



Relationship of the pulmonary disease severity scoring with thromboembolic complications in COVID-19

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Abstract

Purpose To correlate thromboembolic (TE) complications secondary to COVID-19 with the extent of the pulmonary parenchymal disease using CT severity scores and other comorbidities.

Methods In total, 185 patients with COVID-19 and suspected thromboembolic complications were classified into two groups based on the presence or absence of thromboembolic complications. Thromboembolic complications were categorized based on location. Chest CT severity scoring system was used to assess the pulmonary parenchymal disease severity in all patients. Based into severity scores, patients were categorized into three groups (mild, moderate, and severe disease).

Results The final study cohort consisted of 171 patients (99 male and 72 female) after excluding 14 patients with non-diagnostic CT pulmonary angiography. The TE group included 53 patients with a mean age of 55.1 ± 7.1 , while the non-TE group included 118 patients with a mean age of 52.9 ± 10.8 . Patients with BMI $> 30 \text{ kg/m}^2$ or having a history of smoking and HTN were found more frequently in the TE group ($p < 0.05$). Patients admitted to ICU were significantly higher in the TE group ($p < 0.001$). There was statistically significant difference ($p = 0.002$) in chest CT-SS between the TE group (22.8 ± 11.4) and non-TE group (17.6 ± 10.7). The percentage of severe parenchymal disease in the TE group was significantly higher compared to the non-TE group ($p < 0.05$). Severe parenchymal disease, BMI $> 30 \text{ kg/m}^2$, smoking, and HTN had a higher and more significant odds ratio for developing TE complications.

Conclusion The present data suggest that severe pulmonary parenchymal disease secondary to COVID-19 is associated with a higher incidence of thromboembolic complications.

Keywords COVID-19 · SARS-COV-2 · Coronavirus · Thrombosis · Embolism · Ischemia

Key Points

- Assessment of pulmonary parenchymal disease of COVID-19 using chest CT severity scores.
- The greater the CT severity score, The higher incidence of thromboembolic complications in COVID-19 patients.
- Comorbidities like BMI $> 30 \text{ kg/m}^2$, Smoking, and HTN had a higher and more significant odds ratio for developing TE complications in COVID-19 patients

Abbreviations

COVID-19	Coronavirus disease 2019
TE	Thromboembolic
SARS-CoV-2	Acute respiratory syndrome coronavirus-2
MERS	Middle East respiratory syndrome
SARS-CoV-1	Severe acute respiratory syndrome coronavirus-1
RT-PCR	Reverse transcriptase-polymerase chain reaction

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CT-SS	CT severity score
BMI	Body mass index
CKD	Chronic kidney disease
DVT	Deep venous thrombosis
PE	Pulmonary embolism
AMI	Acute mesenteric ischemia
ICU	Intensive care unit

Introduction

Since December 2019, a new type of coronavirus was isolated from the lower respiratory tract samples. It was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1] and later as coronavirus disease 2019 (COVID-19) [2–4]. COVID-19 is a mysterious disease primarily affecting the lungs with a wide range of clinical presentations ranging from asymptomatic illness to deadly severe respiratory disease [5, 6]. In addition to pulmonary disease, COVID-19 may cause a wide spectrum of systemic diseases due to the involvement of different organs by the virus or to complications directly or indirectly related to this infection. Causes of death in COVID-19 disease are numerous and overlapping, including uncontrolled immunological response known as cytokine storm and thromboembolic (TE) events, which necessitates ICU admission. Early studies investigated thromboembolic complications, and surprisingly they were not confined to the lungs with elevated serum thrombogenic proteins such as D-dimer but also seen in the cerebral, abdominal, and peripheral vessels [7]. Similarly, other hemostatic abnormalities were reported in some COVID-19 patients, including mild thrombocytopenia, hyperfibrinogenaemia, increased clot strength, which all indicate a pro-coagulant pattern of COVID-19 [8]. Several postulates have been put forward to explain the higher incidence of thromboembolic events in COVID-19 patients. There are two major theories; progressive endothelial thrombo-inflammatory syndrome or COVID-19 endotheliitis with resultant microangiopathy and the high level of circulating cytokines and inflammatory mediators. Both factors induce an abnormal hypercoagulable state with disseminated thrombosis, resulting in multi-organ failure and death [9].

Evidence is accumulating suggesting different mechanisms that have a role in morbidity and death associated with thromboembolic complications of COVID-19. Even in patients taking therapeutic anticoagulation, clinical and postmortem investigations have demonstrated a significant prevalence of venous and arterial thromboembolic events, including pulmonary embolism [10]. These data have led to recommendations for greater anticoagulation goals, although it is still unclear which individuals are at higher risk and need prophylactic anticoagulation. Even though

fibrinogen and D-dimer levels are typically raised, neither of these parameters accurately identifies people at risk of thromboembolic consequences [11]. So yet, the specific pathomechanisms which lead to the prothrombotic status in these patients remain unclear.

Chest imaging using CT plays a significant role in diagnosis assessing parenchymal severity and follow-up of COVID-19. On chest CT, manifestations resemble those seen in viral pneumonia, with multifocal ground-glass opacities and consolidation in a peripheral distribution being the most common findings [12, 13]. The main aim of our study was to correlate COVID-19 thromboembolic events with the extent of pulmonary parenchymal involvement using CT severity scores. We hypothesized that the greater the CT severity scores, the higher incidence of thromboembolic complications. The secondary aim was to correlate thromboembolic events and other comorbidities.

Materials and methods

Study population

The local institutional review board approved this retrospective study, and a waiver of the consent of medical record review was received. We studied the patients diagnosed with COVID-19 by RT-PCR test and were suspected of having thromboembolic complications. Indication of imaging assessment of TE complications was acute shortness of breath, chest pain or hemoptysis for suspected PE, focal weakness or persistent headache for suspected intracranial thrombosis, severe abdominal pain for suspected visceral ischemia, or signs of peripheral ischemia. Patients with a history of lung malignancy, interstitial lung disease, lobectomy, and tuberculosis were excluded to avoid possible bias because of overlapped pathology. All patients underwent cross-sectional imaging studies to diagnose suspected thromboembolic events. Pulmonary parenchymal severity was scored from chest CT and radiographs that were closest from the date to the imaging study requested to assess thromboembolic complications. Patient demographic, clinical, laboratory, and outcome data were extracted from electronic medical records.

The study included 185 patients and was classified into two groups based on the presence or absence of thromboembolic events. The final study cohort consisted of 171 patients (99 male and 72 female) after excluding 14 patients with non-diagnostic CT pulmonary angiography. The TE group consisted of 53 patients with a mean age of 55.1 ± 7.1 , while the non-TE group consisted of 118 patients with a mean age of 52.9 ± 10.8 .

Thromboembolic complications

Patients were categorized based on the location of suspected TE complications (pulmonary ($n = 116$), cerebral ($n = 33$), visceral ($n = 30$), and peripheral ($n = 6$)). The study flow chart is illustrated in Fig. 1. CT pulmonary angiography was used to assess the extent and site of pulmonary embolism and signs of right ventricular strain. CT and/or MRI were used to assess the site, distribution, and possibility of hemorrhagic nature or transformation of cerebral infarctions. CT angiography was used to assess visceral and peripheral ischemia.

Pulmonary parenchymal disease severity scoring

Chest CT was used to assess the pulmonary parenchymal severity scores in all patients and chest radiographs in 24 patients. CT images and radiographs were independently reviewed by two radiologists with more than 5 and 8 years of experience in thoracic imaging. Reviewers were blinded from the clinical data and the presence of thromboembolic complications. They were requested to assess the pulmonary window of chest CT scans only. A consensus was reached

by a chest radiologist with more than 10 years of experience where there was a disagreement.

Chest CT severity score (CT-SS)

The CT-SS is an adaptation of a method used before to describe GGO, interstitial opacity, and air trapping, which was correlated with clinical and laboratory parameters in patients after SARS [14, 15]. The 18 segments of both lungs are divided into 20 regions. The posterior apical segment of the left upper lobe is divided into apical and posterior segmental regions, and the anteromedial basal segment of the left lower lobe is subdivided into anterior and basal segmental regions. The lung attenuations in all 20 lung regions are subjectively evaluated on chest CT and given a score of 0, 1, or 2 if the parenchymal opacification involved 0%, less than 50%, or equal or more than 50% of each region, respectively. The CT-SS is defined as the sum of each score in the 20 lung segment regions, ranging from 0 to 40 points. We have classified all the CT studies of our patients into three groups according to their total CT-SS, as follows: (i) mild disease: scores from 0 to 13, (ii) moderate disease: scores from 14 to 27, (iii) severe disease: scores from 28 to 40.

Fig. 1 Flow chart of the study population

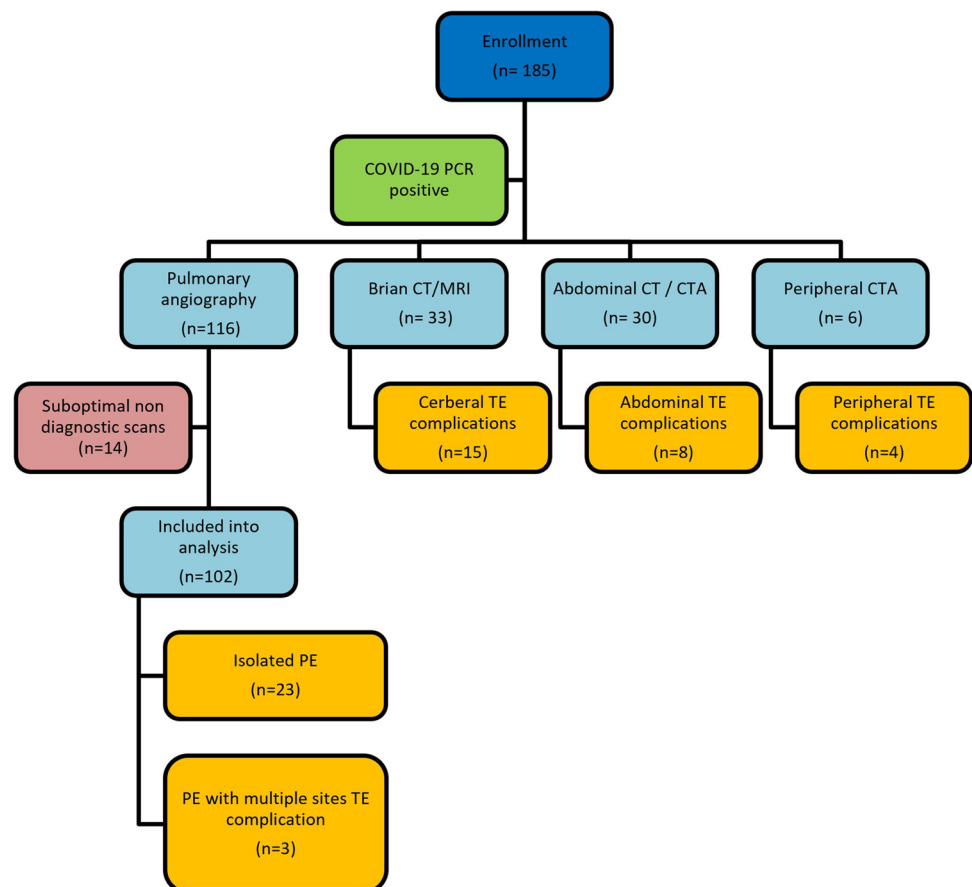


Table 1 Patients' demographics, comorbidities, and ICU admission in both groups

		Thromboembolic disease		<i>p</i> -value
		Yes (<i>n</i> = 53)	No (<i>n</i> = 118)	
Age (mean ± SD)		55.1 ± 7.1	52.9 ± 10.8	0.27
Gender	Male	29 (54.7%)	70 (59.3%)	0.7
	Female	24 (45.3%)	48 (40.7%)	
BMI > 30		31 (58.5%)	38 (32.2%)	0.040*
Comorbidities	Smoking	29 (54.7%)	36 (30.5%)	0.049*
	HTN	34 (64.1%)	42 (35.6%)	0.036*
	DM	22 (41.5%)	43 (36.4%)	0.67
	Previous PE/DVT	7 (13.2%)	12 (10.2%)	0.60
	Dyslipidemia	9 (16.9%)	44 (37.3%)	0.046*
	CKD	6 (11.3%)	10 (8.5%)	0.59
	Malignancy	4 (7.5%)	12 (10.2%)	0.61
	Mild	9 (17%)	44 (37.3%)	0.046*
Parenchymal disease severity	Moderate	20 (37.7%)	46 (39%)	0.91
	Sever	24 (45.3%)	28 (23.7%)	0.043*
ICU admission		41 (77.4%)	30 (25.4%)	< 0.001*
Mortality		14 (26.4%)	12 (10.2%)	0.022*

Data expression [test of significance]: *N* (%) [chi-square or *Fisher's exact test] or mean ± SD

Chest CT imaging was done on a 256-detector CT scanner (Revolution; GE). CT scan parameters: 120 KVP, 350mAs; rotation time: 0.5 s; pitch: 1.0; section thickness: 5 mm; intersection space: 5 mm; additional reconstruction with sharp convolution kernel; and a slice thickness of 1.5 mm. Scans were reviewed at a window width and level of 1000 to 2000 HU and – 700 to – 500 HU, respectively, to assess the lung parenchyma. Reviewers were asked to assess the presence of CT findings associated with COVID-19.

Results

Patients

Out of 171 patients included in this study with positive RT-PCR tests for SARS-CoV-2, only 53 patients (31%) had positive findings of thromboembolic complications. There was no significant difference in the age and gender distribution between TE and non-TE groups. Patients with a body mass index (BMI) > 30 kg/m² were found more frequently in the TE group compared to the non-TE group (58.5% vs. 32.2%, *p* = 0.04). History of smoking and HTN was more common among patients in the TE group (*p* < 0.05). Dyslipidemia was statistically more in the non-TE group than the TE group

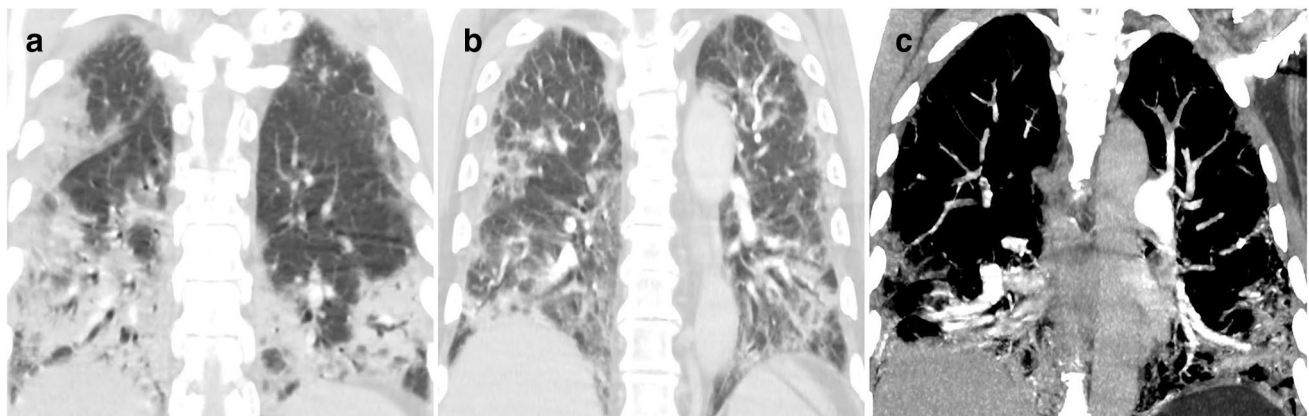
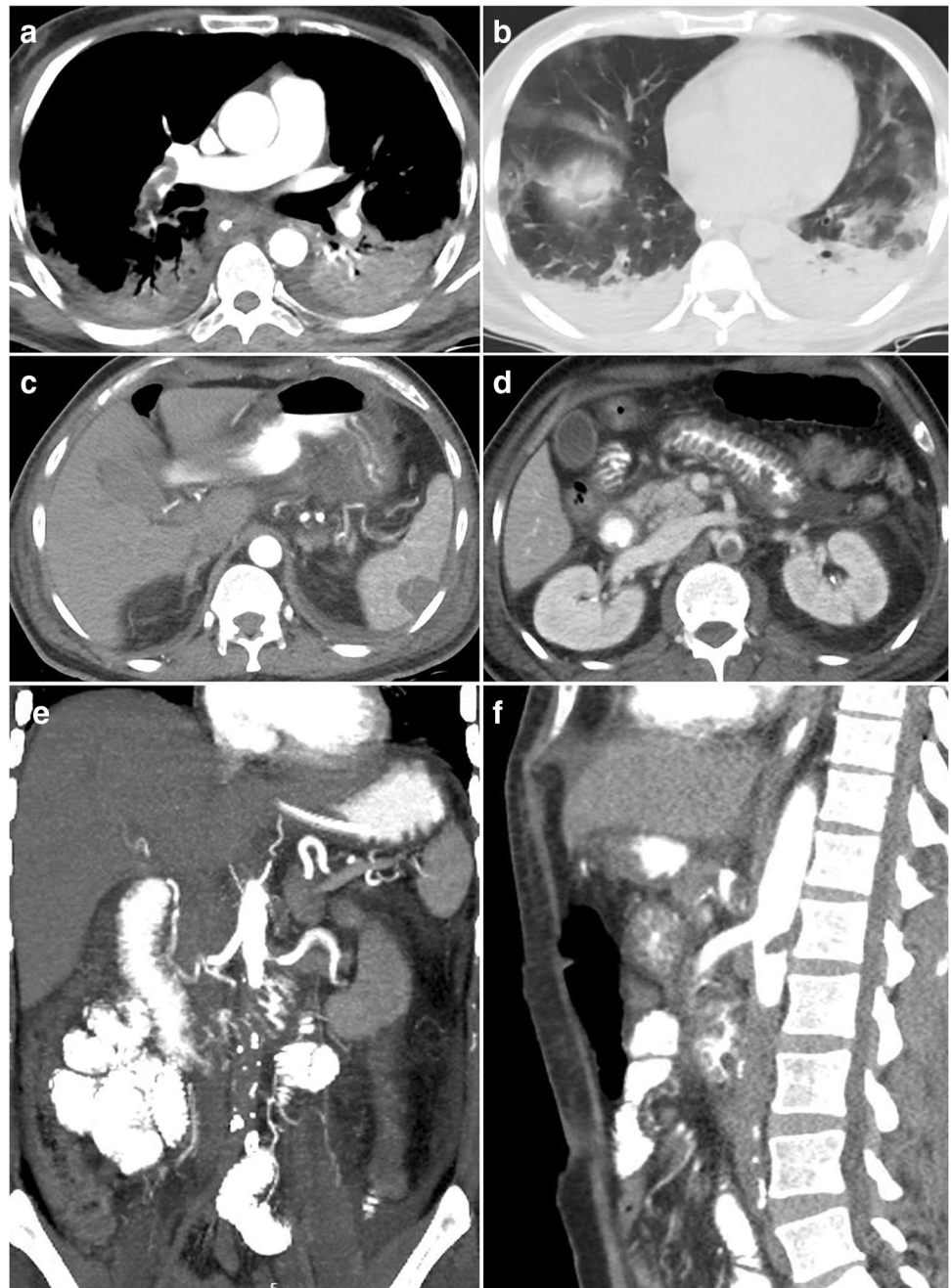


Fig. 2 PE in a 65-year-old male patient with confirmed diagnosis of COVID-19. **a, b** Coronal CT chest in pulmonary window shows bilateral GGO and posteriorly located consolidations, CT-SS = 29. **c** CT

pulmonary angiography shows multiple segmental and subsegmental pulmonary embolism

Fig. 3 Multiple thrombo-embolic complications in a 50-year-old male patient with confirmed diagnosis of COVID-19. **a** Axial CT chest in pulmonary window shows bilateral GGO and posteriorly located consolidations, CT-SS=24. **b** CT pulmonary angiography shows large thrombus in the right pulmonary artery. Axial NCCT brain scan (not shown) shows ischemic infarctions in the left watershed zones. **c, d** Axial contrast enhanced CT scan through the spleen and kidneys shows splenic and left renal infarctions, and mural thickening of small bowel indicative of mesenteric ischemia. **e, f** Coronal and sagittal abdominal CT angiogram shows total occlusion of the infra-renal abdominal aorta and iliac arteries, and hanging thrombus in the abdominal aorta above the obstruction level



(16.9% vs. 37.3%, $p=0.046$). There was no significant difference in the history of DM, CKD, and presence of malignancy as well as previous PE or DVT between both groups. Patients admitted to ICU were significantly more in the TE group (77.4% vs. 25.4%, $p<0.001$). Similarly, mortality was greater in the TE group (26.4% vs. 10.2%, $p=0.02$). Comparison between patients' data among TE-positive and TE-negative groups is demonstrated in Table 1.

TE complications

Pulmonary embolism was detected in 26/102 (25.5%) of study cases (Fig. 2), while D-dimer was elevated in 79/102 (77.5%) of study cases. There was a significant difference ($p=0.001$) between the D-dimer level in the positive group (6863 ± 714) and the negative group (3091 ± 455). The location of the pulmonary embolism was recorded according to the most proximal embolus. Distribution was as follows: 23.1% (6/26) subsegmental PE, 34.6% (9/26) segmental PE, 15.4% (4/26) lobar PE, 23.1% (6/26) central PE, and 3.8%

Fig. 4 Upper limb ischemia in a 36-year-old male patient with confirmed diagnosis of COVID-19. **a** Axial CT chest in pulmonary window shows bilateral GGO and posteriorly located consolidations, CT-SS = 15. **b** CT pulmonary angiography shows thrombi filling the right and left pulmonary arteries. **c** Left upper limb coronal and MIP CTA show totally thrombosed brachial artery with distal collateral filling

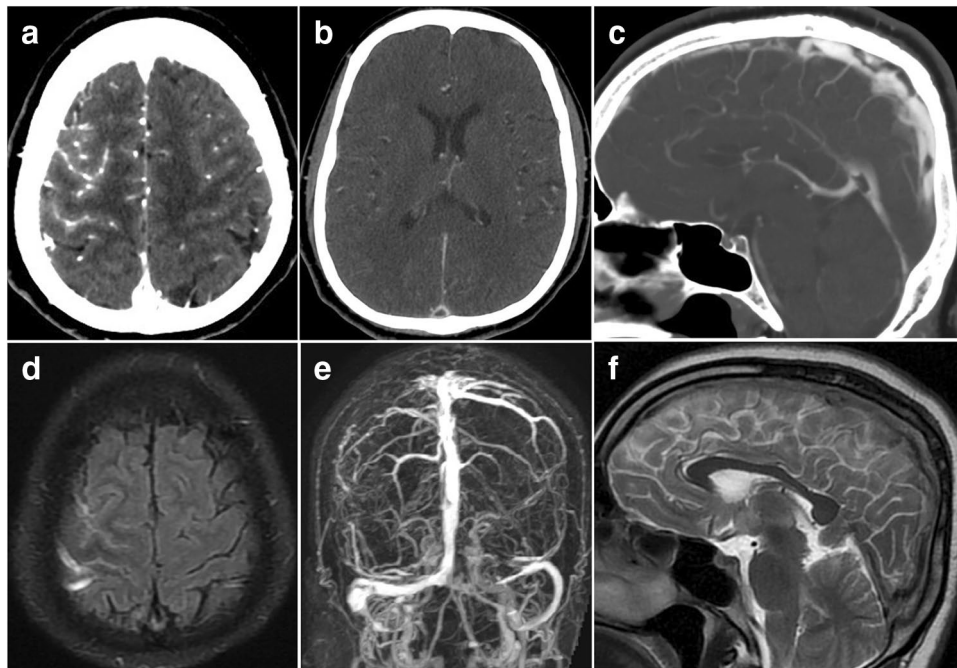
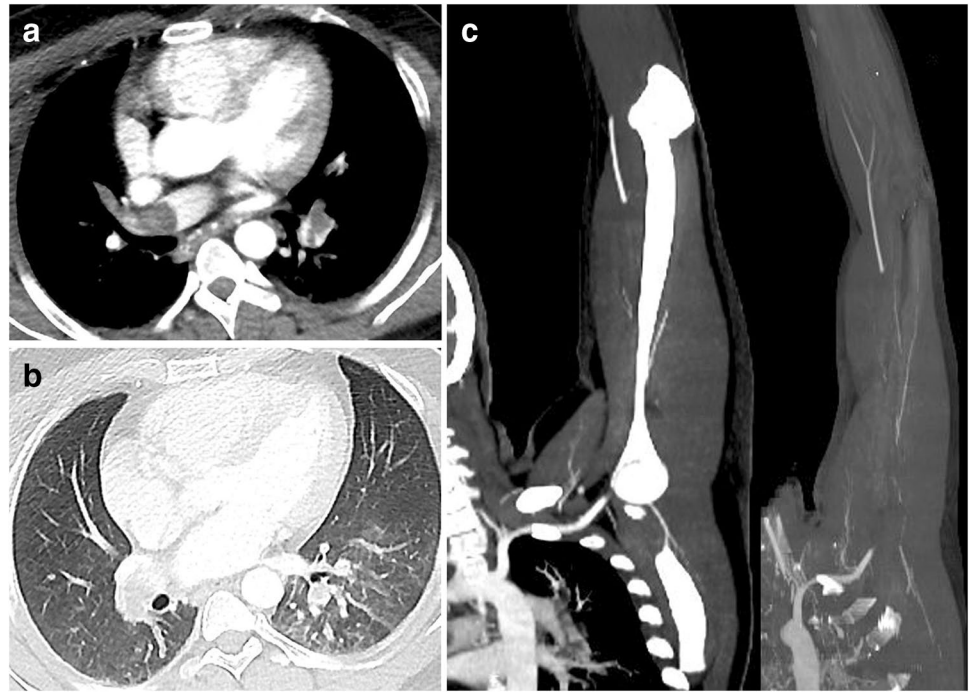
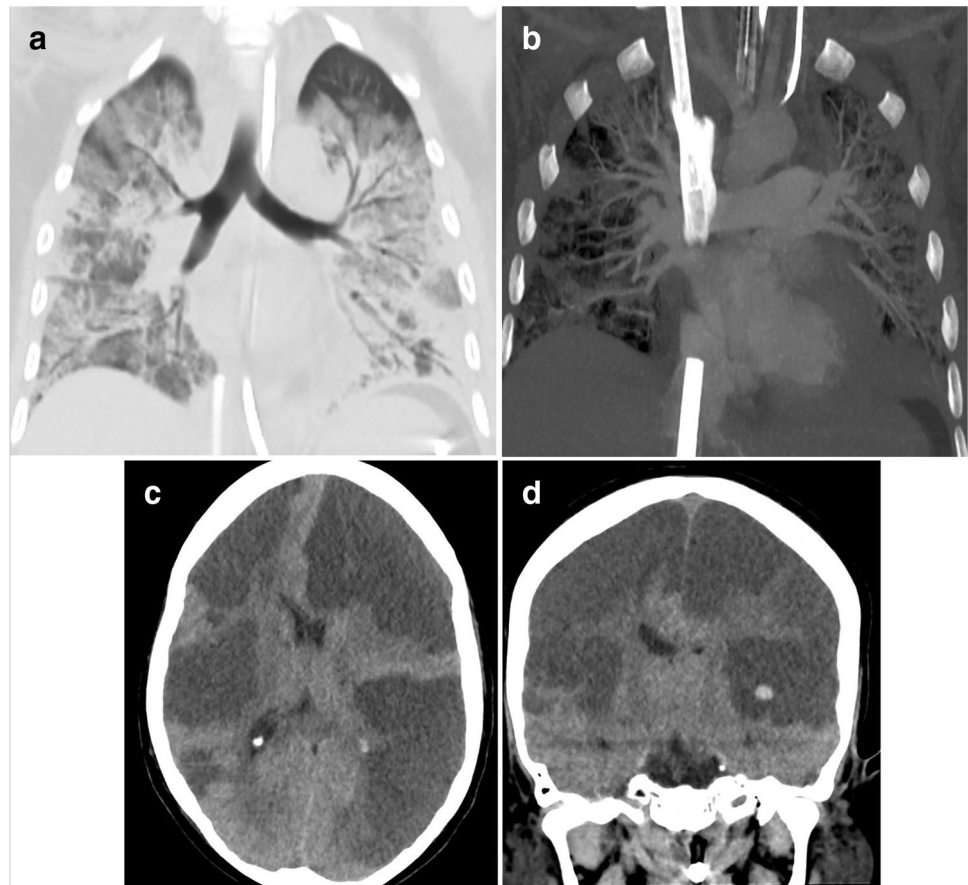


Fig. 5 Dural sinus thrombosis in a 38-year-old male patient who presented by persistent head and confirmed diagnosis of COVID-19. **a** Axial CECT shows right side focal gyral enhancement secondary to venous congestion. **b** Axial CTV shows empty delta sign secondary to thrombosed superior sagittal sinus. **c** Sagittal CTV shows multiple filling defects in the superior sagittal and straight sinuses. **d** Axial

FLAIR image shows right side cortical vein of high signal intensity denoting thrombosis. **e** TOF MRV demonstrates absent flow signal in the right vein of Trolrad, proximal part of the left transverse sinus, and filling defect at the right sigmoid sinus. **f** Sagittal T2 image shows abnormal signal intensity of the superior sagittal and straight sinuses. Chest CT was unremarkable and CT-SS was equal to 0

Fig. 6 Multiple cerebral infarctions in a 35-year-old female patient who was under Extracorporeal Membrane Oxygenation (ECMO) machine as part of COVID-19 management. **a** Coronal chest CT in pulmonary window shows diffuse GGOs involving almost both lung with partial sparing of the left upper lung lobe, CT-SS = 35. **b** Coronal chest CT pulmonary angiography demonstrates pulmonary arteries patency and the ECMO catheters in the SVC and IVC. **c, d** Axial and coronal NCCT brain show bilateral ischemic infarctions and small area of hemorrhagic transformation on the left side



(1/26) saddle PE. CT signs of right heart strain as the deviation of the interventricular septum and increased ventricular ratio were reported in 19.2% (5/26) of patients. Three patients had TE manifestations in multiple sites and they were included in PE group only and were not included in other groups. One patient had cerebral, renal, and splenic infarctions, signs of mesenteric ischemia, thrombosed infra-renal aorta, and the arterial tree of both lower limbs (Fig. 3). The other two cases were presented by peripheral limb ischemia and pulmonary embolism (occluded brachial artery (Fig. 4) and the popliteal artery).

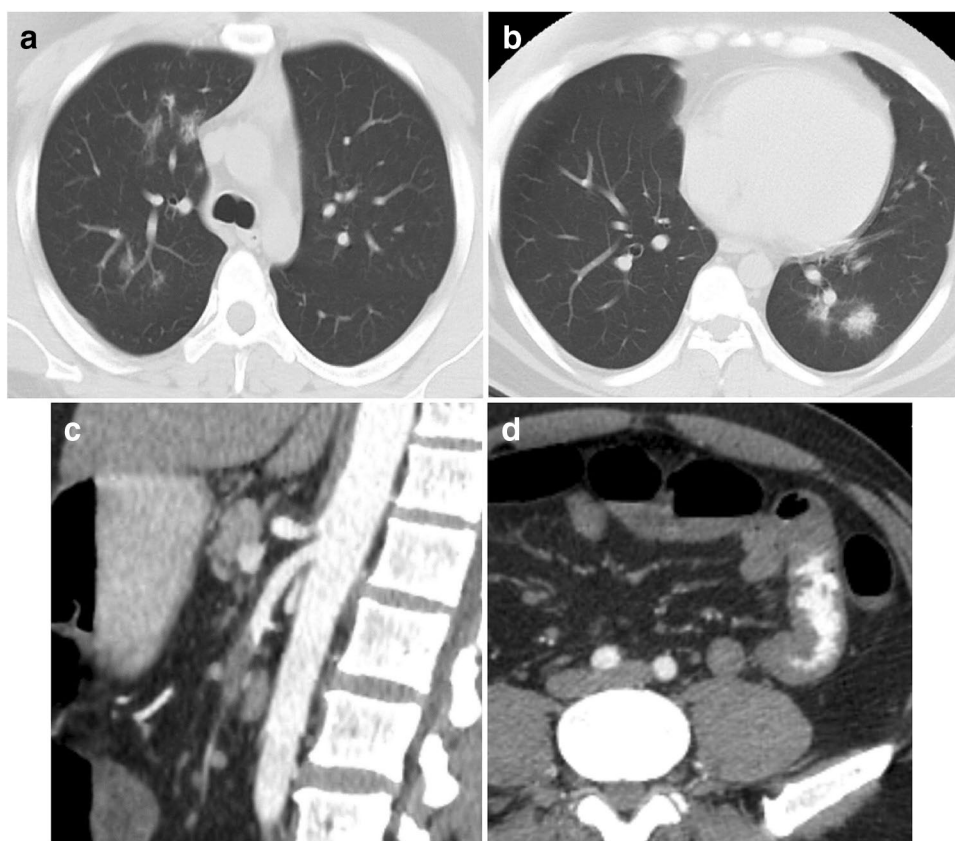
Intracranial TE complications were suspected in 33 patients. All cases were assessed initially by NCCT. Fourteen patients were examined by CTA and ten patients underwent MRI and time of flight MRA or MRV. The overall incidence of TE complications was 45.4% (15/33), 3 of them were dural sinus thrombosis (Fig. 5) while the rest were cerebral infarctions (Fig. 6). Distribution of cerebral infarction was as follows: lobar infarction in 41.6% (5/12), multiple locations in 33.3% (4/12), cerebellar infarction in 16.6% (2/12), and lacunar infarcts in 8.3% (1/12). Hemorrhagic component was detected in four patients (36.4%). CTA detected arterial occlusion in three patients (27.3%) and MRA in two patients (18.2%).

Abdominal CT and CTA were done to investigate abdominal pain for 30 patients with COVID-19. Positive findings related to TE events were detected in 26.6% (8/30). Seven patients showed signs of mesenteric ischemia with variable degrees of mesenteric artery occlusion (Fig. 7). One patient had partial splenic and hepatic artery thrombosis with subsequent splenic infarctions (Fig. 8). Peripheral CTA was done to rule out arterial ischemia in 6 patients. Arterial occlusion was detected in 66.6% (4/6); three of them had (75%) thrombosed lower limb arteries and only one upper limb arterial thrombosis.

Pulmonary parenchymal disease severity scoring

Chest CT was used to assess the severity of pulmonary parenchymal disease in all patients. Severe parenchymal disease in both groups was reported by chest CT in 30.4% (52/171), while moderate parenchymal disease was found in 38.6% (66/171). There was statistically significant difference ($p=0.002$) in chest CT-SS between the TE group (22.8 ± 11.4) and non-TE group (17.6 ± 10.7). Additionally, the percentage of severe parenchymal disease in the TE group was significantly higher compared to the non-TE group (45.3% vs. 23.7%, $p=0.04$). The interobserver

Fig. 7 Mesenteric ischemia in a 43-year-old male patient with confirmed diagnosis of COVID-19. **a, b** Axial chest CT in pulmonary window shows small areas of GGOs in both lungs, CT-SS = 12. **c** Sagittal CTA shows totally thrombosed superior mesenteric artery. **d** Axial CECT of the abdomen shows focal small bowel thickening and reduced enhancement denoting acute mesenteric ischemia



agreement was excellent for chest CT-SS ($\kappa = 0.874$). There was no significant difference in different imaging features detected by chest CT in both groups. Table 2 demonstrates the chest CT-SS and imaging features in both groups.

Univariate analysis

A univariate analysis was developed to predict TE complications and odds ratios for significant results. Severe parenchymal disease had a higher and more significant odds ratio (2.6, 95% CI 1.2–5.3; $p = 0.005$) for developing TE complications than moderate parenchymal disease (0.9, 95% CI 0.5–1.8; $p = 0.9$). Patients with hypertension had the higher odds ratio (3.2; 95% CI 1.5–5.7; $p < 0.001$) for developing TE complications followed by BMI $> 30 \text{ kg/m}^2$ with an odds ratio of 2.9 (95% CI 1.5–5.7; $p = 0.001$) and history of smoking with an odds ratio of 2.7 (95% CI 1.4–5.3; $p = 0.003$). The odds ratio of comorbidities and pulmonary parenchymal disease severity is listed in Table 3.

Discussion

Our study population had tested positive for COVID-19, and they were suspected of having thromboembolic complications; 53 patients (31%) had positive radiological findings

supporting this diagnosis. We used the CT-SS developed by Yang et al. [14] to describe the degree of pulmonary parenchymal involvement. We noticed that severe disease among the TE group was significantly higher compared to the non-TE group and severe parenchymal disease had a higher and more significant odds ratio for developing TE complications. These data confirm that both pulmonary inflammation and thromboembolic complications of COVID-19 cannot be discussed separately.

Deteriorated CT-SS was expressed implicitly in literature discussing the effect of thromboembolic events on the clinical condition of COVID-19 illness, as most of those patients were critically ill or even admitted to the ICU. However, few studies have evaluated parenchymal lung injuries using a clear scoring system to classify pulmonary lesions. In this study, the mean CT-SS for the TE-positive group was 22.8 ± 11.4 vs. 17.6 ± 10.7 for the TE-negative group. Similar findings were reported by Espallargas et al. [16], who examined the CTPA for 47 patients and quantified parenchymal patterns using a score from 1 to 4. According to the severity scoring of the patients, they had 29 (61.7%) severe cases and concluded that significantly high pulmonary parenchymal scores were detected in severely ill COVID-19 patients suffering from PE. In contrary to these findings, Fang et al. [17] concluded that the radiological severity does not differ in subgroups of patients with or

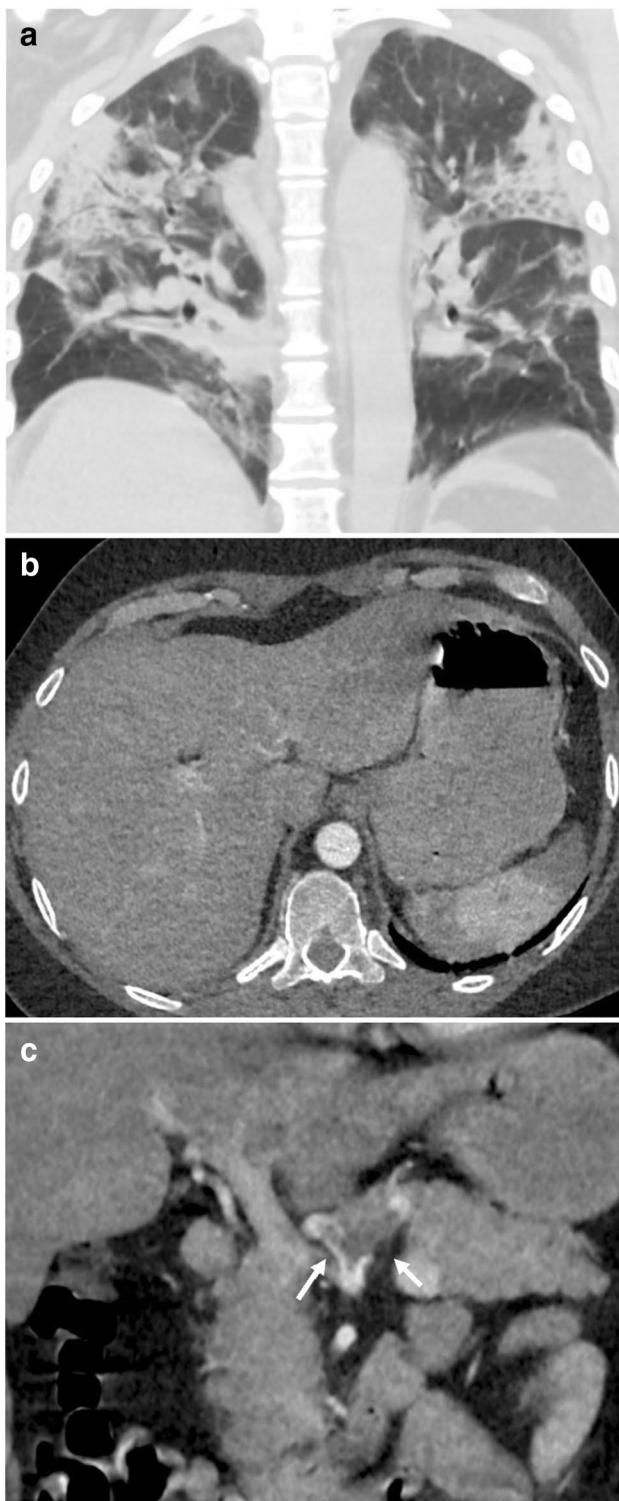


Fig. 8 Splenic infarction ischemia in a 53-year-old male patient with confirmed diagnosis of COVID-19. **a** Coronal chest CT in pulmonary window shows mixed GGOs and consolidations in both lungs, CT-SS=27. **b** Axial CECT of the abdomen shows splenic infarctions. **c** Coronal CTA shows partially thrombosed splenic and hepatic arteries

without PE. They classified their patients according to the CT findings into mild (3/93), moderate (30/93), and severe (59/93). Pulmonary microangiopathy and coagulopathy and their relation to COVID-19 have also been investigated by Patel et al., who used Murray's lung injury score to classify the disease severity in 39 mechanically ventilated patients. The mean CT extent of GGO and dense parenchymal opacifications were 36.3% and 42.7%. In addition, signs of pulmonary angiopathy in the form of dilated peripheral vessels and parenchymal perfusion defects were detected in 21/33 and 18/20 patients. Finally, they concluded that increasing pulmonary dead spaces and parenchymal opacification are strongly correlated by all means with pulmonary hypoperfusion in severely ill COVID-19 patients [18].

In this study, we focused on the identification of comorbidities raising the incidence of COVID-19-associated coagulopathy. Regarding different risk factors affecting those patients, the BMI > 30 kg/m² was statistically more frequent among the TE group than the non-TE group. Many studies proposed similar results, and now it is nearly established that obesity and elevated BMI are among the major risk factors for developing severe COVID-19 illness with all its serious complications [19, 20]. Similarly, smoking and hypertension were also statistically more frequent in TE compared to the non-TE group. These factors induce a hypercoagulable state by changing hemostasis, platelet aggregation, and induction of vascular endothelial damage that certainly worsens the general condition of the patients, especially in the presence of heavy viral loads [9, 21]. Dyslipidemia is a serious risk factor for cardiovascular disease. Nevertheless, our results showed that dyslipidemia was statistically more in the non-TE group than the TE group as most of the COVID-19 dyslipidemic patients were on statin therapy and consequently less vulnerable to develop TE. These results are consistent with the increasing number of studies reporting that dyslipidemic patients benefit from the protective effect of statins against TE events [22, 23]. Although several investigations have suggested that chronic illnesses such as DM, CKD, and pre-existing malignancy are implicated in COVID-19 pathogenesis and complications, we did not find a significant difference between our two study groups regarding these comorbidities [24, 25].

The incidence of ICU admission and mortality rates in this study were statistically more common among the TE group, and this undoubtedly resulted from the negative reciprocal relation between COVID-19 and TE injuries leading to more clinical deterioration. These results were consistent with studies carried out by Klok et al. [26]. Moreover, Roncon et al. [27] suggested that the actual number of ICU patients developing TE complications is underestimated as CTPA was only done for a selected number of patients because of the difficulties in its performance in mechanically ventilated patients. Consequently, the possibility of

Table 2 Chest CT-SS and incidence of imaging features in both groups

	Pulmonary embolism (n = 102)		Cerebral ischemia (n = 33)		Abdominal ischemia (n = 30)		Peripheral ischemia (n = 6)		p-value
	+ ve (n = 24)	- ve (n = 78)	+ ve (n = 15)	- ve (n = 18)	+ ve (n = 8)	- ve (n = 22)	+ ve (n = 4)	- ve (n = 2)	
Disease severity by CT-SS									
• Mild (n = 53)	4	31	3	11	2	14	1	2	0.04*
• Moderate (n = 66)	8	27	4	4	2	4	2	0	0.9
• Sever (n = 52)	12	20	8	3	4	4	1	0	0.04*
CT features:									
• GGO(n = 136)	20	65	11	14	6	14	4	2	0.6
• Consolidation(n = 81)	17	36	6	8	4	7	2	1	0.7
• Crazy paving(n = 40)	14	14	4	2	2	3	1	0	0.03*
• Reversed halo(n = 13)	4	5	2	1	0	1	0	0	0.4
• Subpleural bands (n = 44)	9	18	5	5	2	3	1	1	0.6
• Bronchiectasis(n = 42)	9	19	5	2	2	3	1	1	0.4
• Nodules(n = 4)	1	2	1	0	0	0	0	0	0.6
• Lymphadenopathy(n = 10)	2	3	2	1	1	0	0	1	0.3
• Pleural effusion(n = 18)	6	6	2	1	1	2	0	0	0.2

*Significant results

missed PE among hospitalized patients is highly probable, which explains a large number of deaths among COVID-19 patients. The coagulation disorders were also described during the previous coronaviruses’ outbreaks, but the incidence is remarkably higher with SARS-COV-2 [28, 29].

The history of TE disease had always been a major risk factor for recurrent thrombosis; however, it seemed that this allegation did not work for COVID-19. There was no significant difference between both groups concerning the previous history of DVT or PE in this study. These results are consistent with Roncon et al. [27]. One of this study’s drawbacks is that we did not perform Doppler studies to

assess the presence of co-existing DVT. The high incidence of PE in critically ill COVID-19 patients had directed many researchers to check the presence of DVT to investigate the source of clots, whether it is primarily originating from the pulmonary interstitial and alveolar damage or secondary to lower limb DVT [30].

In our study population, patients clinically suspected of pulmonary embolism were referred to perform a D-dimer test and CT pulmonary angiography. In PE-positive patients, the D-dimer level was significantly elevated compared to the patients with negative CTA. Our study agrees with Poyiadji et al. [23], who described high D-dimer levels in the patients with PE-positive group relative to those with negative PE (9.33 µg/ml vs. 2.54 µg/ml). Despite the large number of studies that have been conducted, there is still some argument about the definite cutoff value of D-dimer associated with a greater risk of mortality and severe illness [31, 32]. In our study, the distribution of pulmonary emboli favored more peripheral location (segmental and sub-segmental involvement represents 61.1%). These results are in agreement with previous reports [33–35] who described similar distribution in COVID-19 patients, which certainly differs from other non-COVID-19 patients and supports the theory of thrombo-inflammatory processes.

The novel coronavirus has a neurotrophic effect resembling other viruses leading to encephalitis and neuropathy. Nevertheless, this time, the unexpected shift in viral behavior was the increasing number of stroke cases [36]. In this study, 12 patients were diagnosed with ischemic stroke and 3 were diagnosed with dural sinus thrombosis. Mao et al. [37] discussed neurological manifestations of COVID-19 and reported 36.4% for

Table 3 Odds ratio and confidence intervals of comorbidities and parenchymal disease severity to develop thromboembolic complications

Variable	Odds ratio	95% CI	p-value
Gender (male)	0.8	0.4–1.5	0.8
BMI > 30	2.9	1.5–5.7	0.001*
Smoking	2.7	1.4–5.3	0.003*
HTN	3.2	1.6–6.3	<0.001*
DM	1.2	0.6–2.4	0.5
Previous PE/DVT	1.3	0.5–3.6	0.5
Dyslipidemia	0.4	0.2–0.8	0.01
CKD	0.3	0.1–0.7	0.006
Malignancy	0.7	0.2–2.3	0.6
Parenchymal disease severity			
- Mild disease	0.3	0.1–0.8	0.009*
- Moderate disease	0.9	0.5–1.8	0.9
- Severe disease	2.6	1.3–5.3	0.005*

*Significant results

neurologic symptoms and 5.7% for acute cerebrovascular disease. Belani et al. [38] reported a 46.3% stroke incidence among COVID-19-positive patients compared to the non-COVID-19 control group. Large vessel occlusion had the highest incidence among stroke patients in this study; interestingly, this was in line with other studies carried out by Beyrouti et al. [39] and Avula et al. [40]. Other stroke phenotypes included infarctions in multiple sites. These findings are also consistent with Tan et al. [41] conducted a meta-analysis of the neuroimaging data of published 103 cases, and they reported that most of the cerebral stroke was large vessel occlusion (62.1%), followed by multiple vascular occlusion (26.2%).

The incidence of COVID-19 patients presenting with gastrointestinal symptoms is about 10%, and these symptoms are rarely related to acute mesenteric ischemia [42, 43]. We had seven patients diagnosed with variable degrees of mesenteric artery occlusion and signs of AMI, including edematous dilated intestinal loops and absence of intestinal wall enhancement. Two case studies carried out by Fan [44] and Cheung et al. [45] described cases of AMI with no significant predisposing factors for TE events. In our study, we also had one patient who presented with partial splenic artery thrombosis and subsequent splenic infarctions. The described cases of splenic involvement by COVID-19 in literature are rare, with no definite reported incidence [46].

The association between peripheral arterial thrombosis and COVID-19 infection has been reported. Goldman et al. [47] reported a significant thrombus burden and a high frequency of thromboses involving proximal vessels associated with COVID-19. One patient in this study presented with extensive thrombosis of the abdominal aorta and both lower limb arteries. COVID-19 may predispose to disseminated intravascular coagulopathy as we encountered thromboembolic complications in multiple locations in three patients. Besutti et al. [48] report combined visceral infarctions with splenic and renal infarctions, while Azouz et al. [49] described AMI in association with MCA occlusion and a free-floating aortic thrombus.

This study has few limitations that should be addressed. The existence of additional entities such as neurogenic pulmonary edema in stroke patients or frequently seen aspiration in intubated patients might overestimate the severity scoring. They are non-COVID clinical contributors to disease severity and challenging to differentiate from pre-existed parenchymal changes secondary to COVID-19. Most of the study data was driven from PE-related parenchymal disease with relatively low sample numbers of non-PE-related parenchymal disease. A further large-scale study

with a separate analysis for PE and non-PE thromboembolic complications is needed.

Conclusion

The present data suggests that thromboembolic complications can be correlated with the severity of the pulmonary parenchymal disease. Therefore, both pulmonary and thromboembolic complications of COVID-19 cannot be discussed separately, especially when TE complications add much burden to the clinical condition of COVID-19 patients leading to further deterioration.

Author contribution All authors have contributed, read, and approved the manuscript.

Data availability All data generated during this study are included in this published article.

Declarations

Ethics approval and consent to participate Institutional Review Board approved this study.

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Conflict of interest The authors declare that they have no conflict of interest.

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