and segmental branches supplying bilateral lower lobe)

Abbreviations

COVID-19: Coronavirus disease 2019
CT: Computed tomography
CTPA: CT pulmonary angiography
RT- PCR: Reverse transcriptase polymerase chain reaction
CRP: C-Reactive protein; PE: Pulmonary embolism
ICU: Intensive care unit
RSNA: Radiological Society of North America
NCCT: Non-contrast CT
WBC: White blood cells
DVT: Deep vein thrombosis

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