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Letter to the Editors-in-Chief

Delayed catastrophic thrombotic events in post-acute COVID-19

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The ongoing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or COVID-19 pandemic which began in China in December 2019 has infected over 542.1 million individuals and caused about 63.29 lakh deaths worldwide as of 29th June 2022 [1]. The natural history of SARS-CoV-2 is evolving from an asymptomatic, mild, moderate, or severe clinical illness characterized by acute respiratory failure, septic shock, and multiple organ failure in the acute phase of infection to the persistence of symptoms beyond 4 weeks from onset of initial symptoms, called post-acute COVID-19 syndrome or long COVID [2,3].

COVID-19 virus is highly prothrombotic and leads to formation of micro and macro-vascular thrombi, which are a major cause of multi-system organ dysfunction, including respiratory failure [4]. Previous studies on thrombotic outcomes for patients discharged after COVID-19 infection reported a higher incidence of thrombotic complications in the acute-phase in critically ill patients with comorbid risk-factors but the risk diminishes quickly thereafter [4]. Considering widespread vasculitis described in COVID-19, low-grade endotheliatis may persist in the convalescent phase and continue to pose threat of delayed thrombotic events (TE) [5]. Wang et al. reviewed coagulation abnormalities and pathophysiological mechanisms of thrombosis in long COVID and proposed early prophylactic anticoagulation to prevent thrombotic sequelae [3]. Some recent studies [6,7] have reported post-discharge TE in COVID-19 patients despite pharmaceutical thromboprophylaxis. However, there is limited information on delayed thrombotic complications in patients with either no or mild symptoms in the acute-phase of COVID-19.

We report a-series of COVID-19 cases who presented with delayed TE at our COVID centre equipped with 300 intensive-care and 700 in-patients beds. During period from 16th March 2020 through 31st August 2021, about 4762 COVID-19 patients were provided in-patient care. The study was undertaken from 1st March 2021 through 31st August 2021 after obtaining approval of Institution's Ethics Committee, during which 2846 COVID-19 patients were hospitalized. The study period correlated to second COVID-19 wave in India triggered by 'Delta' variant. Case-records of COVID-19 in-patients referred to Department of Radiodiagnosis for imaging studies for suspected TE during the study period were retrospectively evaluated for demographic, clinical and imaging data, including initial hospital course and condition at discharge, if previously hospitalized for COVID-19. Patients who developed thrombotic complications ≥4 weeks after diagnosis of COVID-19 were included whereas patients diagnosed with TE in acute-phase of illness during in-patient care; individuals with comorbid risk-factors viz.; obesity, diabetes, hypertension, cardiovascular disease, or malignancy; and patients previously hospitalized elsewhere for COVID-19, were excluded. Patients suspected of TE underwent imaging for affected region according to primary manifestations. Non-contrast computed tomography (CT) of the head and diffusion-weighted magnetic resonance imaging (MRI) of the brain were evaluated in stroke patients for location and extent of cerebral ischemia and associated haemorrhage. CT pulmonary angiography and Doppler Ultrasound (DU) of lower limbs was performed in patients suspected of acute pulmonary embolism (PE). CT abdominal angiogram was performed in patients suspected of gastrointestinal TE and evaluated for evidence of thrombosis and bowel ischemia. Solid abdominal organs were assessed for infarction. Patients with suspected limb ischemia underwent DU of the affected limb followed by CT angiography for positive cases. All CT scans were performed on a 128-slice multidetector CT scanner while MRI was performed on 1.5 Tesla machine. Images were reviewed by two independent radiologists for presence of vascular thrombosis.

During six-months study period, 11 post-acute COVID-19 patients (9 men, 2 women; age range, 29–82 years; mean age ± SD, 52 ± 19.7 years) were diagnosed with various TE in imaging studies. The demographic and clinical details of patients with thrombotic complications is presented in Table 1. As evident, 4 patients were under 40 years of age, 3 were middle aged, and 4 were ≥60 years of age. TE in these cases

Abbreviations: CRP, C-reactive protein; CTPA, computed tomography pulmonary angiogram; DU, doppler ultrasound; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NCCT, non contrast computed tomography; PE, pulmonary embolism; RT-PCR, real-time polymerase chain reaction; RV, right ventricle; SARS-CoV-2, severe acute respiratory syndrome coronavirus -2; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SOB, shortness of breath; TE, thrombotic event.

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Table 1
Showing demographic and clinical data of post-acute COVID-19 patients with delayed thrombotic complications.

S no	Age (years)/ sex	Symptoms	Findings of imaging studies	Thrombotic event (TE)	Date of TE	No. of days from positive COVID -19 RT PCR to TE	Severity of COVID 19 at initial diagnosis	Hospital course (If previously admitted for COVID-19)	Days after discharge from hospital to TE	Peak D-dimer and CRP level at presentation of TE/ other investigations
Venous thrombotic events										
1	33/M	Abdominal pain, nausea, and vomiting	IV Contrast Enhanced Abdominopelvic CT scan: Ischemia of transverse colon and small bowel with gangrene of jejunum.	Thrombosis of SMV, its venous arcade, portal vein and splenic vein[a]	5 May 2021	48 days	Moderate	Oxygen support, discharged after 15 days (Normal D-dimer and negative COVID 19 RT PCR at discharge)	25 days	D-Dimer- 12.5 μg/mL (normal <0.5 μg/mL) CRP- 35 mg/dL (Normal <5 mg/dL)
2	39/M	SOB, Chest pain	CTPA: Thrombosis in right descending PA with multifocal pulmonary infarcts in lower lobe of right lung Lower limb DU: Echogenic thrombus in right popliteal vein and tibioperoneal trunk	PA thrombosis with DVT[a]	20 May 2021	49 days	Mild	Uneventful at home	–	D-Dimer- 2.5 μg/mL CRP- 4.0 mg/dL Normal Echocardiography
3.	44/M	SOB, Chest Pain	CTPA: Small PA thrombus in descending branch of left PA Lower limb DU- Normal	PA Thrombosis without DVT	11 June 2021	67 days	Asymptomatic	Uneventful at home	–	D-Dimer- 2.0 μg/mL CRP- 3.5 mg/dL Normal Echocardiography
4	75/M	SOB, Chest pain	CTPA: Thrombi in segmental and sub-segmental branches of PA supplying right upper lobe. Partial thrombosis in right descending PA, lobar and segmental branches of all segments of right middle and lower lobes. Lower limb DU- Normal	PA Thrombosis without DVT	16 June 2021	57 days	Severe	NIV, Discharged after 28 days (Normal D-dimer and negative COVID 19 RT PCR at discharge)	25 days	D-dimer-5.5 μg/mL, CRP- 23.5 mg/dL Normal Echocardiography
5	29/M	SOB, Restlessness, Chest pain, and Haemoptysis	CTPA: PA thrombus involving confluence of pulmonary trunk (saddle thrombus) with bilateral segmental and subsegmental extension Lower limb DU- Normal	PA Thrombosis without DVT	23 August 2021	75 days	Mild	Uneventful at home	–	D-Dimer- 4.6 μg/mL CRP- 10 mg/dL ECG- RV Strain, Echocardiography- RV dysfunction
Arterial thrombotic events										
1.	82/M	Dizziness, speech problem, right hemiparesis with numbness	NCCT Head: Left side infarction of external capsule & claustrum	Thrombosis of deep branches of left MCA	15 April 2021	30 days	Moderate	Oxygen Support, discharged after 13 days (Normal D-dimer and negative COVID 19 RT PCR at discharge)	11 days	D-Dimer −14.5 μg/mL CRP- 35 mg/dL
2	68/M	Pain, swelling, and blackish	Lower Extremity CT Angiography: Complete	Thrombosis of large arteries of	22 May 2021	60 days	Severe	NIV, discharged after 26 days	27 days	D-Dimer −12 μg/mL CRP -25 mg/dL

(continued on next page)

Table 1 (*continued*)

S no	Age (years)/ sex	Symptoms	Findings of imaging studies	Thrombotic event (TE)	Date of TE	No. of days from positive COVID -19 RT PCR to TE	Severity of COVID 19 at initial diagnosis	Hospital course (If previously admitted for COVID-19)	Days after discharge from hospital to TE	Peak D-dimer and CRP level at presentation of TE/ other investigations
		discoloration of both legs	thrombosis of bilateral popliteal arteries, collateral filling of bilateral posterior tibial arteries, non-opacification of bilateral anterior tibial and peroneal arteries.	both lower limbs[a]				(Normal D-dimer and negative COVID 19 RT PCR at discharge)		
3	30/F	Right Loin Pain	IV Contrast Enhanced Abdominopelvic CT scan: Segmental thrombus in right main renal artery with acute infarct of right kidney	Right renal artery thrombosis	25 May 2021	51 days	Moderate	Oxygen support, discharged after 12 days (Normal D-dimer and negative COVID 19 RT PCR at discharge)	33 days	D-Dimer- 3.8 μg/mL CRP- 3.5 mg/dL
4	43/M	Pain, numbness and right hand and forearm cold to touch	Upper Extremity CT Angiography: Thrombosis and narrowing of right brachial and radial arteries	Thrombosis of large arteries of right upper limb	1 June 2021	30 days	Asymptomatic	Uneventful at home	–	D-Dimer −2.0 μg/ mL CRP-5.5 mg/dL
5	54/F	Pain abdomen, Nausea, and vomiting	IV Contrast Enhanced Abdominopelvic CT scan: Splenic infarct and bilateral multiple small renal infarcts with normal splenic & renal blood vessels. Partial Thrombosis of SMA with no bowel ischemia	Possibly Microvascular thrombosis of spleen and both kidneys, Partial Thrombosis of SMA[a]	4 June 2021	64 days	Severe	NIV, discharged after 28 days (Normal D-dimer and negative COVID 19 RT PCR at discharge)	25 days	D-Dimer- 2.5 μg/mL CRP- 11.0 mg/dL
6	75/M	Pain, swelling and left lower limb cold to touch	Lower Extremity CT Angiography: Thrombosis of left common iliac artery	Thrombosis of left common iliac artery	5 July 2021	76 days	Moderate	Oxygen Support, discharged after 19 days (Normal D-dimer and negative COVID 19 RT PCR at discharge)	50 days	D-Dimer −10.5 μg/ mL CRP-15.0 mg/dL

Abbreviations: CRP- C-Reactive Protein, CTPA- CT Pulmonary Angiogram, DU- Doppler Ultrasound, DVT- Deep Vein Thrombosis, IV- Intravenous, MCA- Middle Cerebral Artery, NCCT- Non-Contrast Computed Tomography, NIV- Non-Invasive Ventilation, PA- Pulmonary Artery, RT PCR- Real Time Polymerase Chain Reaction, RV- Right Ventricle, SMA- Superior Mesenteric Artery, SMV- Superior Mesenteric Vein, SOB- Shortness of Breath, TE- Thrombotic Event.

[a] Thrombotic events at multiple (>1) sites.

were delayed and occurred 30–76 days after diagnosis of COVID-19 (mean ± SD; 55.2 ± 15.6 days). While 5 patients were identified with venous thrombosis, arterial thrombosis was diagnosed in 6 individuals. Four patients had multiple (>1) thrombotic events whereas seven cases had single thrombotic event. As presented in Fig. 1, while 10 cases had macrovascular thrombosis, 1 patient had both macrovascular and microvascular thrombosis.

Venous TE included pulmonary artery (PA) thrombosis in 4 patients while 1 patient had thrombosis of superior mesenteric vein, portal vein and splenic vein. A patient of PA thrombosis had concomitant deep vein thrombosis (DVT). Arterial TE included acute lower limb ischemia in 2 cases, and 1 patient each of acute upper limb ischemia and acute ischemic stroke. While 1 patient had partial thrombosis of superior mesenteric artery, splenic infarcts, and bilateral multiple renal infarcts despite patent splenic and renal blood vessels; the other patient had acute right renal infarct due to thrombosis of right main renal artery. Dimerized plasmin fragment D (D-dimer) levels were raised (mean ± SD, 6.6 ± 4.8 μg/mL; range, 2–14.5 μg/mL) in all patients at presentation of TE whereas C-reactive protein (CRP) was elevated (mean ± SD, 15.5 ± 12.2 mg/dL; range, 3.5–35 mg/dL) in 8 patients. The platelet counts, however, were normal in all cases.

Some characteristics of TEs in our cases are as follows: first, delayed TE in previously asymptomatic to mild COVID-19 patients ($n = 4$) after 30–75 days of COVID-19 diagnosis (mean ± SD, 55.2 ± 17.3 days); second, post-discharge TE in moderate to severe COVID-19 cases ($n = 7$) after 11–50 days (mean ± SD, 28.0 ± 11.7 days) of discharge from

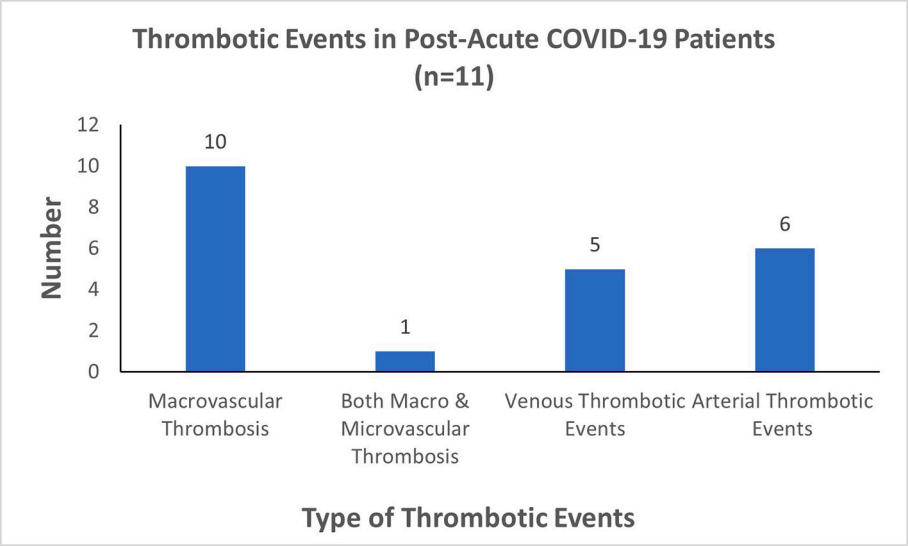

Fig. 1. Type of Thrombotic Events in Post-Acute COVID-19 Patients.

hospital despite thromboprophylaxis [standard-dose low molecular weight heparin (LMWH) in moderate cases, intermediate-dose LMWH in severe cases] for the duration of hospital stay and normal pre-discharge D-dimer and CRP levels and platelet count; third, thrombotic complications without pre-existing comorbidities or evidence of arteriosclerotic disease in imaging, indicating independent thrombotic risks of COVID-19; fourth, arterial and venous TE with similar frequency; fifth, predominantly macrovascular thrombosis with few solid-organ-infarcts despite patent blood vessels suggesting microvascular thrombosis; sixth, mostly PA thrombosis without concomitant DVT signifying in-situ thrombosis; and seventh, no bleeding events were noted in our cases. However, the number of patients in our study is too low to deduct general consequences.

Currently, there is emerging evidence about risk of thrombosis in COVID-19 patients within 90-days after discharge from hospital. In a prospective study, the authors reported post-discharge venous thromboembolism and arterial thromboembolism rates of 1.55 %, 1.71 %, respectively [6]. In another study [7], 1.3 % COVID-19 patients had post-discharge venous thromboembolism while 0.5 % patients had arterial thromboembolism. A Swedish study reported an increased risk of DVT up-to 3-months, PE up-to 6-months and bleeding event up-to 2-months after COVID-19 with a higher risk in patients with comorbidities and severe disease [8].

Due to lack of systematic follow-up of COVID-19 patients at our institution, it may be difficult to determine incidence of post-discharge TE as only cases referred for imaging were evaluated. Moreover, follow-up of large number of patients during an epidemic may be unrealistic. Nevertheless, with only 7 (0.25 %) of 2846 hospitalized patients diagnosed with thrombotic event(s) during the study period within 50-days of discharge from hospital, the estimated incidence of post-discharge thrombosis at our institution may be about 1.8 % per 100 patient-years [95 % confidence interval 0.61 to 3.68] against typical annual incidence of venous thromboembolism in local population of India of about 0.1 % [9].

Currently, there is considerable debate on post-discharge thromboprophylaxis for COVID-19 patients. Some authors recommend assessing predischarge D-dimer and CRP levels for decision to continue thromboprophylaxis. Pin et al. [7] in a cohort of 2832 hospitalized COVID-19 patients observed that those with a predischarge D-dimer level >3 μg/mL, and C-reactive protein level >10 mg/dL were more likely to experience venous thromboembolism after discharge. Some authors [6] have found significant reduction in TE in hospitalized patients with severe COVID-19 and cardiovascular risk-factors prescribed anticoagulants at prophylactic-doses at hospital discharges. The post-discharge thrombosis risk of 0.25 % at our institution is by itself quite low, even lower than 0.32 % risk of venous thromboembolism after hospitalization for haemorrhoidectomy, suggesting that this population should not systematically require post-discharge thromboprophylaxis. Though predischarge D-dimer and CRP levels were normal in our patients with TE, low number of cases is limitation of the study.

At our institution four patients who later presented with a TE earlier had asymptomatic to mild COVID-19 infection. Their COVID-19 diagnosis was based on positive RT-PCR test. Their home-isolation period remained uneventful as monitored telephonically. These patients were not advised any investigation. One of these patients had only a small PA thrombus in descending branch of left PA while the other 3 patients had catastrophic TE in the form of multiple thrombi in branches of right PA with pulmonary infarcts; saddle thrombus at confluence of pulmonary trunk with right ventricular dysfunction; and thrombosis of right brachial and radial arteries, respectively. A recent paper on four young asymptomatic COVID-19 positive individuals developing delayed catastrophic TE [10] demonstrates unpredictable course of COVID-19. It is suggested that medical practitioners should remain vigilant and continue observing patients for TE during post-acute phase, irrespective of severity of COVID-19 and absence of risk-factors.

Now when COVID-19 virus has mutated as Omicron and thrombosis risks appear to have dropped, it raises question whether reduction in COVID-19 associated thrombosis is because of COVID-19 vaccination [8] or if some virus strains are less prothrombotic? Unfortunately, none of our patients with TE previously received COVID-19 vaccination.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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