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Review

COVID-19 and peripheral arterial complications in people with diabetes and hypertension: A systematic review

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ABSTRACT

Aims: Identify the prevalence, risk factors and outcomes of lower extremity ischemic complications.
Methods: A systematic review was conducted by searching PubMed and SCOPUS databases for SARS-CoV-2, COVID-19 and peripheral arterial complications.
Results: Overall 476 articles were retrieved and 31 articles describing 133 patients were included. The mean age was 65.4 years. Pain and gangrene were the most common presentation. Hypertension (51.3%), diabetes (31.9%) and hypercholesterolemia (17.6%) were associated co-morbidities. Overall, 30.1% of patients died and amputation was required in 11.8% patients.
Conclusions: COVID-19 patients with diabetes or hypertension are susceptible for lower limb complications and require therapeutic anti-coagulation.

Introduction

The global pandemic of COVID-19 has stirred the scientific community not only because of the scale of infection affecting millions of individuals but also because of the varied presentations involving multiple organ systems. Though, COVID-19 characteristically involves the respiratory system causing acute respiratory distress syndrome (ARDS) even more distinctive is the complications of COVID-19 pertaining to the vascular system. COVID-19 is associated with cytokine storm that precipitates disseminated intravascular coagulation and thrombotic microangiopathy involving the medium and small size vessels.[1] Multiple thrombotic complications and presentations have been ascribed to COVID-19 mainly acute coronary syndrome, pulmonary thromboembolism, stroke, mesenteric ischemia, renal artery thrombosis and peripheral arterial disease (PAD) [2].

Involvement of the peripheral vasculature is relatively uncommon but there has been a surge in reported cases of peripheral gangrene after COVID-19 infection [2,3]. The cutaneous changes in COVID-19 secondary to arterial and venous thrombotic events manifest as gangrene of the extremities. The risk factors for peripheral gangrene in COVID-19 may be directly related to SARS-CoV-2 infection or secondary to cytokine storm, disseminated intravascular coagulation, hypercoagulability, thrombotic microangiopathy, use of inotropes in critically ill patients, cold antigen induced auto-immune phenomenon and complement activation or worsening of pre-existing diabetic peripheral vascular disease [4]. Peripheral gangrene in COVID-19 is more likely in patients with prior endothelial dysfunction secondary to hypertension or diabetes [4]. Patients with diabetes and foot complications are known to have poor survival and limb outcomes in the presence of co-existing peripheral arterial disease [5]. Studies have shown that patients with acute arterial thromboembolic lower limb complications due to COVID-19 are likely to have higher mortality (around 50%) compared to compared to similar patients without COVID-19 [6]. Therefore, we performed a systematic review of the reported cases of peripheral gangrene in COVID-19 patients, co-existing comorbidities, specific treatment given, and outcomes of limb amputations or death.

Methods

We conducted a literature search in the electronic database of PubMed central and SCOPUS using MeSH terms “COVID-19”; SARS-CoV-2″AND “gangrene”, “peripheral gangrene”, “peripheral arterial disease”. The words were used interchangeably for articles

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published in any language from Jan 2020 until June 5, 2021. Two authors conducted an independent search for case reports, case series, intervention studies, original articles reporting peripheral gangrene as outcome in COVID-19 patients. Papers that included patients who became COVID-19 positive after the occurrence of peripheral ischemia were excluded from the analysis. All articles retrieved were collated, duplicates were removed and final list prepared. In addition, reference list of the included articles were checked for additional cases. The demographic characteristics of patient population, symptom onset and duration, risk factors for peripheral arterial disease other than COVID-19 like the presence of diabetes, hypertension, hyperlipidaemia, coronary artery disease, and smoking status were noted. The duration of hospital stays, treatment offered for peripheral gangrene and outcomes in the form of limb amputation, mortality and reasons for mortality were noted.

Results

Overall, 474 articles that described ischemic complications in COVID-19 patients were retrieved from PUBMED and SCOPUS. After removing duplicates, the title and abstract of 424 publications were studied. We further excluded publications that were unrelated to peripheral gangrene but focused on gangrene of other organs example. intestine, Fournier gangrene etc. Of the selected publications, 76 were review articles, commentaries or editorial and were excluded (Fig. 1). Finally, 31 articles describing 133 patients with peripheral gangrene in COVID-19 were included for analysis as shown in Table 1 [7–37]. The mean age of the subjects was 65.4 years with 81 males and 35 females (gender was not mentioned for 17 subjects). Mean duration of symptoms before hospital presentation was 7.4 days. Pain, paraesthesia, and gangrene of the affected extremity were the most common symptoms in addition to the COVID-19 related symptoms of fever, cough and respiratory complaints. Other presentations related to peripheral extremities included swelling of leg, acrocyanosis, limb weakness, asthenia and ischemic ulcer. Majority of the articles did not mention the time from SARS-CoV-2 positivity to the onset of gangrene.

Details of pre-existing co-morbidities were available for 119 patients; hypertension was the most common associated co-morbidity present in 61 patients (51.3%), followed by diabetes in 38 (31.9%), hypercholesterolemia in 21 (17.6%), prior CAD in 19 (16.0%), COPD in 6 (5.0%), chronic kidney disease in 4 (3.4%), atrial fibrillation and prior stroke in 2 subjects each and hypothyroidism (0.84%) in one patient (Fig. 2). Anticoagulants were added to the COVID specific treatment for peripheral ischemia in 78.9% (n = 105) of patients. Heparin was the most prescribed anti-coagulant (n = 98), followed by dual anticoagulants (apixaban along with heparin) in 5 patients, warfarin only and apixaban only in one patient each. Overall, 30.1% of patients (n = 40) died during the hospital stay. COVID related ARDS and multiorgan failure (n = 26, 65%) were the most common cause of death followed by acute coronary event (n = 9, 22.5%) followed by invasive aspergillosis, pulmonary thromboembolism, stroke, terminal ileal perforation and intestinal bleeding in one patient each. All deaths were ascribed to severe COVID-19 illness. Amputation of the affected digit/limb was required in 11 of the 93 surviving of participants (11.8%).

Discussion

We analyzed the prevalence, presentation and outcomes of peripheral vascular complications in people with COVID-19. Although millions of people are afflicted with COVID-19 globally, peripheral extremity complications are uncommon. Lower limb pain and gangrene are the most frequent presentations amongst those with peripheral arterial complications. More than two-third of patients had risk factor for peripheral arterial disease including hypertension and diabetes. Almost one-third of the patients died and one in ten required limb amputations during the illness suggesting a poor prognosis.

COVID-19 is associated with a prothrombotic state and various thrombotic events predominantly involving the pulmonary and coronary vasculature in critically ill patients [38,39]. The thrombotic events in COVID-19 may manifest as pulmonary thromboembolism and acute coronary events. The incidence of clinically manifest thrombotic events is much higher in SARS-CoV-2 infection as compared to other respiratory infections such as acute influenza or other viral infections [40]. However, autopsy studies have shown that alveolar microthrombi are nine times more common in COVID-19 patients [41]. The risk of arterial thrombotic events in COVID-19 correlates with the severity of the illness as most of the events are described in critically ill patients. The risk of thrombotic events prevails in COVID-19 patients despite thromboprophylaxis with heparin or low molecular weight heparin that is routinely administered to all admitted patients [39]. A good correlation has been found between systemic markers of inflammation like D-dimer, fibrinogen levels and risk of thrombosis in COVID-19 [42]. However, a study by Tan et al. found a similar incidence of venous thromboembolic episodes in COVID-19 and non-COVID-19 patients admitted during the COVID-19 pandemic and no correlation between D-dimer or fibrinogen and thromboembolic events.[39]The coronary, pulmonary and venous thromboembolism are found to be more common than arterial thrombosis in COVID-19 which is testimony to very few cases of peripheral arterial manifestations in the literature. Peripheral arterial disease may manifest as acute lower limb pain, paraesthesias, livido reticularis, gangrene, or asymptomatic chilblain like lesions. We found that pain in the affected extremity and gangrene were the most common presenting features of peripheral arterial involvement in COVID-19 patients.

Thromboembolic risk in COVID-19 seems to be a systemic phenomenon secondary to disseminated intravascular coagulation as highlighted by markedly increased levels of inflammatory cytokineslike Il-6 and TNF-a. Also, there is a consistently increased level of fibrinogen, D-dimer, factor VIII, von Willebrand factor (vWF), and decreased antithrombin leading to a prothrombotic milieu in COVID-19. It is known that immobilized patients with critical illness are at heightened risk of thromboembolism, and COVID-9 further heightens the risk owing to a unique hypercoagulable mileu through a profound pro-inflammatory state [43]. It is proposed that viral entry into pneumocytes incites an inflammatory response that sets off a cascade of thrombosis initially localised to pulmonary vasculature and subsequent systemic response. COVID-19 is associated with endothelial injury as SARS-CoV-2 docking sites are the ACE2 receptor present on endothelial cells. It is known that SARS-CoV2 docks through its spike protein on to angiotensin-converting enzyme (ACE-2) present on the cell membrane and enters the cells. ACE-2 degrades angiotensin −II (Ang-II) and depletion of ACE-2 after binding of SARS-CoV2 to ACE-2 is associated with excess Ang-II. Ang-II binds to the Angiotensin receptor −1 and exacerbates the hypercoagulable state by increasing cytokine levels and induction of plasminogen activator inhibitor 1 (PAI-1) expression on endothelial cells. People with hypertension, diabetes and prior cardiovascular disease have reduced expression of ACE-2 that additionally contributes to high Ang-II levels in COVID-19. In addition, it has been proposed that heightened activation of monocytes and complement system confirmed by histopathological demonstration of pauci-inflammatory vasculitis with complement deposits in the affected

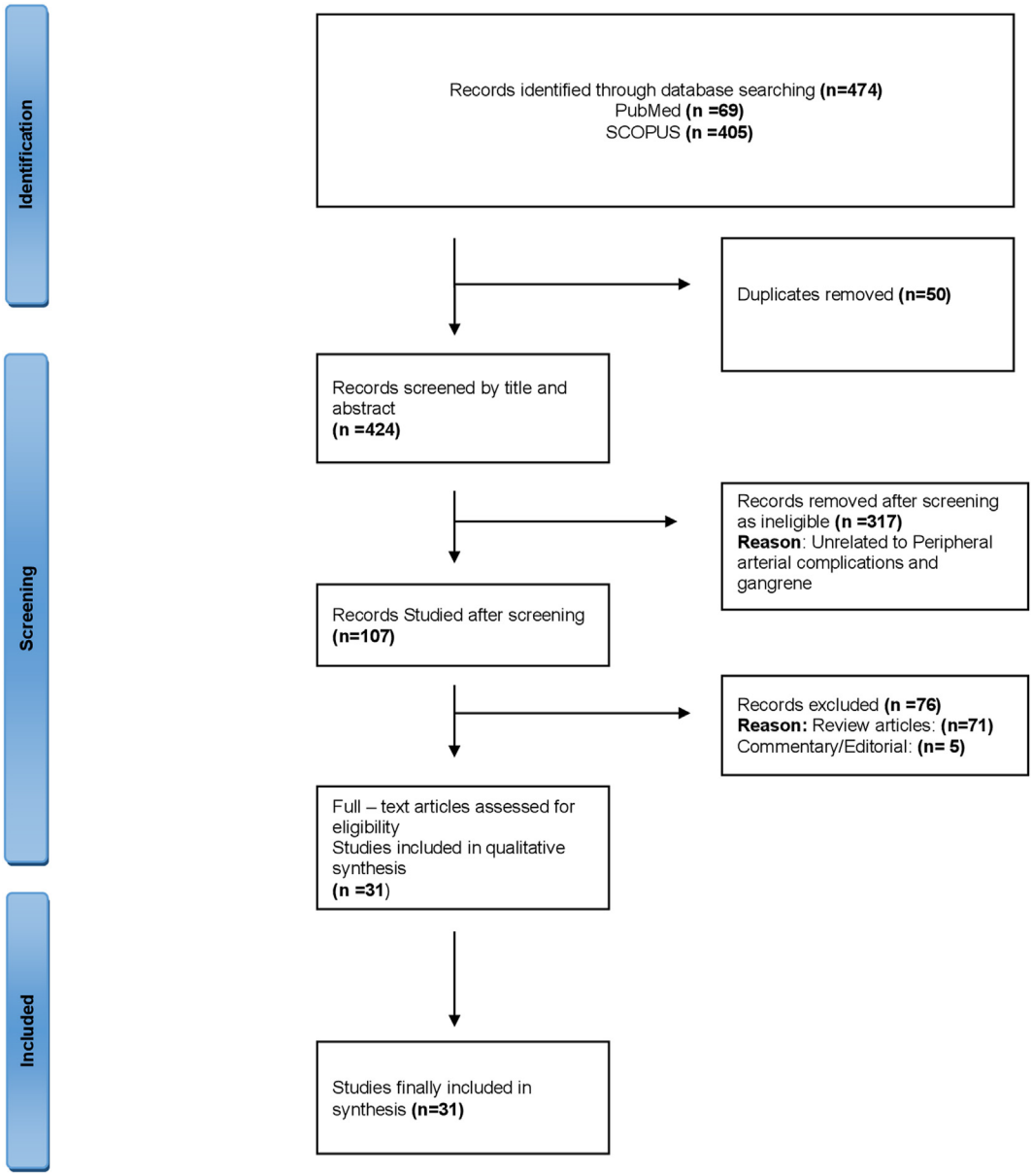

Fig. 1. PRISMA flowchart depicting records screened and study included for data synthesis.

vessel may also contribute to thrombotic microangiopathy [41]and peripheral gangrene in COVID-19.

We found that almost two-thirds of patients with reported peripheral arterial complications in COVID-19 had background hypertension, diabetes or dyslipidaemia. The risk of thrombotic peripheral arterial complications is increased manifold in patients with pre-existing endothelial dysfunction like hypertension and diabetes [44]. Diabetes (odds ratio of 2.72) and smoking (odds ratio of 1.88) are considered as the strongest risk factor for PAD [45]. It is known that diabetes being a pro-inflammatory state contributes to endothelial dysfunction, abnormal vascular smooth muscle cell (VSMC) migration into the intima layer of vessels, decreased endothelial nitric oxide synthase (eNOS) activity and platelet dysfunction that adds to hypercoagulability of COVID-19.[46] Almost one-fifth to one-third of people with diabetes have PAD that is related to the duration and severity of diabetes [47]. People with uncontrolled diabetes are more susceptible to severe COVID-19, requiring hospitalisation, thus increased likelihood of detection of peripheral arterial complications. We noticed that 10% of the subjects required limb amputation over a short duration of hospital stay and almost one fourth of the patients with COVID-19 identified in the present systematic review died due to acute coronary events that may be or not related to COVID-19. This emphasises the need for heightened screening for thrombotic complications amongst hospitalised patients with diabetes and COVID-19.

We found that almost all the patients were on therapeutic anticoagulation in the form of subcutaneous heparin (most frequent). Considering increased thrombotic risk in COVID-19, prophylactic or therapeutic anticoagulation is routinely prescribed in clinical practice. Though, the doses and duration of anticoagulation were inadequately described amongst the reported cases suggesting lack of consensus. Similarly, there is controversy regarding the prophylactic or therapeutic use of anticoagulation especially for people with co-morbidities like diabetes. The risk of thrombotic complications persists despite appropriate prophylactic anticoagulation with increased thrombotic events especially in

Table 1
Characteristics of subjects with COVID-19 and peripheral arterial complications.

	NAME OF THE AUTHOR	PLACE	NO. OF PATIENTS	AGE	GENDER	COMORBIDITY					DURATION OF SYMPTOMS (IN DAYS)	TREATMENT				OUTCOME
						DM	HTN	CAD	OBESITY	Others		ANTIBIOTICS	ANTIVIRAL	ANTICOAGULANT	OTHER	
1	Zhang et al. [7]	CHINA	n = 7	71	F	–	–	–	–	–	11	–	–	Y (n = 6)	–	5 DEATH
				63	F	–	–	–	–	–	13	–	–		–	2 IMPROVED
				59	M	Y	Y	–	–	–	11	–	–		–	
				49	M	–	–	–	–	–	7	–	–		–	
				56	M	Y	Y	Y	–	–	16	–	–		–	
				65	M	–	Y	–	–	Cerebral Infarction	13	–	–		–	
				56	F	–	–	–	–	–	3	–	–		–	
2	Novara et al. [8]	ITALY	n = 1	78	F	–	Y	Y	–	Diverticulosis, Brady Arrhythmia	–	–	Y	Y	Amiodarone	DEATH
3	Alonso et al. [9]	SPAIN	n = 24	AGE-44-78 Mean = 62.4	F:M 7:17	Y n = 7	Y n = 15	Y n = 8	Y n = 8	Dyslipidemia, Cancer, Autoimmune Disease Etc	–	Y	Y	Y	Interferon, Glucocorticoids, Tocilizumab, Cyclosporine, Colchicine	3 DEATH 21 IMPROVED
4	Mathilde et al. [10]	GERMANY	n = 1	73	F	Y	Y	–	Y	Peripheral Arteriosclerosis, Pulmonary Disease, Lichen Simplex Chronicus	–	Y	–	Y	–	IMPROVED
5	Khalid et al. [11]	UAE	n = 1	41	M	Y	–	–	–	–	14	–	Y	Y	Tocilizumab, Interferon Beta	AMPUTATION
6	Bamgboje et al. [12]	USA	n = 1	61	M	–	Y	–	–	–	14	Y	Y	Y	–	IMPROVED
7	Singh et al. [13]	India	n = 1	64	F	–	–	–	–	Venous Insufficiency, Vertigo, Migraine Headaches, Hypothyroidism, Tobacco Abuse	–	Y	Y	Y	Apixaban	IMPROVED
8	Ramachandran et al. [14]	India	n = 1	44	M	Y	–	–	–	–	3	Y	–	Y	Npwti, Pirfenidone	AMPUTATION
9	Shubhra et al. [15]	India	n = 1	65	M	–	–	–	–	–	10	Y	–	Y	Aspirin, Cilastazole, Inj. Pentoxifylline	DEATH
10	Chaudhary et al. [16]	India	n = 1	8	M	–	–	–	–	Red Eyes And Generalized Erythematous Rash	7			Y	IVIG, Methylprednisolone, Prednisone, Ceftriaxone, Aspirin	IMPROVED
11	Adekiigbe et al. [17]	USA	n = 1	47	M	Y	–	–	–	Chronic Back Pain	10		y	Y	Azithromycin, Ceftriaxone, Apixaban, Methylprednisolone,	AMPUTATION
12	Baccellieri et al. [18]	Italy	n = 1	67	M	–	Y	–	Y	–	5			Y		IMPROVED
13	Chun et al. [19]	USA	n = 1	51	M	–	–	–	–	Congenital Tricuspid Atresia, Pulmonary Stenosis	2			Y		AMPUTATION
14	Sores et al. [20]	Brazil	n = 1	67	M	Y	Y	–	–	Smoker	–	Y	Y	Y	Corticosteroid	DEATH
15	Qian et al. [21]	China	n = 1	53	M	–	–	–	–	–	9	Y	Y	Y		IMPROVED
16	Martino et al. [22]	Italy	n = 1	86	F	–	–	–	–	Acute Coronary Syndrome	–			Y		AMPUTATION
17	Ilonzo et al. [23]	USA	n = 4	62	M	Y	Y	–	–	CKD, Smoker, Chronic Pulmonary Disease	2			Y		AMPUTATION

				79	M	–	Y	–	–	Gastroesophagal Reflux	14		Y		AMPUTATION
				69	F	Y	Y	–	–	Hyperlipdemia	2		Y		AMPUTATION
				89	F	–	–	–	–	CKD, Atrial Fibrillation	–		Y		AMPUTATION
18	Valle et al. [24]	Spain	n = 3	–	–	–	–	–	–	–	17		Y		IMPROVED
				_	–	–	–	–	–	–	24		Y		IMPROVED
				_	–	–	–	–	–	–	28		Y		IMPROVED
19	Mascia et al. [25]	Italy	n = 14	AGE-65-81 Mean =	F:M –	Y n = UK	Y n = UK	Y n = UK	Y n = UK	CKD, Smoking, Dyslipidemia	–		Y		DEATHS n = 2 IMPROVED n = 1 UKNOWN n = 11
20	Etkin et al. [26]	USA	n = 49	AGE-58-75 Mean =	F:M 12:37	Y n = 17	Y n = 26	Y n = 8	Y n = 28	CKD	Mean: 6		Y		DEATHS n = 21 IMPROVED n = 25 UKNOWN n = 3
21	Perini et al. [27]	Italy	n = 2	53	M	–	–	–	–	–	7		Y		DEATH n = 1
				37	M	–	–	–	–	–			Y		IMPROVED n = 1
22	Maureree et al. [28]	USA	n = 1	60	M	–	Y	–	Y	–	10		Y		IMPROVED
23	Borrelli et al. [29]	Italy	n = 2	54	M	–	–	–	–	Dyslipidemia	1		Y	Clopidogrel, Aspirin	IMPROVED
				58	M	Y	Y	–	–	–	1		Y		IMPROVED
24	Singh et al. [30]	USA	n = 3	71	F	–	–	–	–	Parkinson, Dementia, Depression	–		Y		DEATH
				70	M	–	Y	–	–	–	–		Y		IMPROVED
				70	F	Y	Y	–	–	–	7		Y		IMPROVED
25	Kathryn et al. [31]	USA	n = 2	70	F	–	–	–	–	–	7		Y	Apixaban	DEATH
				43	M	–	Y	–	Y	Hyperlipidemia	7	Y	Y		IMPROVED
26	Veyre et al. [32]	France	n = 1	24	M	–	–	–	–	–	–		Y	Aspirin	IMPROVED
27	Khattab et al. [33]	Egypt	n = 3	75	F	–	Y	–	–	Atrial Fibrillation	–		Y	Catecholamine	DEATH
				76	F	Y	Y	–	–	–	–		Y		IMPROVED
				73	F	–	–	–	–	Non-Hodgkin Lymphoma	–		Y		DEATH
28	Ali et al. [34]	USA	n = 1	74	M	Y	–	–	–	–			Y	Argatroban	AMPUTATION
29	Muhammed et al. [35]	UK	n = 1	49	M	–	–	–	–	–		Y	Y	Aspirin, Atorvastatin	IMPROVED
30	Patel et al. [36]	USA	n = 1	73	M	–	Y	–	–	Smoker			Y		DEATH
31	Showers et al. [37]	USA	n = 1	63	F	Y	Y	–	–	Charcot Foot, Asthma		Y	Y	Aspirin, Atorvastatin, , Methylprednisolone,	AMPUTATION

CAD: Chronic Artery Disease; CKD: Chronic Kidney Disease; DM: Diabetes mellitus; HTN: Hypertension; IVIG: Intravenous immunoglobulin.

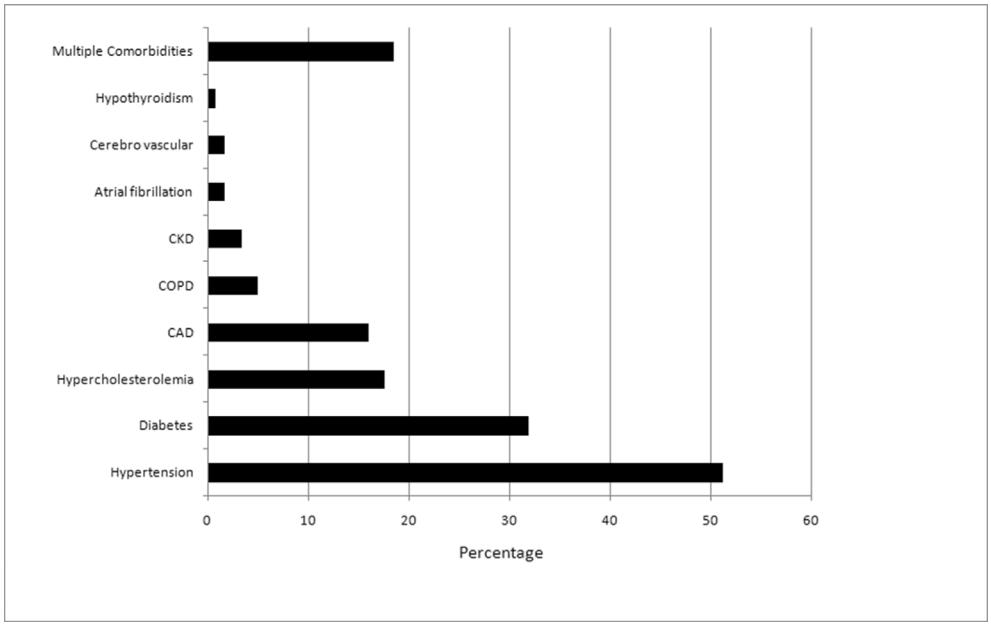

Fig. 2. Pre-existing co-morbidities in patients with COVID-19 and peripheral arterial complications.

Table 2
Clinical management of pro-thrombotic state in COVID-19.

Thromboprophylaxis and COVID-19
1. Consider thromboprophylaxis* in •Acutely ill hospitalized patients with COVID-19 •Critically ill patients with COVID-19 *Contraindicated in those with active bleeding and platelet count less than 25×10^9/L 2. How to provide thromboprophylaxis? • Anticoagulant thromboprophylaxis with low-molecular-weight heparin (LMWH) or fondaparinux may be preferred over unfractionated heparin (UFH) • Antiplatelet agents are not given for VTE prophylaxis • Standard dose anticoagulant thromboprophylaxis is preferred over intermediate doses of LMWH BID or weight-based dosing except in patients with heightened risk of thrombosis like diabetes 3. How long to continue thromboprophylaxis? • Only for the duration of the hospital stay and discontinued at discharge 4. Routine ultrasound for detection of DVT is not required unless clinically indicated

people with diabetes, though less frequent in those receiving therapeutic doses of anticoagulants [48]. On the other hand, there is a risk of fatal bleeding episodes on higher or therapeutic anticoagulation which require careful evaluation. However, a recent study found reduced rate of thrombotic complications without bleeding risk with therapeutic anticoagulation of LMWH (dose.

(100 IU/kg/12 h SC) or (UFH (500 IU/kg/24 h) [49]. Also, a systematic review found a slightly reduced mortality in patients of COVID-19 receiving therapeutic anticoagulation [50]. Thus, people with heightened risk of thrombotic complications like diabetes may be offered therapeutic anticoagulation immediately on hospitalisation with severe COVID-19 (Table 2).

In conclusion, COVID-19 is a unique thrombo-inflammatory condition and patients with background diabetes or hypertension are more susceptible for lower limb complications due to peripheral arterial disease presenting as gangrene. The outcomes of COVID-19 with peripheral arterial complications are poor in terms of limb preservation and mortality. Considering the heightened risk of peripheral thrombotic complications in COVID- 19, therapeutic anticoagulation must be considered. Future studies are urgently needed to assess such treatments to reduce amputation and mortality.

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