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General Review

Arterial Thrombosis in Coronavirus Disease 2019 Patients: A Rapid Systematic Review

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Background: Emerging evidence suggests that severe form of coronavirus disease 2019 (COVID-19) is mediated, in part, by a hypercoagulable state characterized by micro- and macro-vascular thrombotic angiopathy. Although venous thrombotic events in COVID-19 patients have been well described, data on arterial thrombosis (AT) in these patients is still limited. We, therefore, conducted a rapid systematic review of current scientific literature to identify and consolidate evidence of AT in COVID-19 patients.

Methods: A systematic search of literature was conducted between November 1, 2019, and June 9, 2020, on PubMed and China National Knowledge Infrastructure to identify potentially eligible studies.

Results: A total of 27 studies (5 cohort, 5 case series, and 17 case reports) describing arterial thrombotic events in 90 COVID-19 patients were included. The pooled incidence of AT in severe/critically ill intensive care unit–admitted COVID-19 patients across the 5 cohort studies was 4.4% (95% confidence interval 2.8–6.4). Most of the patients were male, elderly, and had comorbidities. AT was symptomatic in >95% of these patients and involved multiple arteries in approximately 18% of patients. The anatomical distribution of arterial thrombotic events was wide, occurring in limb arteries (39%), cerebral arteries (24%), great vessels (aorta, common iliac, common carotid, and brachiocephalic trunk; 19%), coronary arteries (9%), and superior mesenteric artery (8%). The mortality rate in these patients is approximately 20%.

Conclusions: AT occurs in approximately 4% of critically ill COVID-19 patients. It often presents symptomatically and can affect multiple arteries. Further investigation of the underlying mechanism of AT in COVID-19 would be needed to clarify possible therapeutic targets.

INTRODUCTION

Since the initial reports in late December 2019 in Wuhan, China, the coronavirus disease 2019

(COVID-19) has rapidly spread to other parts of the world and has been declared a public health emergency of international concern by the World Health Organization.¹ As of June 9, 2020, the disease had spread to more than 203 countries and territories, with >7,039,918 confirmed cases and >404,396 fatalities.²

The clinical spectrum of COVID-19 spans from an asymptomatic form to severe disease characterized by hypoxemic respiratory failure, septic shock, and multiorgan dysfunction (MOD) that require invasive mechanical ventilation and other forms of organ support in critical care units.^{3,4} Emerging evidence suggests that these severe and critical forms of COVID-19 are mediated, in part, by a hypercoagulable state characterized by micro- and macro-vascular thrombotic angiopathy.^{5,6} This

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hypothesis is supported by the laboratory profile seen in patients with severe COVID-19, typified by significant elevation in D-dimer, prothrombin, and fibrinogen levels.^{7,8} Furthermore, severe COVID-19 is associated with systemic hyperinflammation with elevated proinflammatory cytokines (tumor necrosis factor, interleukin [IL]-6, and IL-1 β),^{9,10} which may contribute to the development of intravascular coagulopathies. In their recent report, Klok et al. reported a cumulative incidence of thrombotic complications of 49% in a cohort of critically ill COVID-19 Dutch patients who had received standard doses of thromboprophylaxis, further supporting the occurrence of thrombotic events.¹¹

Although there is a substantial pool of evidence of venous thrombotic and thromboembolic events in COVID-19 patients,^{5–8,11–14} there are a few scattered reports on intra-arterial thrombosis (AT) in these patients. We, therefore, conducted a rapid systematic review of current scientific literature to identify and consolidate data on the incidence of AT in COVID-19 patients, age and sex distribution of these patients, as well as the clinical presentation, anatomical distribution, and outcomes of AT.

METHODS

A rapid systematic review of scientific literature was conducted to consolidate currently available evidence of arterial thrombotic complications in COVID-19 patients. Rapid reviews accelerate the process of evidence synthesis while maintaining a systematic approach.

Literature Search Strategy

A comprehensive and systematic search of literature from November 1, 2019, to June 9, 2020, was conducted on the Medline (PubMed interface) and China National Knowledge Infrastructure to identify studies eligible for inclusion. The electronic search was carried out using the strategy as follows: (1) ((COVID-19) OR (SARS-CoV-2)) OR (2019-nCoV), (2) (((((Arterial Thrombosis) OR (Thrombotic Complication)) OR (Limb Ischemia)) OR (Cerebral Ischemia)) OR (Myocardial Ischemia)) OR (Mesenteric Ischemia), (3) 1 AND 2. No language restriction was applied. When the articles were published by the same study group and there was an overlap of the search period, only the most recent article was included to avoid duplication of data. The PubMed function “related articles” was used to extend the search. Also, we searched major infectious disease, hematology, and general medicine journals reporting articles about COVID-19

infection to look for additional studies. We then performed handsearch of the bibliography of included studies to detect other potentially eligible investigations.

Eligibility Criteria

The search results were screened by title and abstract, with those of potential relevance evaluated by full text. Studies were deemed eligible for inclusion if they fulfilled the following criteria: (1) were case reports/case series/cohort studies, (2) included patients with a reverse transcriptase polymerase chain reaction–confirmed COVID-19 diagnosis, (3) monitored the patients for the development of complications during the course of admission, and (4) reported clear extractable data on arterial thrombotic complications.

Data Extraction

Data extraction was conducted by 3 independent reviewers (I.C., V.K., and B.N.). For each study, the following information was extracted: the surname of the first author and the year of publication, the geographical region where the study was performed, the type of study (case report/case series/cohort), sample size, demographic characteristics, number of patients with arterial thrombotic complications, anatomical location of the thrombi, imaging modality used in the diagnosis of AT, concurrent venous thrombosis, and comorbidities and mortality in patients with AT. Any variances arising during this were resolved by a consensus.

Synthesis of Findings

The synthesis of results was carried out in 2 steps. First, findings on all eligible studies reporting AT in COVID-19 patients were presented in the form of a summary of findings table (Table 1) accompanied by a narrative description. Thereafter, a pooled analysis incorporating only cohort studies with sample ≥ 50 patients was conducted to estimate pooled incidence of AT in severe/critically ill intensive care unit (ICU)-admitted COVID-19 patients using the MetaXL (software version 5.3; EpiGear International Pty Ltd., Sunrise Beach, Australia). A random effects model was applied. The magnitude of heterogeneity among the included studies was assessed using the chi-squared test (Chi²) and I-squared statistic (I²). For the Chi² test, a Cochrane's Q *P* value of <0.10 was considered significant. An I² of $<40\%$ was considered not significant. In addition, a leave-one-out sensitivity analysis was performed

Table I. Characteristics of the included studies

Author	Country	Study design	Sample size	Patients with AT, n (%)	Demographic characteristics of patients with AT		Anatomical location of the thrombi	Imaging modality used in the diagnosis of AT	Other concurrent thrombotic events	Comorbidities in patients with AT	Mortality rate in patients with AT
					Age (years)	Male, n (%)					
Andrea et al. ¹²	Italy	Case Report	1	1	58	1 (100)	Lower limb (anterior and posterior tibial arteries)	Ultrasound	None	None	0 (0)
Ahmed et al. ¹³	UK	Case report	1	1 (100)	29	0 (0)	CNS (basilar artery)	CT head	None	DM, RTA, asthma	1 (100)
Azouz et al. ¹⁴	France	Case report	1	1 (100)	56	-	CNS (right MCA), aorta, and GIT (SMA)	CT scan	None	NR	0 (0)
Baldacini et al. ¹⁵	France	Case report	1	1 (100)	62	0 (0)	CNS (left and right MCA, left ICA, BA, left PCA)	CT angiography	None	Acute myelogenous leukemia	1 (100)
De Brarry et al. ¹⁶	France	Case report	1	1 (100)	79	0 (0)	Abdomen (SMA and jejunal artery)	CT abdomen	Portal vein thrombosis	None	1 (100)
Beccara et al. ¹⁷	Italy	Case report	1	1 (100)	52	1 (100)	Abdomen (SMA)	CT abdomen	None	None	0 (0)
Bellosta et al. ¹⁸	Italy	Case series	20	20 (100)	75 ± 9	18 (90)	Lower limb (infrainguinal 16; aortoiliac 3); upper limb 1	CT angiography	None	HTN, Afib, CKD, obesity, COPD, diabetes, and CAD	8 (40)
Fraisse et al. ¹⁹	France	Cohort	92	6 (6.5)	62	-	CNS (2), heart (coronary 1), limb (2), abdomen (SMA 3)	Not reported	Pulmonary and deep venous thrombosis	HTN, Afib, CKD, COPD, diabetes	Not reported
Gaicomelli et al. ²⁰	Italy	Case report	1	1 (100)	67	1 (100)	Aortic graft thrombosis	Doppler ultrasound	None	Abdominal aortic aneurysm repair	1 (100)
Goldberg et al. ²¹	USA	Case report	1	1 (100)	64	1 (100)	CNS (ICA)	CT head	None	Hypertension	1 (100)
Gomez-Arbelaiz et al. ²²	Spain	Case series	4	4 (100)	50–76	3 (75)	Aortoiliac 2; CNS-1; aortic arch 1; thoracic aorta 1; common carotid 1	CT angiography	DVT, PE	HTN, dyslipidemia	1 (25)
Harari et al. ²³	USA	Case report	1	1 (100)	40	0 (0)	Heart (left coronary artery)	Coronary angiography	None	DM, HTN, hyperlipidemia, and schizophrania	1 (100)

(Continued)

Table I. Continued

Author	Country	Study design	Sample size	Patients with AT, n (%)	Demographic characteristics of patients with AT		Anatomical location of the thrombi	Imaging modality used in the diagnosis of AT	Other concurrent thrombotic events	Comorbidities in patients with AT	Mortality rate in patients with AT
					Age (years)	Male, n (%)					
Helms et al. ²⁴	France	Cohort	150	4 (2.7)	-	-	CNS (cerebellar arteries) (2); lower limb (1); abdomen SMA (1)	MRI and CT	None	Cardiovascular disease, diabetes, chronic renal disease	Not reported
Kashi et al. ²⁵	France	Case series	7	7 (100)	64–82	4 (57)	Aorta (2); lower limb-Femoro-popliteal (5)	Color doppler duplex ultrasonography and/or CT angiography	VTE in 2 patients	DM, HTN, COPD, Afib, stroke, CKD	Not reported
Kaur et al. ²⁶	USA	Case report	1	1 (100)	71	1 (100)	Upper limb (right brachiocephalic and axillary artery)	CT angiography	None	DM	1 (100)
Klok et al. ¹¹	The Netherlands	CNS (5)	-	-	-	-	Netherlands patients); peripheral arteries (2 patients)	Cohort Not reported	184 VTE	7 (3.8) Not reported	- Not reported
Le Barre et al. ²⁷	France	Case report	1	1 (100)	71	1(100)	Aorta	CT angiography	PE	None	0 (0)
Lodigiani et al. ²⁸	Italy	Cohort	362	ICU: 4 (8.3) General ward: 9 (2.9)	55–86	7 (70)	CNS (9 patients) and 4 (coronary arteries)	Not reported	VTE	DM, active smoking, HTN	2 (20)
Malentacchi et al. ²⁹	Italy	Case report	1	1 (100)	81	1 (100)	CNS (MCA)	CT angiography	Dural venous sinus thrombosis	Myasthenia gravis, leukemia, prostate cancer	1 (100)
Mestres et al. ³⁰	Spain	Case series	4	4 (100)	71	3 (75)	Lower limb: infrapopliteal (all distal veins in one leg [1 patient]; all distal veins in both legs [2 patients]; femoropopliteal [1 patient]), upper limb: radioulnar (1 patient)	CT angiography	VTE	Not reported	0 (0)

Nassabein et al. ³¹	Canada	Case report	1	1 (100)	66	0 (0)	Aorta (descending thoracic and abdominal)	CT angiography	None	HTN, osteopenia	0 (0)
Perini et al. ³²	Italy	Case series	2	2 (100)	37 and 53	2 (100)	Lower limb (aortoiliac); upper limb (humeral artery)	CT angiography	None	None	1 (50)
Rey et al. ³³	Spain	Case report	1	1 (100)	59	1 (100)	Cardiac (left and right coronary arteries)	Coronary angiography	None	HTN, DM	0 (0)
Thomas et al. ³⁴	UK	Cohort	63	2 (3)	-	-	Heart (coronary artery)	Coronary angiography	Not reported	Not reported	Not reported
Valdivia et al. ³⁵	Spain	Case series	4	4 (100)	53, 70, 72, 72	-	Lower limb (iliac artery and infrainguinal arteries)	Not reported	None	COPD, DM, HTN	1 (25)
Viguiet et al. ³⁶	France	Case report	1	1 (100)	66	1 (100)	Left common carotid artery	CT angiography	None	None	0 (0)
Vuillamy et al. ³⁷	UK	Case series	2	2 (100)	60 and 75	1 (100)	Aortoiliac and SMA	CT angiography	None	None	0 (0)

Afib, atrial fibrillation; BA, basilar artery; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive lung disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; GIT, gastrointestinal system; HTN, hypertension; ICA, internal carotid artery; LAD, left anterior descending artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; RTA, renal tubular acidosis; SMA, superior mesenteric artery.

to assess the robustness of the results and to further probe the sources of interstudy heterogeneity.

RESULTS

Study Identification

The initial search produced 185 potentially relevant articles. After the removal of duplicates and primary screening, 85 articles were assessed by full text for eligibility in the meta-analysis. Of these, 58 were excluded because the primary and secondary outcomes of the study did not match that of this review. Thus, a total of 27 articles were included in this systematic review and meta-analysis (Fig. 1 and Table I).

Characteristics of the Included Studies

A total of 27 studies describing arterial thrombotic events in 90 COVID-19 patients were included.^{11–37} The majority of the studies were from Europe (23 studies; France: 8, Italy: 7, Spain: 4, the United Kingdom: 3, and the Netherlands: 1), whereas the rest were from North America (the United States of America: 3 and Canada: 1). Of the included studies, 5 were cohort, 5 were case series, and the rest were case reports. Essential characteristics of the included are outlined in Table I.

Data Synthesis

Incidence of AT. Five cohort studies ($n = 537$ patients) reported data on the incidence of AT in severe/critically ill ICU-admitted COVID-19 patients, with the incidence ranging from 2.7%–8%.^{11,19,24,28,34} The pooled incidence of AT across these 5 studies was 4.4% (95% confidence interval 2.8–6.4), with no interstudy heterogeneity observed ($I^2 = 0\%$, Cochran's $Q = 3.908$; $P = 0.419$; Fig. 2). No significant changes in the pooled incidence were observed in the leave-one-out sensitivity analysis.

Age and Sex Distribution of Patients with AT. The majority of the patients with arterial thrombotic events were male. The reported age of these patients ranged from 29 to 86 years. Across all case reports and case series, only 3 patients were aged <50 years. Although the cohort studies did not report the specific ages of AT patients, the median age of the whole cohort in all the 5 studies was >60 years.

Comorbid Conditions in Patients with AT. The majority of the AT patients had pre-existing conditions, such as hypertension,^{18,19,21,23,28,31} cardiovascular disease,^{18–20,24} atrial fibrillation,^{18,19,25} chronic

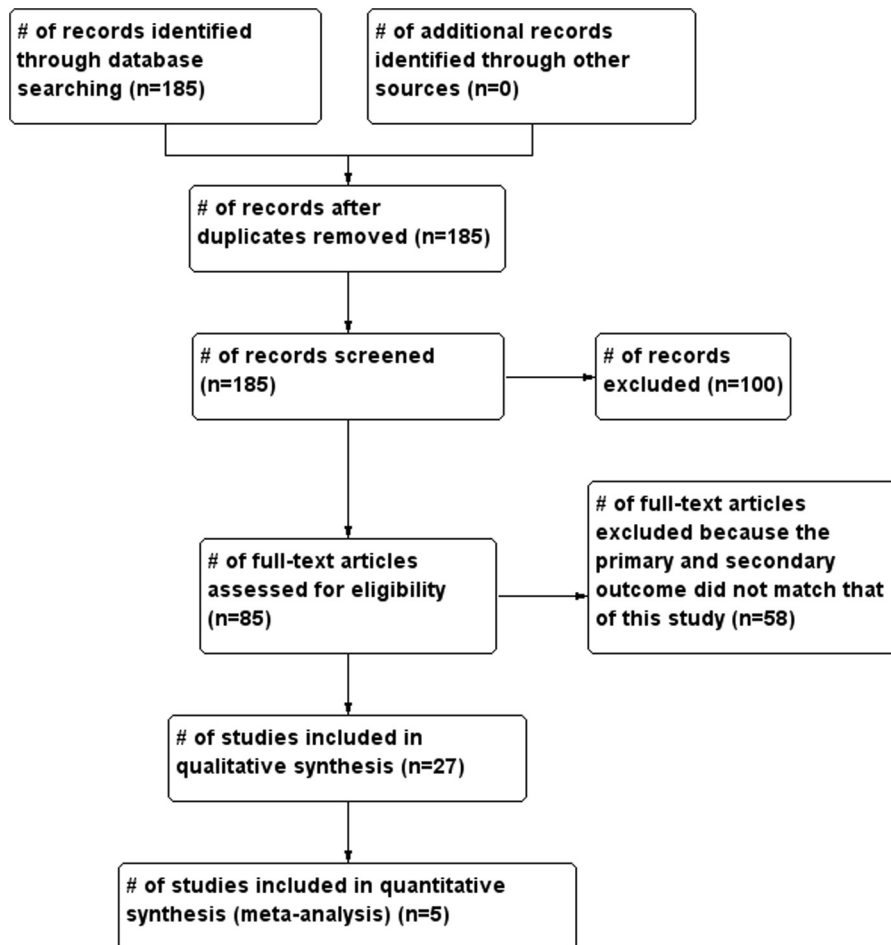


Fig. 1. PRISMA flowchart showing the flow of studies through the meta-analysis.

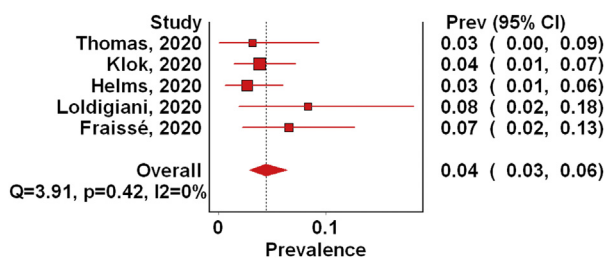


Fig. 2. Forest plot for the pooled incidence of arterial thrombosis in severe/critically ill COVID-19 patients.

kidney disease,^{18,19,25} chronic obstructive lung disease,^{18,19,25,35} obesity,¹⁸ hyperlipidemia,^{22,23} diabetes mellitus,^{13,18,19,23,24,28,35} asthma,¹³ leukemia,^{14,29} and renal tubular acidosis.¹³ Only 5 studies reported AT in patients with no comorbid conditions.^{12,16,17,27,32}

Clinical Presentation of Patients with AT. AT was incidentally discovered in 2 patients.^{27,31} It was

symptomatic in the rest, manifesting as acute limb ischemia,^{11,12,18,19,21,24–26,30,32,35,37} acute cerebral ischemia,^{11,13–15,19,21,22,24,28,29} acute mesenteric ischemia,^{14,16,17,19,24,37} and acute myocardial ischemia.^{19,23,33,34}

Vascular Territory of AT. AT occurred in native vessels in all but one patient, where it occurred in a prosthetic aortic graft.²⁰ Multiple arterial thrombi were observed in 16 patients (17.7%). The distribution of arterial thrombotic events in the 90 patients are as follows: the anatomical distribution of arterial thrombotic events was wide, occurring in limb arteries (39%), cerebral arteries (24%), great vessels (aorta, common iliac, common carotid, and brachiocephalic trunk; 19%), coronary arteries (9%), and superior mesenteric artery (8%; Table I).

Mortality in Patients with AT. Across the 21 case reports and case series that reported outcome data in AT patients, 10 of 52 patients (19.2%) died. Only one cohort study reported mortality

specifically in patients with AT, with the mortality rate being 20%.²⁸

DISCUSSION

The literature reviewed in this article documents AT as a complication of COVID-19. Severe COVID-19 is characterized by among other features hypoxemic respiratory failure, septic shock, and MOD. Of these complications, intra-AT in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is scarcely documented.

The present study documents that AT develops in approximately 4.4% of severe/critically ill COVID-19 patients. The mechanisms of AT in these patients is still unclear. Emerging evidence suggests that COVID-19 is associated with endotheliitis, characterized histologically by diffuse endothelial damage and infiltration by inflammatory cells.³⁸ Damage to the endothelium could be as a result of direct viral infection,^{39,40} which is facilitated by the overexpression of angiotensin-converting enzyme receptor 2, the receptor for cell entry of SARS-CoV-2, in endothelial cells.^{41,42} COVID-19 is also associated with a hypercoagulable state, characterized by elevation of D-dimers, prothrombin, and fibrinogen,^{7,8} with consequently reduced clot formation time and higher maximum clot firmness.⁴³ The hyperviscosity is thought to be as a result of systemic extrapulmonary hyper inflammation and hypercytokinemia, which activate the coagulation cascade.^{9,10} These 2 factors (endotheliitis and hypercoagulability), together with prolonged immobilization of critically ill COVID-19 patients complete the Virchow's triad, providing a plausible explanation for the mechanisms of AT. It is noteworthy that AT developed even in patients without gross evidence of atherosclerosis,³² which is an established precursor for AT.

The majority of the patients with AT were elderly, which is consistent with the already well-established age-associated increase in the plasma concentration of coagulation factors such as fibrinogen, factors V, VII, VIII, and X, as well as the von Willebrand's factor.^{44,45}

Arterial thromboembolism in the general population commonly affects more males compared with females.^{46,47} This observation was similarly reflected in our analysis and has been explained by the differences in hormonal and genetic profiles of the 2 sexes^{46,47} with female sex hormones producing a favorable immune modulation.⁴⁸ Furthermore, the prevalence and severity of COVID-19 has since been established to be higher in males than in females.⁴⁹

Most of the AT patients had pre-existing comorbidities, supporting the current evidence that pre-existing chronic illnesses increase both the incidence and severity of COVID-19.^{50,51} A similar observation has been reported in pediatric populations where the presence of congenital cardiovascular disease predisposed affected children to severe human coronavirus infections.⁵² Viral infections have been known to worsen pre-existing vasculitic conditions besides directly inducing both myocardial and vascular injury.^{53–55} Vascular inflammation is an established precursor to the pathogenesis of AT.⁵⁶ Pre-existing cardiac diseases have been known to prejudice one to low-grade vascular inflammation,^{56,57} which could be exacerbated by the SARS-CoV-2 infection and hence the enhanced prevalence of AT in these particularly predisposed individuals.

The varied presentation of AT in COVID-19 reveals the widespread arterial involvement reflected in our analysis. The nonuniform distribution in the involved arteries reveals that this was an acute thrombotic occlusion since, in acute states, there exist intraindividual regional differences in arterial thrombogenicity.⁵⁸

Findings from this study suggest that the mortality rate in COVID-19 patients with AT could be around 20%, and this is mainly driven by the presence of end-organ injury as evidenced by the various acute ischemic events as recorded in our analysis.

Our study was limited by the small number of included studies, which were mainly case reports and case series. Larger well-designed studies are urgently needed to confirm these findings.

In conclusion, AT occurs in approximately 4% of critically ill COVID-19 patients. The majority of the patients are male, elderly, and have comorbid conditions. It often presents symptomatically and can affect multiple arteries. Further investigation of the underlying mechanism of AT in COVID-19 would be needed to clarify possible therapeutic targets.

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