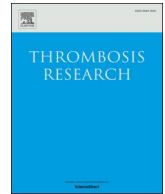




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Letter to the Editors-in-Chief

Severe arterial thrombosis associated with Covid-19 infection



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Dear Editor

We were very interested to read the article published by Klok et al. reporting the incidence of thrombotic complications in critically ill ICU patients diagnosed with Covid-19 [1]. The article highlighted the high rate of venous thromboembolism (VTE) and arterial thrombotic events within this population. Many publications have reported cardiovascular complications associated to SARS-CoV2 infection [1–4]. However, few are focused on systemic arterial embolism [1].

We report seven cases of severe arterial thrombotic events in patients infected with Covid-19. These patients developed rapidly progressive lower limb ischemia or formation of mobile aortic thrombi (Table 1). Covid-19 diagnosis was made by PCR assay and/or chest computed tomography (CT) associated to respiratory symptoms in all cases. In case of respiratory deterioration, CT pulmonary angiography was performed to look for an acute pulmonary embolism (PE). Symptomatic arterial thrombosis was diagnosed clinically and confirmed by a color Doppler duplex ultrasonography (CDDUS) and/or CT angiography (CTA).

All patients had a history of cardiovascular disease (Table 1). Five patients were diagnosed with irreversible lower limb ischemia. Three patients were hospitalized in the intensive care unit (ICU) under therapeutic anticoagulation for acute or chronic arrhythmia or thrombophilia. In two cases, therapeutic anticoagulation had to be switched to a prophylactic dose 72 hours before the arterial event because of melena. A conservative treatment was decided by a multidisciplinary team considering the severity of respiratory distress and multiple organ dysfunction. In two cases, asymptomatic floating thoracic aortic thrombi were detected on a pulmonary angiography that had been performed after respiratory deterioration. No previous images were available for comparison.

Two patients had history of lower limb vascular surgery. One of them underwent surgery after lower limb CDDUS confirmed long segment occlusion from the right common iliac artery to the femoral tripod. On day one post revascularization and transfemoral amputation, despite therapeutic anticoagulation, severe left leg ischemia prompted the performance of an abdominal CTA. We diagnosed a suspended thrombus in the deep femoral artery with intra-abdominal floating thrombi. The second patient occluded a previously patent femoral

artery bypass in the absence of known triggers.

In addition, among all patients, two of them also presented VTE, one deep vein thrombosis and one segmental PE.

We describe very severe arterial thrombotic complications occurring in COVID-19 patients despite the use of antiplatelet or anticoagulant therapy, including irreversible lower limb ischemia and free floating thrombi in the thoracic aorta. Since the beginning of the pandemic we have noticed an unusual severity of lower limb ischemia, partly explained by the healthcare system saturation resulting in delayed patient presentation. We were also confronted with unusual extension or localization of arterial thrombosis diagnosed in a short period of time.

Other studies have shown cardiovascular disease to be an independent risk factor of pejorative outcome, and myocardial injury to be associated to a heavy mortality rate in COVID-19 [2–4]. Recent publications have highlighted a coagulation disorder in severely diseased patients [3,5], responsible for a hypercoagulable state which might explain disseminated intravascular coagulation and organ failure. Some hypothesize a direct effect of coronavirus on vascular endothelial cells to justify acute arterial thrombosis [4,6]. As a result, systematic thrombosis prophylaxis in patients presenting sepsis induced coagulopathy score ≥ 4 or D-dimer $> 3.0 \mu\text{g/mL}$ is recommended [6]. Klok et al. brought to light VTE occurring in ICU patients despite this prophylaxis, and suggested a need to increase dosage of anticoagulant treatment for patients with high venous thrombotic risk.

Further studies and publications about SARS-CoV2 infection with a focus on arterial thrombotic complications are needed to characterize arterial consequences of coronavirus and to evaluate the necessity of therapeutic anticoagulation in COVID-19 patients with peripheral arterial occlusive disease or thrombophilia.

Declarations of interest

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Table 1

Characteristics of patients and cardiovascular events

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Baseline characteristics							
Age (years), gender	67, female	58, female	69, male	71, male	59, male	82, male	64, male
Medical history	Diabetes	Hypertension, Diabetes	Stroke, Essential thrombocythaemia, Hypertension	Homozygous factor V Leiden mutation, Hypertension, Deep vein thrombosis	Flutter, Hypertension, COPD, active smoking (44 PY)	Atrial fibrillation, Chronic renal failure, Hypertension, PAOD	Hypertension, PAOD, Weaned smoking (50 PY)
BMI (kg/m ²)	30	22	25	30	46	25	27
Usual antithrombotic treatment	No	No	Aspirin 75mg/day	Rivaroxaban 20mg/day	Apixaban 10 mg/day	Aspirin 75 mg/day, Warfarin	Aspirin 160 mg/day
Antithrombotic treatment at time of arterial event	No	No	Aspirin 75mg/day and prophylactic anticoagulation*	Prophylactic anticoagulation*	Apixaban 10 mg/day	Aspirin 75mg/day and prophylactic anticoagulation*	Aspirin 160 mg/day
Covid infection							
Diagnosis	PCR	Positive	Positive	Positive	Positive	Positive	Positive
Treatment	Chest CT Oxygen therapy Vasopressors	Positive Yes, Nasal oxygen No	Positive Yes, Non-rebreather mask No	Positive Yes, intubation Yes	Positive Yes, intubation Yes	Positive Yes, non-rebreather mask No	Positive No No
Arterial thrombosis							
Thrombus localisation	NA	Descending thoracic aorta	Aortic arch and descending thoracic aorta	Right popliteal artery	Left common femoral artery	Right: iliac artery and femoral tripod Left: deep femoral artery	Right femoro-popliteal bypass
Days from disease onset to thrombotic event	13	0	14	4	0	Right : 15 Left : 18	0
Symptomatology at the time of diagnosis	Bilateral irreversible lower limb ischemia	Incidental diagnosis	Incidental diagnosis	Irreversible ischemia of the right leg	Irreversible ischemia of the left leg	Irreversible ischemia of the right leg and contralateral acute ischemia at day 1	Irreversible ischemia of the right leg
Imaging exam	No	CTA	CTA	CDDUS	CTA	CDDUS CTA	CDDUS, CTA
Treatment	Medical	Medical	Medical	Medical	Medical	Medical and thrombectomy + amputation	Medical and amputation
VTE associated	No	No	PE	Deep vein thrombosis of the left popliteal vein	No	No	No
D-dimer (µg/L)	NA	1200	3700	> 20000	> 20000	NA	NA
Fibrinogen (g/L)	NA	7.1	6.8	6.4	2.3	NA	7.7
Platelets (/mm ³)	120000	308000	700000	80000	60000	367000	173000

BMI: Body mass index, PY: Pack-years, COPD: Chronic obstructive pulmonary disease, PAOD: Peripheral arterial occlusive disease, *: curative anticoagulation suspended due to melena, PCR: Polymerase chain reaction, CT: Computed tomography, CTA: CT Angiography, CDDUS: Color doppler duplex ultrasonography, VTE: Venous thromboembolism, PE: Pulmonary embolism, NA: Not Applicable.

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