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COVID-19 and Peripheral Artery Thrombosis: A Mini Review

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Abstract: For more than 2 years, health care systems have been floundering in a massive crisis of coronavirus disease 2019 (COVID-19) pandemic. While acute respiratory distress syndrome is the main complication in patients with COVID-19, as the pandemic continues, more data about the nonrespiratory effects of the coronavirus is obtained, including developing Coagulopathy-related manifestations, in the form of venous and arterial thromboembolism. Although arterial thrombosis a rare complication of this disease, it proves to be an effective factor in the mortality and morbidity of COVID-19 patients. The pathophysiology of thrombosis reveals a complex relation between hemostasis and immune system that can be disrupted by COVID-19. Thrombectomy, anticoagulant therapy, and thrombolysis are the main treatments in these patients. In addition, appropriate thromboprophylaxis treatment should be considered in COVID-19 patients. In this article, we have successfully reviewed the arterial thrombotic events in patients reported around the world, including the diagnostic and management method of choice. (Curr Probl Cardiol 2022;47:100992.)

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Introduction

Emerging in December 2019, Coronavirus Disease 19 (COVID-19) has been declared as a pandemic by WHO; reporting 198,778,175 confirmed cases and 4,235,559 deaths by August 4 2021.[1] COVID-19 shows a wide spectrum of clinical presentation and continues to intrigue medical professionals with its variety of symptoms ranging from mostly asymptomatic to fatal conditions following multi-organ involvement mainly involving respiratory system.[2] Prior outbursts of coronaviruses, (ie, severe acute respiratory syndrome coronavirus 1 [SARS-CoV-1] and Middle-Eastern respiratory syndrome [MERS]) have shown a significant association with increased risk of thrombosis.[3] Likewise, COVID-19 appears to generate a prothrombotic state as evidenced by a surge in global pulmonary embolisms, deep vein thrombosis, cardiac thrombosis, catheter related thrombosis, and arterial thrombosis. Moreover, laboratory tests of COVID-19 patients demonstrate the prothrombic state of patients; including increased level of D-dimer, fibrinogen, factor VIII, and von Willebrand factor.[4] Although there has been an extensive focus on deep vein thrombosis and pulmonary embolism as the complications of the COVID-19, there is limited number of studies in fields of peripheral arterial thrombosis. Furthermore, the studies performed on arterial thrombotic events are majorly along with the studies of venous thromboembolism, which decreases the focus on diagnostic and treatment options for this complication. We aim to investigate the literature focusing on arterial thrombotic complications, including the location, method of localization and diagnosis, and management procedure.

Methods

In order to achieve an accelerated qualitative analysis, we performed PubMed search using MeSH (medical subject headings) terms in search strategies mentioned below:

(1 "COVID-19″[Mesh] OR "SARS-CoV-2″[Mesh], (2) "Arteries" [Mesh], "Thrombosis"[Mesh], and "Blood Coagulation"[Mesh], (3) combination and snowballing of (1) and (2). We select the relevant articles to arterial thrombotic events for the purpose of this review. In order to decrease the level of bias, data were extracted independently by FY and EG in a double data extraction method, followed by a thorough reassessment of included articles by AR and IK.

Pathophysiology

COVID-19 may lead to an increased risk of thrombotic events through various pathophysiological means (Fig 1):

1. Disseminated intravascular coagulation: Disseminated intravascular coagulation is commonly observed in critically ill patients. Generally, it elicits the initiation of the tissue factor pathway of the coagulation cascade and deposition of platelet-fibrin thrombi in the microvasculature. This ultimately consummates the platelets and the procoagulant factors, resulting in a correlated bleeding diathesis.[5]
2. Inflammatory cytokines: Excessive cytokine release is assumed to be the cause of the severe illness noted in adolescent patients without prior comorbidities. Higher serum levels of several inflammatory cytokines and chemokines have been related to severe illness and death in several studies.[6]
3. Macrophage activation syndrome (MAS): MAS may contribute to the aspects of the cytokine storm and hypercoagulopathy observed in COVID-19 patients. MAS occur when activated antigen presenting cells cannot be lysed by CD8+ T cells or natural killer cells. After an initial inflammatory trigger, elevated IL-6 has been shown to diminish natural killer cells cytolytic capacity. Hence, there is a substantial interaction among innate and adaptive immune system that additionally promotes cytokine storm, phagocytosis, and multiorgan dysfunction.[7]
4. Complement system activation: Complement system activation may also recruit and activate leukocytes, resulting in significant release of the proinflammatory cytokines (ie, IL-1, IL-6, IL-8, and interferon-γ) and promoting microvascular damage. Complement system is strongly activated in sepsis and inhibiting the complement cascade can improve coagulopathy and endothelial dysfunction in animal models with sepsis.[8]
5. Renin angiotensin system (RAS) overactivation: Angiotensin-converting enzyme 2 (ACE2) is a membrane-bound protein mainly distributed in the lungs, heart, arteries, and veins.[9] Angiotensin II(Ang II), the product of ACE2, promotes vasoconstriction, proinflammation, and prothrombotic effects via the Angiotensin II receptor type I (AT1R) and Angiotensin II receptor type IV (AT4R). ACE2 inhibits the RAS activity in 2 ways. First, ACE2 degrades Ang I and Ang II, reducing the substrate for activation of AT1R via the classical RAS. Secondly, Ang II is directly degraded into Angiotensin-(1-7), a

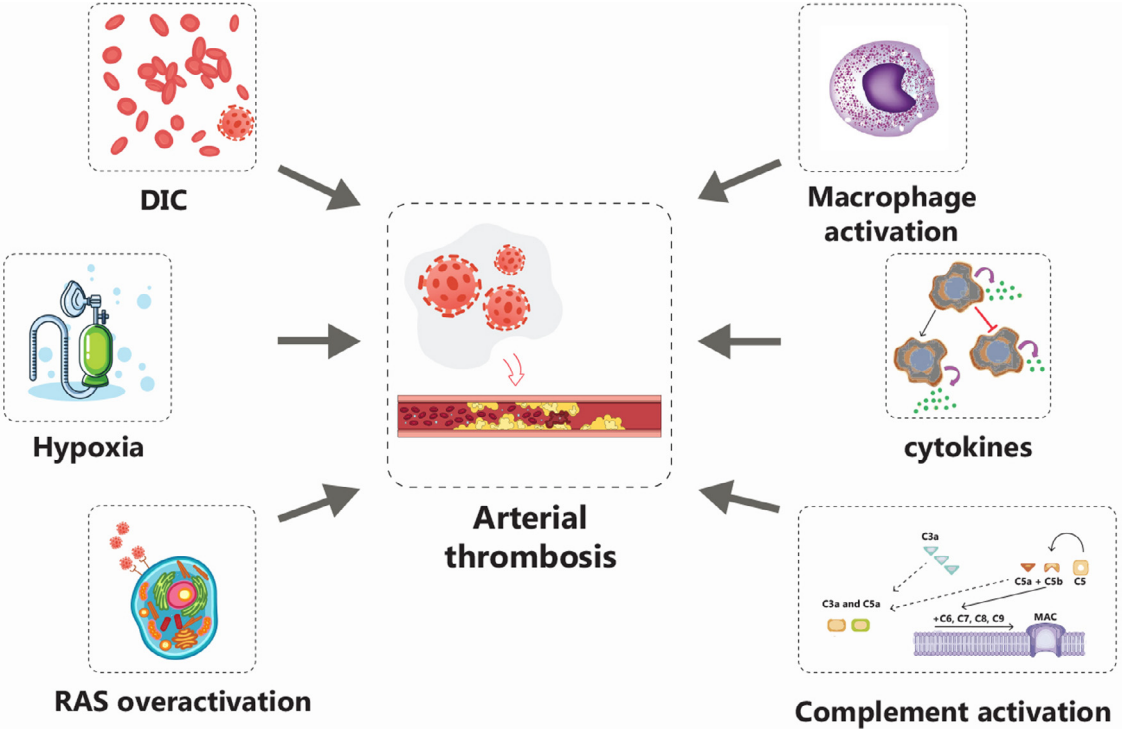

FIG 1. Mechanisms of thrombosis in Covid-19.

vasodilatory peptide with anti-inflammatory effects. COVID-19 uses ACE2 for cellular entry. Through this process, it is assumed that the downregulation of pulmonary of ACE2 is followed by moving the balance towards proinflammatory and prothrombotic effects of Ang II and AT1R.[10]

6. Hypoxia: Hypoxia-inducible factors can activate platelets and coagulation factors, causing an increased expression of tissue factor and plasminogen activator inhibitor 1, meanwhile inhibiting the endogenous anticoagulant protein leading to worsening of the hypercoagulable state.[11]

Review of Cases

We reviewed 46 patients ranging from 24 to 83 years old with average and median of 61.4 and 61 years old, respectively. Covid 19 infection was confirmed in all patients included in the study by using standard methods that are acceptable worldwide; including polymerase chain reaction, chest X ray, chest computer tomography scan (CT), and serological tests. Details of each case are provided in Table 1. Male sex, smoking, hypertension, diabetes, chronic kidney disease, and obesity are corelated with preexisting endothelial dysfunction which is a risk factor for thrombosis.[12,13] We illustrated these risk factors in Figure 2. We divided these thromboses to 5 groups based on location: 1- head and neck, 2- aorta, 3- abdomen, 4- upper limb, and 5- lower limb. Each group includes several arteries which is illustrated bellow:

Head and Neck

We reviewed 7 cases of thrombosis in central retinal artery, ophthalmic artery, internal carotid artery, common carotid, and middle cerebral artery. CT-angiography (CTA) was used as the diagnostic method for 3 patients, CT for 1 patient, and other methods in 3 patients. For treatment, low molecular weight heparin (LMWH) was given in 3 patients, unfractionated heparin (UFH) in 2 patients, and thrombectomy and endarterectomy were performed each in 1 patient.

Thoracic Aorta

We observed 16 cases of arterial thrombosis localized in the thoracic Aorta as a result of covid-19 infection; Of which ascending aorta (n = 2), aortic arch (n = 6), and descending aorta (n = 8) were specifically

TABLE 1. Review of literature on Covid-19 peripheral artery thrombosis, and what kind of diagnosis modality and management method was chosen.

	Age/Sex	Medical history	Sign and symptoms related to thrombosis	Localization of thrombosis (arteries)	Timing of thrombosis	Diagnosis of thrombosis	Complications	treatments	Outcome and follow up
Case 1[18]	60, M	HTN, DLP, CAD, COPD	Painless vision loss in right eye	Right central retinal	12 days after covid test +	assessment of intraocular pressure	None	NR	NR
Case 2[19]	59, M	HTN, hyperuricemia, sickle cell anemia	Painless vision loss in left eye	left central retinal	14 days after covid symptoms	Optical coherence tomography	None	NR	NR
Case 3[20]	48, M	Obese, sleep apnea	Painless vision loss in right eye	Right ophthalmic	38 days after covid test +	Funduscopic examination	DVT	LMWH	Discharged
Case 4[21]	61, M	HTN, asthma	left hand weakness and numbness	right common carotid	14 days after covid symptoms	CTA	None	Endarterectomy, UFH, LMWH	Discharged
Case 5[22]	76, M	HTN, DLP, DM	Right sided loss of strength, aphasia, hemiplegia	Left internal carotid, multiple thrombosis in ascending aorta	28 days after covid symptoms	CTA	None	LMWH	Discharged
Case 6[23]	76, F	HTN, DLP, psoriasis	None	Aortic arch, left common carotid	15 days after covid symptoms	CTA	Cerebral infraction	UFH	Discharged
Case 7[24]	56, NR	NR	Abdominal pain, vomiting	Right middle cerebral, aortic arch, superior mesenteric	Same day as covid test +	CT	None	Thrombectomy, resection of small intestine	NR
Case 8[25]	69, M	Stroke, ET, HTN	Accidentally found	Aortic arch, descending thoracic aorta	14 days after covid symptoms	CTA	PE	Medical treatments*	NR
Case 9[26]	59, M	Schizophrenia, epilepsy, PAD	Mottled skin of lower limb extending to sub umbilical	Midaorta	9 days after covid symptoms	ultrasound	DVT	Norepinephrine, thrombolysis, UFH	Expired
Case 10[23]	69, M	None	Accidentally found	Descending thoracic aorta	15 days after covid symptoms	CTA	PE	anticoagulant	Discharged
Case 11[27]	53, F	None	Dyspnea	Aortic arch	10 days after covid symptoms	CT	PE	UFH, thrombolysis, argatroban	NR

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TABLE 1. (*continued*)

	Age/Sex	Medical history	Sign and symptoms related to thrombosis	Localization of thrombosis (arteries)	Timing of thrombosis	Diagnosis of thrombosis	Complications	treatments	Outcome and follow up
Case 12[22]	78, M	DLP, urothelial carcinoma	None	Aortic arch, descending aorta	9 days after covid symptoms	CTA	Multiple PE	LMWH	Expired
Case 13[22]	64, M	Former smoker, HTN, obstructive sleep apnea, hepatitis B, obese	None	Multiple thrombosis in Descending aorta	11 days after covid symptoms	CT	None	UFH bridged to LMWH	NR
Case 14[25]	58, F	HTN, DM	Accidentally found	Descending aorta	Same day as covid test +	CTA	Non	Medical treatment*	NR
Case 15[28]	61, F	DM2, HTN, DLP, GERD, and bipolar disorder	Abdominal pain	Thoracic aorta, abdominal aorta	14 days after covid symptoms	CTA	RV thrombosis	thrombolysis, LMWH bridged to rivaroxaban	Discharged
Case 16[29]	49, M	DM, CAD, obese	Pain and loss of heat in right lower limb	Descending aorta, right femoral	40 days after covid symptoms	CT	none	Thrombectomy, fasciotomy, right below knee amputation	Discharged
Case 17[30]	71, M	None	Left iliac fossa and flank pain	Ascending aorta, left renal	23 days after covid symptoms	CTA	None	UFH bridged to apixaban, clopidogrel	Discharged
Case 18[31]	83, F	HTN, DM2	Cyanotic and pale lower limbs, distended abdomen	Descending thoracic aorta, abdominal aorta, iliac, superior mesenteric, renal	Same day as covid test +	CT	PE	Comfort measures	NR
Case 19[32]	75, M	None	Abdominal pain, vomiting	Descending thoracic aorta, superior mesenteric	16 days after covid symptoms	CTA	None	thrombolysis, resection of small intestine	NR
Case 20[33]	56, M	DM2, HTN, obese	Weakness and hypoesthesia in left lower limb	Aortic arch, aortoiliac, deep femoral, bilateral popliteal	Same day as covid test +	CT, angiography	Recurrent thrombosis	UFH, thrombectomy	Still admitted in ICU

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TABLE 1. (*continued*)

	Age/Sex	Medical history	Sign and symptoms related to thrombosis	Localization of thrombosis (arteries)	Timing of thrombosis	Diagnosis of thrombosis	Complications	treatments	Outcome and follow up
Case 21[23]	50, M	None	NR	Aortoiliac	12 days after covid symptoms	CTA	DVT, cerebellar infarction	Bilateral thrombectomy	Discharged
Case 22[23]	67, M	HTN	pain, coldness, and paleness in lower limbs	Aortoiliac	17 days after covid symptoms	CTA	None	Bilateral thrombectomy, limb amputation	Expired
Case 23[34]	73, M	HTN, smoker	Bilateral hip and buttock pain, lower limb paresthesia and paralysis	Aortoiliac, common deep and superficial femoral, bilateral popliteal, tibial	Same day as covid test +	CT	Thrombosis at aortic aneurysm site	thrombolysis, thrombectomy, UFH	expired
Case 24[32]	60, M	NR	Weakness, hypoesthesia, and ischemia in lower limbs	Aortoiliac	14 days after covid symptoms	CTA	None	Thrombectomy	NR
Case 25[35]	70, F	HTN, DM2	cold, pulseless, mottled, and pale left limb	Abdominal aorta, left common iliac, internal iliac, external iliac, popliteal	Same day as covid test +	CTA	Splenic vein, SMV and IMV thrombosis	Thrombectomy, thrombolysis, UFH bridged to warfarin	Discharged
Case 26[29]	70, M	HTN, smoker, DLP	Abdominal and lower limbs pain	Abdominal aorta	29 days after covid symptoms	CT	None	thrombectomy	Expired
Case 27[36]	46, M	None	Abdominal pain, diarrhea	right renal branches	1 day after covid symptoms	CT	None	UFH bridged to LMWH	Discharged
Case 28[37]	82, F	atrial fibrillation for over 4 years, CKD, HTN	abdominal pain and distention	Superior mesenteric	3 days after covid test +	CT	None	None	Expired during preparation for surgery
Case 29[38]	45, M	None	abdominal pain, vomiting	Superior mesenteric	5 days after covid symptoms	CTA	SMV thrombosis	UFH, thrombectomy, resection of small intestine	NR

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TABLE 1. (*continued*)

	Age/Sex	Medical history	Sign and symptoms related to thrombosis	Localization of thrombosis (arteries)	Timing of thrombosis	Diagnosis of thrombosis	Complications	treatments	Outcome and follow up
Case 30[39]	79, F	None	Epigastric pain, diarrhea	Superior mesenteric, jejunal	8 days after covid symptoms	CT	Portal vein thrombosis	resection of small intestine and right colon, thrombolysis, thrombectomy	Expired
Case 31[40]	52, M	NR	Diarrhea, vomiting, abdominal pain	superior mesenteric	23 days after covid symptoms	CT	None	resection of small intestine	Discharged
Case 32[41]	69, M	NR	epigastric pain, constipation, eructation	superior mesenteric, ileocolic branches	NR	CTA	None	resection of small intestine, thrombectomy	Discharged
Case 33[42]	61, F	DM, HTN	abdominal pain with distention, vomiting	distal superior mesenteric	4 days after covid test +	CT	None	UFH, ecosprin, clopidogrel, resection of small intestine	Expired
Case 34[43]	44, M	Uncontrolled DM	pain and paresthesia in right upper limb, hypoesthesia in fingers, gangrene of distal arm, forearm, and hand	Right axillary	13 days after covid symptoms	CTA, ultrasound	Recurrent thrombosis	First time: thrombectomy Second time: steroids, LMWH, antibiotics, right limb amputation above elbow	Discharged
Case 35[44]	50, F	HTN, DLP, DM1, CKD, MGUS	Swelling and ischemic signs in the right upper limb	Distal radial	6 days after covid test +	CTA	None	heparin, iloprost, Amlodipine Forearm amputation	NR
Case 36[45]	71, M	DM	Severe pain in right upper limb	right brachiocephalic, subclavian, axillary, brachial, radial, ulnar	More than 15 days after covid symptoms	ultrasound, CTA	None	UFH bridged to LMWH, thrombectomy, endarterectomy	Expired
Case 37[46]	68, M	HTN, ESRD	Cold and mottled right upper limb	Right brachial, radial, ulnar	1 day after covid test +	NR	None	thrombectomy, heparin	Expired

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TABLE 1. (*continued*)

	Age/Sex	Medical history	Sign and symptoms related to thrombosis	Localization of thrombosis (arteries)	Timing of thrombosis	Diagnosis of thrombosis	Complications	treatments	Outcome and follow up
Case 38[47]	46, M	HTN, DM	Left sided weakness mainly in lower limb, right upper limb pain, weakness, cyanosis, and coolness, fourth right finger necrosis	Brachial, radial, ulnar	NR	CTA	None	Anticoagulant, limb heating, antibiotics, corticosteroids	Discharged
Case 39[48]	31, M	CF, bilateral lung transplantation, chronic lung allograft dysfunction, SVC syndrome	Painful and cold limbs, loss of motricity, and sensitivity on the right side	left internal iliac, Common femoral	39 days after covid symptoms	CTA	LV thrombosis	thrombectomy, LMWH bridged to vitamin K antagonist, aspirin	Discharged
Case 40[25]	82, M	AF, CKD, HTN, PAOD	Ischemia of right lower limb	Right iliac, right femoral, left deep femoral	Right 15 and left 18 days after covid symptoms	CTA, ultrasound	None	Medical treatment*, thrombectomy, amputation	NR
Case 41[49]	70, M	lung cancer surgery 4 years ago	ecchymosis of the right lower limb, bluish-purple swelling, and pain to palpation of the lower limb	right femoral, superficial femoral	23 days after covid symptoms	ultrasound	None	LMWH, lower right extremity amputation	Expired
Case 42[25]	59, M	HTN, COPD, smoker, obese, flutter	Ischemia of the right lower limb	Left common femoral	Same day as covid test +	CTA	None	Medical treatments*	NR
Case 43[25]	64, M	HTN, PAOD, former smoker	Ischemia of the right lower limb	Right femoropopliteal	Same day as covid test +	CTA, ultrasound	None	Medical treatments*, amputation	NR
Case 44[50]	24, M	NR	right lower limb pain, intermittent claudication	right common femoral, profunda femoral, tibial posterior, popliteal	Few days after covid symptoms	ultrasound	None	LMWH, aspirin, thrombectomy	Discharged

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TABLE 1. (*continued*)

	Age/Sex	Medical history	Sign and symptoms related to thrombosis	Localization of thrombosis (arteries)	Timing of thrombosis	Diagnosis of thrombosis	Complications	treatments	Outcome and follow up
Case 45[25]	71, M	HTN, DVT, obese, homozygous factor V Leiden mutation	Ischemia of the right lower limb	Right popliteal	4 days after covid symptoms	Ultrasound	DVT	Medical treatments*	NR
Case 46[51]	40, M	NR	Left lower limb pain	Right popliteal	NR	Ultrasound	None	NR	NR

AF, atrial fibrillation; CAD, coronary artery disease; CF, cystic fibrosis; CKD, chronic kidney disease; COPD; chronic obstructive pulmonary disease; CT, computer tomographic; CTA, computer tomographic angiogram; DVT, deep venous thrombosis; DLP, dyslipidemia; DM, diabetes mellitus; ESRD, end stage renal disease; ET, essential thrombocytopenia; F, female; GERD, gastroesophageal reflux disease; HTN, hypertension; IMV, inferior mesenteric vein; LMWH, low molecular weight heparin; LV, left ventricle; M, male, MGUS, monoclonal gammopathy of undetermined significance; NR, not reported; PAD, peripheral arterial disease; PAOD, peripheral arterial occlusive disease; PE, pulmonary embolism; RV, right ventricle; SVC, superior vena cava; SMV, superior mesenteric vein; UFH, unfractionated heparin.

*Medical treatments: exact treatment was not mentioned in the original literature.

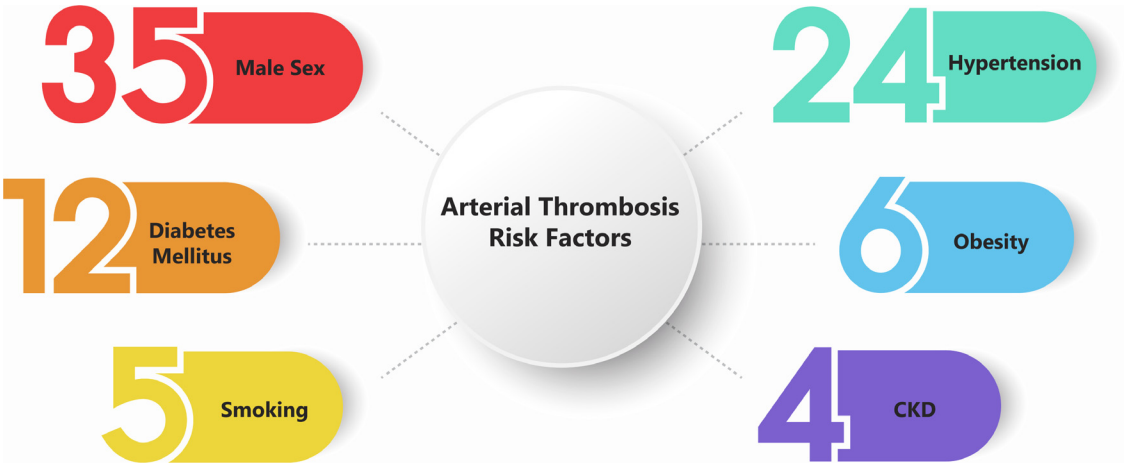

FIG 2. Risk factors of arterial thrombosis in Covid-19. The numbers represent the count of each risk factor associated with 46 cases.

mentioned as the region of involvement. Two studies did not mention the exact region of the thrombosis. CTA was the method of choice for diagnosis in 9 patients, CT in 6, angiography in 1, and ultrasound in 1 patient. For treatment purposes UFH was given in 6 patients, LMWH in 4, thrombolysis in 4, and thrombectomy in 3. Other treatments that were not commonly used include norepinephrine, clopidogrel, direct oral anticoagulants, and argatroban. Two case reports did not accomplish to address the exact treatment and management method.

Abdomen

We reviewed 20 cases of abdominal thrombosis occurring in abdominal aorta, superior mesenteric, jejunal, ileocolic branch arteries, and renal arteries. The most common diagnostic method included CT (n = 10) and CTA (n = 9), followed by angiography (n = 1) and ultrasound (n = 1). Common treatment choices consisted of thrombectomy (n = 10), resection (n = 7), UFH administration (n = 7), thrombolysis (n = 5), clopidogrel (n = 2), and LMWH administration (n = 2). Less frequent treatments were apixaban, warfarin, vit K antagonist, aspirin, and ecosprin.

Upper Limb

We reviewed 5 patients of the upper limb thrombosis in brachiocephalic, subclavian, axillary, brachial, radial, ulnar as a result of covid-19 infection. The diagnostic method was CTA alone (n = 2) or CTA and Doppler-ultrasound (n = 2). UFH (n = 3) and LMWH (n = 2) were administered to the patients for treatment. Thrombectomy was performed in 3 patients. Amputation was carried out in 2 patients.

Lower Limb

We reviewed 16 cases of lower limb thrombosis in common iliac, internal, and external iliac, deep, and superficial femoral, popliteal, tibial, and posterior tibial as a result of covid-19 infection. Diagnostic methods included CTA (n = 8), ultrasound (n = 6), CT (n = 4), and angiography (n = 1). For management, thrombectomy (n = 9) and amputation (n = 6) were performed. The remaining patients underwent medical treatment with LMWH (n = 3), UFH (n = 2), thrombolysis (n = 1), and aspirin (n = 1).

Concomitant Venous Thrombosis and Pulmonary Embolism

Overall, there were 4 patients with pulmonary embolism and 8 patients with venous thrombotic events classified in 4 patients with deep vein thrombosis, 3 with inferior/superior mesenteric vein and 1 with portal vein thrombosis. there were also 2 patients with cardiac thrombosis with thrombi located in the ventricles.

Discussion and Conclusions

Thrombotic events are frequently seen in COVID-19 and contribute to poorer outcome.[7] As for the other reviews have frequently discussed pulmonary embolism, vein thrombosis and cardiovascular thrombotic events, the purpose of this review is to fill the gap in the literature about arterial thrombosis along with future perspectives regarding diagnostic and therapeutic methods. Here we summarized 46 cases of arterial thrombosis categorized into 5 groups based on location of event.

Cheruiyot et al[14] reported the majority of the COVID-19 patients with arterial thrombosis have been male patients, and the median age has been 50 years old. However, due to the fact that venous and arterial involvement has not been separated in this literature, the data reported for arterial involvement have been missing the age-sex information. The other possible pitfall in this field is that the prevalence of COVID-19 infection is more in male population and the median age of infection is 50 years old.[3] Hence, it should be further investigated whether the male sex and age is indeed a risk factor for arterial thrombosis, or the predominance of arterial thrombosis in male patients in certain age group is merely a result of age-sex prevalence of COVID-19 infected patients.

Comparing the venous thromboembolism, arterial thrombosis is an uncommon event. Di Minno et al[15] reported the incidence of venous thromboembolism 24.3-39.2% in a meta-analysis, whereas the incidence of arterial thrombosis is 4.4%.[14] Higher D-dimer value is mentioned as a risk factor of both venous and arterial thromboembolic events.[15,16] Both asymptomatic and symptomatic venous thrombosis show high levels of D-dimer. Contrarily, there are limitations in studying d-Dimer level in asymptomatic arterial thrombosis, as a result of lower prevalence rate of arterial thrombosis in COVID-19 patients.

Most frequently used diagnostic methods were CTA, CT, and ultrasound. CTA was the most used diagnostic method with 24 times in all discussed categories, followed by CT (n = 13), and ultrasound (n = 9). The therapeutic method of choice was thrombectomy with total of 18 times. In the next place UFH with 13 and LMWH with 12 times were

used. Additionally, amputation or resection were performed 14 times and thrombolysis therapy 7 times.

Future Therapeutic Targets and Areas of Research

Elevated levels of D-dimer were seen at least in 31 patients. Previously collected data clearly suggests that an elevated D-dimer, and presence of coagulopathy, indicates a poorer prognosis in COVID-19 patients.[2,17] Heightened clinical vigilances and observation of D-dimer levels is needed in hospitalized covid-19 patients, although the decision-making process should be case-based for every individual. Thrombosis is a major complication in COVID-19 patients with optimal thromboprophylaxis being unknown. At least 14 patients were given anticoagulant as prophylaxis which was proven inadequate and highlights the necessity of novel or additional therapeutic approaches.

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