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COVID-19 Associated Pulmonary Thromboembolic Events in Anti-Coagulated Patients: Case Series from a Tertiary Facility in Ghana

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ABSTRACT

Severe/critical Coronavirus Virus Disease 2019 (COVID-19) patients face increased risk of pulmonary embolism (PE) and other thromboembolic events. This risk exists even in patients who are on prophylactic and therapeutic doses of anticoagulant. We present three cases of Severe/critical COVID-19 patients who developed PE despite being placed on prophylactic doses of anticoagulants. Clinicians should be keenly aware of this and urgently institute appropriate diagnostic measures if PE is suspected.

Keywords

Anticoagulation, COVID-19, SARS-CoV-2, Sub-Saharan Africa, Thromboembolism.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) typically affects the respiratory system leading to a clinical picture ranging from asymptomatic presentation to catastrophic respiratory failure [1]. SARS-CoV-2 enters the cell through binding of its spike protein to the Angiotensin Converting Enzyme 2 receptor, which is found on arterial and venous endothelial cells, type II alveolar cells, heart, kidneys, liver, small intestine and other organs [2]. This widespread distribution may partly explain the protean manifestations of the virus; including but not limited to enteritis, myocarditis, acute kidney injury, liver injury, hyperglycaemia, lymphopaenia, skin rash and multi-organ damage [2,3].

Mounting evidence from various case series and other research articles has revealed that SARS-CoV-2 also has a predilection for causing arterial and venous thrombotic events such as ischaemic strokes [4], myocardial infarction [5], pulmonary thrombi or pulmonary thromboembolism (PE) and deep vein thrombosis [1,4,5]. The hypoxia associated with pulmonary thrombi/PE can negatively affect patient prognosis by compounding the already existent pronounced hypoxia seen in patients with severe or critical COVID-19 [6]. Although there are still a lot of grey areas in the pathophysiology of these thrombotic events, they are proposed to be due to endothelial injury/dysfunction secondary to viral entry into the lungs leading to activation of inflammatory cells and release of cytokines; the latter stimulate activation of the coagulation pathway [2].

Data on thrombotic events in sub-Saharan Africa (SSA) is scarce and this case series hopes to raise awareness of the occurrence of such events among severe COVID-19 patients (despite being on prophylactic or treatment doses of anticoagulation) in SSA where logistical challenges often prevent imaging investigations from being carried out routinely. SARS-CoV-2 infection in the patients in this case series had been confirmed using reverse transcriptase polymerase reaction (PCR) on naso or oropharyngeal swabs before their admission to the Highly Infectious Isolation Unit (HIIU) at Komfo Anokye Teaching Hospital, a tertiary facility in Ghana.

Case 1

An 81-year-old man with a known history of hypertension was admitted at HIIU with a 2-week history of dry cough and fever associated with loss of appetite and general malaise.

At presentation, he was afebrile, had dry oral mucosa and a respiratory rate of 26 cycles per minute (cpm) and blood pressure of 151/96mmHg (Table 1**)**. He had expressive dysphasia and right-sided weakness (power of 4/5 in upper and lower limbs). He was hypoxic with an oxygen saturation (SpO_2) of 89% in room air (RA) and 97% on oxygen delivered via non-rebreather mask (NRM) at 12 litres/minute (L/min). In addition to severe COVID-19, a diagnosis of stroke with right hemiparesis and expressive aphasia was also made. A non-enhanced head computed tomography (CT) scan showed subacute left cerebellar bilateral occipital lobe and pontine infarcts; and chronic right internal capsular and left thalamic lacunar infarcts with background microvascular disease and age-related brain atrophy.

He was started on IV dexamethasone 8mg 8hourly, IV fluids, SC enoxaparin 40mg daily and the following oral medications – azithromycin 500mg stat, then 250mg daily for 4days, vitamin C 1000mg once daily, zinc 40mg daily, atorvastatin 40mg nocte and amlodipine 10mg daily. He was also given tocilizumab 400mg stat and remdesivir 200mg stat, then 100mg daily for 4 days according to the recommendations of the National COVID-19 Treatment Guidelines.

On Day 2 of admission, the patient's SpO_2 on NRM was 95% @ 15L/min. His inflammatory markers came back markedly elevated (Table 1) with D-dimers 5.48 ng/ml, C-reactive protein (CRP) 82.23 mg/l and ferritin 613 ng/ml. Due to the worsening oxygenation and elevated D dimers the dosage of enoxaparin was empirically increased to 80mg twice daily to manage for a possible pulmonary thrombus/PE. On Day 4 of admission, a CT pulmonary angiogram (CTPA) was done and showed evidence of acute left main pulmonary and segmental artery embolism (Image 1). SC enoxaparin was continued at 80mg twice daily.

On Day 7 of admission, the patient's SpO_2 on RA was 93% and 98% on intranasal oxygen (INO2) at 4L/min. The rest of the vital signs were normal. SC enoxaparin was switched to oral rivaroxaban 15mg twice daily.

On Day 10 of admission, the patient was de-escalated to 4L/min of INO_2 and was saturating at 94%. A naso-pharyngeal sample for repeat COVID-19 PCR test was taken and came out negative. He was then transferred to the general internal medicine ward for continuation of care by the neurology and cardiology teams.

Case 2

A 46-year-old, hypertensive and diabetic male who had defaulted on his medications for several months presented with cough, fever, and breathlessness of 3 days duration.

Table 1: Vital signs and laboratory findings of patients 1 and 2.

Parameter	Patient 1			Patient 2			
	Day 1	Day 4	Day 10	Day 1	Day 6	Day 16	Day 21
Blood Pressure (mmHg)	151/96	126/72	130/70	154/102	128/84	114/75	136/91
Heart rate (beats/min)	89	72	64	118	83	94	93
Temperature (degree Celsius)	35.8	36.2	35.8	36.6	35.7	36.3	
Oxygen saturation (%)	89 RA 97 NRM @12L/min	91 NP@6L/min 96 NRM @15L/min	94 NP @4L/min	80-83 on NRM@ 15L/min 90 on CPAP	92 on CPAP	98 on NRM	96% on INO2 @ 6L/min
Respiratory Rate (cycles/min)	26	22	18	29	25	30	22
Hemoglobin (11.5-16.5 g/dl)	8.2	7.7	7.3	14.3	13.2		
WBC (4-10x10^3/µL)	13.5		14.7	14.40	13.05		
Neutrophils (1.5 -7x10^3/ µL)	9.38		3.81	12.00	11.93		
Lymphocytes (1-3.7x10^3/ µL)	1.26		1.70	1.02	6.60		
Plt count (140-440x10^3/ µL)	303		247	234	506		
ALT (0-33 U/L)	44						
AST (0-32 U/L)	48						
GGT (<38 U/L)	144			67.7			
ALP (35 -105U/L)	88			132.0			
Albumin (39.7-49.5g/L)	29			34.7			
Urea (2.9-8.2mmol/L)	9.4			11.13			
Creatinine (44 -80 µmol/L)	106			77			
Hep BsAg	Negative			Positive			
Hep CAb	Negative			Negative			
HIV antibodies	Negative			Negative			
Ferritin (11-306.8ng/ml)	613.0			-			
D-Dimer (<0.5µg/mL)	5.48			-			
C-Reactive Protein (<5mg/L)	82.23			-			

Abbreviations: RA, room air; NRM, non-rebreather mask; NP, nasal prongs; CPAP, continuous positive airway pressure; WBC, white cell count; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HepBsAg, hepatitis B surface antigen; Hep CAb, hepatitis C antibody; HIV, human immunodeficiency virus.

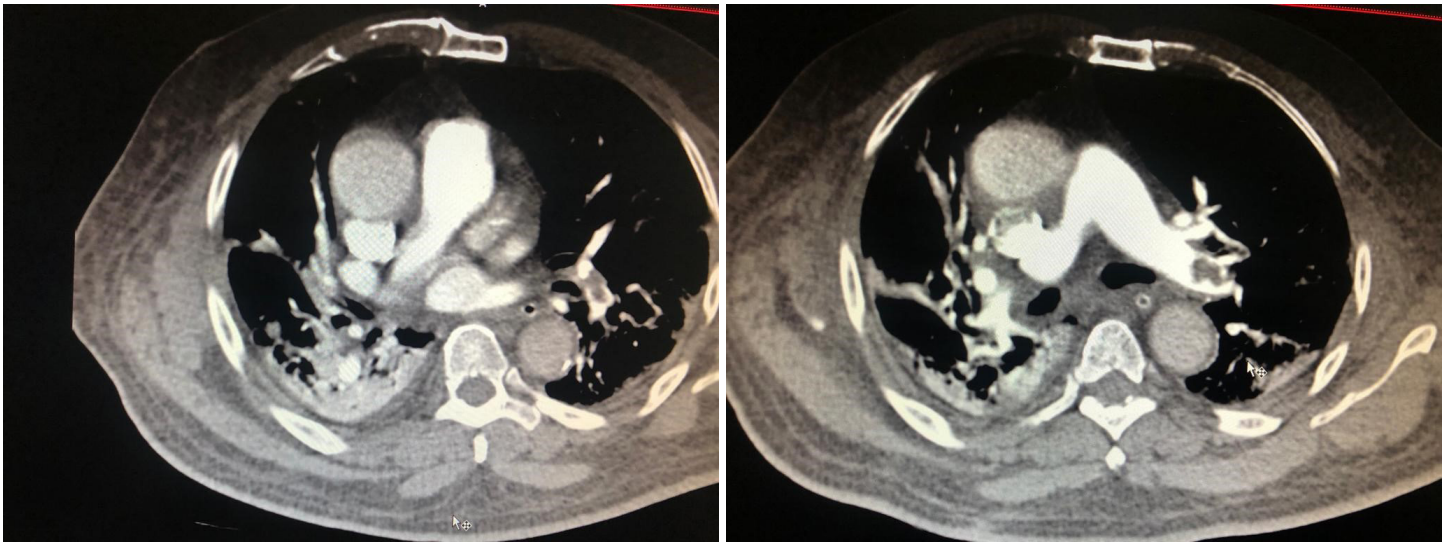

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Image 1: CT pulmonary angiogram of patient 1.

On presentation, he was afebrile and tachycardic with a pulse rate of 118 beats/minute (bpm). His blood pressure was 154/102 mmHg. His respiratory rate was 58 cpm and SpO_2 ranged from 75% in RA to 80-83% on oxygen delivered via NRM at 15L/min. His hypoxia progressed shortly after admission warranting admission to the intensive care unit (ICU). He was put on continuous positive airway pressure (CPAP), and with an FiO2 of 100% and PEEP of 10 his saturation rose to 90% (Table 1).

He was started on IV dexamethasone 8 mg 8 hourly and SC enoxaparin 80mg twice daily. Oral medications like zinc 40mg daily, vitamin C 1000mg daily, nifedipine 30mg twice daily and losartan 100mg daily were also started. Due to financial constraints, his inflammatory markers could not be done because these laboratory investigations were not covered by health insurance. Based on the severity of his condition, IV tocilizumab 400mg stat and IV remdesevir 200mg stat, then 100mg daily for 3 days were also prescribed but he could only afford the stat dose of remdesivir.

On day 2 of admission, his SpO_2 was still 90% on CPAP with an improvement in respiratory rate to 26cpm. All other vitals were normal.

On day 6, his SpO2 improved to 92% on CPAP and he was stepped down to oxygen delivery via NRM. However, he had to be put back on CPAP after a couple of days because he couldn't sustain good oxygen saturations on NRM.

Due to his persistently high oxygen requirement, a CTPA was done on day 12 of admission. It showed bilateral, acute PE and multifocal peripheral ground glass opacities in the upper lung zones bilaterally (Image 2).

Oral warfarin (5mg) was added to the SC enoxaparin and his international normalized ratio was monitored. A repeat COVID-19 test done on day 19 of admission came back negative.

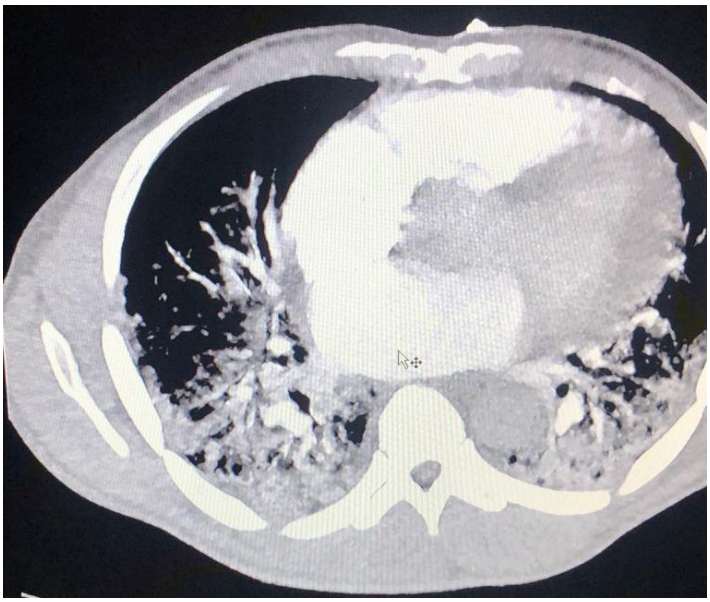

Image 2: CT Pulmonary Angiogram of patient 2.

He was eventually de-escalated to INO_2 with SpO_2 of 96% at 6L/min and on day 21 he was transferred to the general medical ward for continuation of care.

Case 3

A 69-year-old male with systemic hypertension and type II diabetes mellitus presented with cough and breathlessness of 4 days duration.

At presentation, he was afebrile and tachycardic with a pulse rate of 109 bpm and blood pressure of 153/88 mmHg. He was in respiratory distress with a respiratory rate of 46 cpm. His SpO_2 was 61% in RA and 76% on oxygen delivered via NRM at 15L/min. His random blood sugar was 22.4 mmol/l. He was admitted to

Table 2: Vital signs and Laboratory findings of Patient 3.

Parameter	Patient 3			
	Day 1	**Day 6**	**Day 10**	**Day 24**
Blood pressure (mmHg)	153/88	137/89	101/74	125/66
Heart rate (beats/min)	109	102	101	93
Temperature (°C)	36.2	36.4	36.7	36.0
Oxygen saturation (%)	100% on CPAP 76% NRM @ 15L/min	94 on NRM	93% on NP @ 6L/min 89% on RA	98% on NP @ 6L/min. 92% on RA
Respiratory rate (cycles/min)	46	46	18	24
Hemoglobin (11.5 – 16.5 g/dL)	13.7	13.7		
WBC (4-10x10^{-9}/L)	17.21	6.34		
Neutrophil (1.5 -7 x 10^{-9}/L)		4.79		
Lymphocytes (1-3 x10^{-9}/L)	2.04	0.85		
Platelet count (140-440 x10^{-9}/L)	402	511		
ALT (0-33 U/L)	11.5	73.9		
AST (0-32U/L)	18.4	64.5		
GGT (<38U/L)	62.0	238.3		
ALP (35-105U/L)	135.4	162.5		
Albumin (39.7 -49.5g/L)	24.5	29.2		
Urea (2.9 – 8.2 mmol/L)	2.54	9.12		
Creatinine (44-80 µmol/L)	31	84		
Hep BsAg	Negative			
Hep CAb	Negative			
HIV antibodies	Negative			
Ferritin (11-306.8 ng/ml)	564.3			
D-Dimer (<0.5µg/ml)	2.24			
C-Reactive Protein (<5mg/L)	118.45			

Abbreviations: RA, room air; NRM, non-rebreather mask; NP, nasal prongs; CPAP, continuous positive airway pressure; WBC, white cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; HepBsAg, hepatitis B surface antigen; Hep CAb, hepatitis C antibody; HIV, human immunodeficiency.

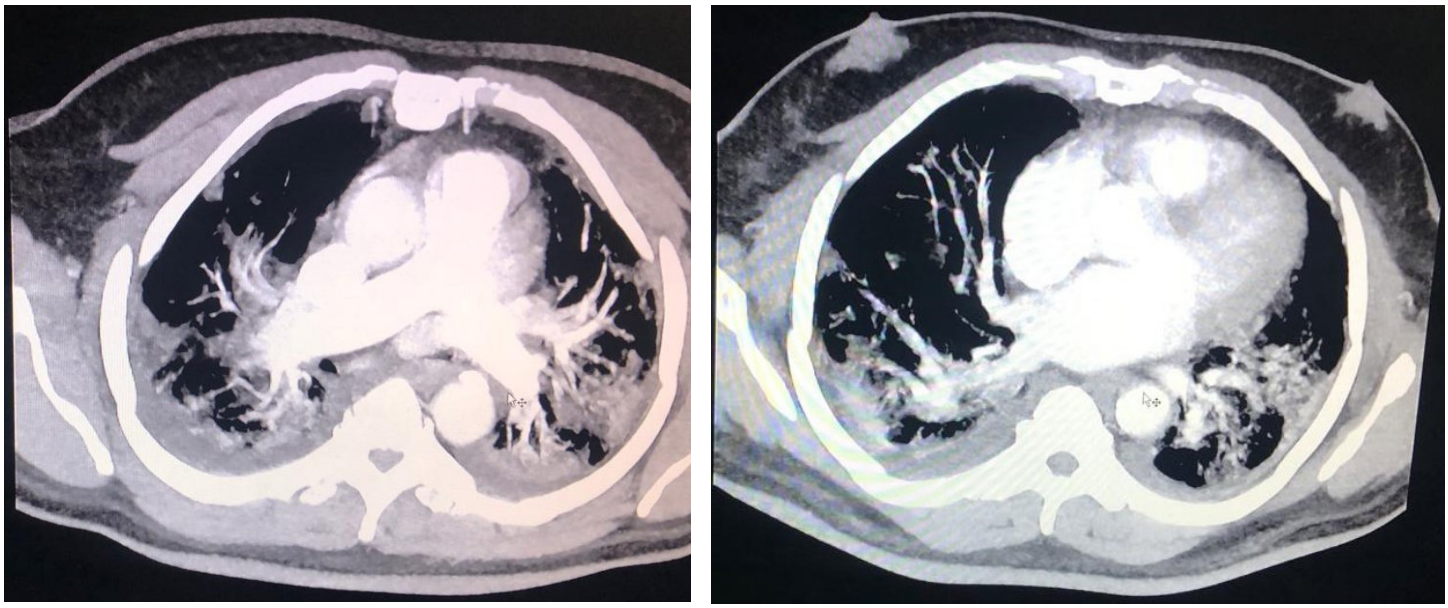

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Image 3: CT Pulmonary Angiogram of patient 3.

the ICU and immediately put on CPAP with a resultant rise in his SpO_2 to 100% (Table 2).

He was given IV dexamethasone 8 mg 8 hourly, SC enoxaparin 80mg twice daily, IV remdesivir 200mg stat, then 100mg daily for 3 days, oral zinc 40mg, vitamin C 1000mg, amlodipine 10mg daily and losartan 50mg daily. His inflammatory markers came back elevated (Table 2). Tocilizumab was also prescribed but he could not afford it.

The patient did well on the CPAP for 3 days where his oxygen saturations were around 96-99% and so he was stepped down and put on NRM mask on day 5 with SPO_2 of 94%.

On day 10 of admission, he was stepped down to INO_2 at 6L/min. His oxygen saturations ranged from 94-98% on oxygen but his RA saturation persistently hovered around 89%. Due to the persistently low RA saturation, a CTPA was done on the 24th day of admission and it revealed bilateral PE with patchy areas of consolidation in both lung fields (Image 3). A repeat COVID-19 test was done on the 20th day of admission, which came back negative. The patient was transferred to the ward after the CTPA and managed for the PE.

Discussion

This case series draws attention to thrombotic/embolic events in three patients with severe COVID-19 who were on prophylactic (Patient 1) and therapeutic (Patients 2 and 3) doses of anticoagulant.

Two of the patients were over 50 years and all the patients had co-morbidities. Old age and co-morbidities such as hypertension, diabetes mellitus, heart and kidney diseases have been documented as risk factors for severe COVID-19 [7].

In addition to having a pulmonary thrombus**,** patient 1 also had sub-acute cerebellar and pontine infarcts although this may also have been a consequence of his long-standing hypertension. Studies have reported the occurrence of arterial and venous thrombotic incidences in COVID-19 patients and this is especially common in patients with severe or critical disease [4,6,8-10]. Of note, these thrombotic episodes have rarely been documented in patients with mild COVID-19 and those not requiring hospitalisation as evidenced by large cohort studies [11,12]. Overall, venous thrombotic events have been reported more commonly than arterial thrombosis in COVID-19 patients [13]. The mechanisms leading to these thrombotic episodes are still not well elucidated. They are thought to be due to binding of SARS-CoV-2 to the ACE2 receptors on endothelial cells leading to endothelial dysfunction and release of platelet activation factors such as von Willebrand Factor (vWF) and tissue plasminogen activator-1 (tPA-1) [1,5]. In addition, complement activation and release of inflammatory cells such as macrophages and neutrophils, result in production of inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-10 and TNF-a, so leading to the cytokine storm [1,2,10]. Moreover, vWF and tPA-1 promote the further recruitment of inflammatory cells and release of cytokines leading to an overwhelming, positive feedback process [1,14]. In our case series, this heightened inflammation was evidenced by the high inflammatory CRP levels (seen in patients 1 and 3). These cytokines stimulate the coagulation cascade with increase in thrombotic events [15]. Lupus anticoagulant has also been implicated in the hypercoagulable process.

Initially, this pro-inflammatory/hypercoagulable state is limited to the lungs but as the inflammatory process worsens there may be progression to disseminated hypercoagulability [1,8].

Furthermore, there is evidence that the fine balance between thrombotic and fibrinolytic pathways seen in healthy individuals is tilted towards increased thrombotic activity. In our case series, in addition to pronounced inflammation, traditional risk factors such as prolonged immobility [2] (from fatigue, myalgia and ventilatory support), age and hypertension [16] may also have contributed to the thrombotic/embolic events.

It is interesting to note that all the patients in this report developed PE despite being on prophylactic or therapeutic doses of anti-coagulant therapy. In a French study, involving 150 COVID-19 patients admitted to the ICU, 16.7% developed pulmonary embolism despite being on prophylactic or therapeutic anticoagulation [17]. Klok et al [4] also reported a 31% cumulative incidence of thrombotic events – mainly venous (27%) - in 184 ICU patients who were at least on prophylactic doses of anticoagulant. Other researchers have reported similar observations [6,18]. There is some controversy concerning the optimum anticoagulant dosage in COVID-19 patients. Most guidelines recommend prophylactic anticoagulant doses of anticoagulants in severe and critical patients in the absence of contradictions [19]. Data from other studies however suggest that enhanced or treatment dose anticoagulation as prophylaxis in hospitalised patients improves survival rates [20-22]. A major concern associated with increased doses of anticoagulants is the risk of bleeding [21]. However, an increased bleeding risk has not been reported in some studies in keeping with our findings [22,23]. Indeed, there appears to be a higher incidence of thrombotic events compared to bleeding episodes [24].

Diagnosis of PE can pose quite a challenge in COVID-19 patients due to an overlap in respiratory clinical presentations in patients with PE and those with severe COVID-19 [25]. Moreover, researchers have documented a rise in D-dimer levels in patients with severe COVID-19 even in the absence of thromboembolism, with elevated D-dimer levels being a predictor of increased mortality [26,27]. CTPA is the gold standard for diagnosing PE [16]. However, there may be financial and logistic limitations in accessing CTPA especially in resource restrained settings, with the added challenge of exposure of technicians to COVID-19 patients [13,28]. These hindrances may lead to delayed/missed diagnosis and increased chances of mortality.

Conclusion

In conclusion, this case series highlights the occurrence of thrombotic episodes in severe and critical COVID-19 patients,

in SSA, who were on prophylactic and therapeutic doses of anticoagulation. This suggests that severe and critical COVID-19 patients in SSA are also at high risk of thromboembolic events and may benefit from high intensity anticoagulation. However, this is just a small case series from which concrete conclusions cannot be drawn. There is a pressing need for well-powered, prospective, interventional studies to better define the optimal prophylactic anticoagulant dose options for prevention of VTE as well as the timing of initiation of therapy based on stratification of severity. Secondly, there is a need for identification of markers (other than D-dimers), which can reliably be used in diagnosing pulmonary thrombotic events in settings where CTPA and Doppler ultrasonography may not be readily available. Furthermore, clinicians should have a low threshold of suspicion of PE in severe/critical COVID-19 patients (including those on thromboprophylaxis) especially in the face of raised inflammatory markers such as D-dimers, CRP and ferritin as well as persistently high oxygen demand after treatment with antiviral and anti-inflammatory agents and the appropriate investigations and management should be instituted as a matter of urgency if PE is suspected. Early initiation of therapeutic anticoagulation should also be considered in such cases in the absence of contraindications and such patients should be closely monitored for bleeding.

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Ethical approval

Ethical approval (reference no. GHS-ERC027/08/20) was obtained from the Ghana Health Service Ethics Review Committee.

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