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A comprehensive review of vascular complications in COVID-19

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Abstract
This study aims to review the available literature pertinent to vascular complications in COVID-19. A systematic search was performed using PubMed and Google Scholar to identify all relevant studies based on our study objective. Multiple studies have reported widespread systemic inflammation and procoagulant/hypercoagulable state in COVID-19, including thrombotic microangiopathy, endothelial dysfunction, bleeding disorder, and thrombosis. However, large specialised studies on vascular complications are lacking despite current evidence indicating dysfunctional coagulation pathways. Furthermore, there are no clear and definitive recommendations regarding thromboprophylaxis or full therapeutic anticoagulation in COVID-19. Several studies have reported hypercoagulability and vascular complications as important predictors of patient outcome in COVID-19. Therefore, it is important to understand the pathogenesis, epidemiology, management, and outcomes of patients who develop venous or arterial thrombosis and those with a pre-existing thrombotic disease who contract COVID-19 for risk stratification, thromboprophylaxis, optimal antithrombotic therapy during active infection and long-term anticoagulation following discharge or recovery.

Keywords COVID-19 · Vascular complications · Blood coagulation disorders, review

Highlights

- SARS-CoV-2 induces proinflammatory cytokines and/or procoagulant factors that could activate coagulation cascades, leading to thrombosis, atherosclerotic plaque rupture, and ischemia.
- Noting changes in coagulation profile in critically ill COVID-19 patients are of utmost importance, as studies have shown that hypercoagulability and vascular complications are important predictors of optimal patient outcomes.
- Despite current evidence indicating dysfunctional coagulation pathways, specific studies concerning vascular complications in COVID-19 are lacking.
- It is crucial to have large-scale multicentre studies to establish and ascertain the vascular complications in COVID-19 and formulate management strategies.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an aggressive infection, coronavirus disease 2019 (COVID-19), with potentially serious health consequences [1]. Although COVID-19 primarily causes respiratory infection, recent studies have shifted the attention to vascular complications, including alarming thromboembolism [2,3]. Studies have shown alterations in the coagulation pathway such as elevated D-dimer levels, fibrin breakdown, reduced anti-thrombin levels, and reduced prothrombin and thrombin time [4–10]. Noting changes in coagulation profile in critically ill patients is of utmost importance as several studies have reported hypercoagulability and vascular

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complications as important predictors of patient outcome. As new evidence is unfolding, we aim to review the available literature pertinent to the vascular complications in COVID-19.

Methods

A literature review was performed using PubMed and Google Scholar to identify all relevant studies based on our study objective. Non-specific combinations of the search strings included, (i) Coronavirus OR Severe acute respiratory syndrome OR 2019-nCoV OR SARS-CoV-2 OR Severe acute respiratory syndrome coronavirus 2 OR Coronavirus disease 2019 OR COVID-19, (ii) Vascular complications OR Vascular injury OR Vascular pathology OR Vasculitis (iii) Endothelial dysfunction, (iv) Thrombosis OR Thromboembolism, and (v) Coagulation dysfunction OR Coagulopathy. Only the studies pertinent to vascular complications reported within the background of the COVID-19 infection were included. Independent analysis of all the studies was performed due to the unavailability of randomised clinical trials (RCT). A secondary reference search was conducted to find any additional studies. In total, we included 80 studies amongst the 291 studies that we analysed based on the study objective and search strategy.

Emergence of evidence

During the early stage of the COVID-19 pandemic, Zhang et al. [11] compared the clinical and pathologic features of the severe acute respiratory syndrome (SARS) and SARS-CoV-2. Diffuse alveolar damage (DAD) was the most common histological feature in non-survivors. Furthermore, haemorrhagic necrosis and lymphocyte depletion were found in lymph nodes and the spleen, indicating a pathological basis of lymphocytopenia. However, micro thrombosis was primarily found in extrapulmonary organs in SARS-CoV-2, something which was less common in previous SARS outbreaks.

Varga et al. [12] studied the mechanism responsible for vascular dysfunction by examining the post-mortem of three COVID-19 patients. There were viral inclusion structures in the endothelial cells, which could be due to the viral targeting of angiotensinogen converting enzyme 2 (ACE2) receptors present on endothelial cells. Endothelial dysfunction occurred by the recruitment of immune system mediators, inducing damage and apoptosis. As the vascular endothelium is critical for maintaining vascular tone and homeostasis, dysfunction increases vasoconstriction, leading to ischemia and inflammatory consequences such as oedema and pro-coagulation. COVID-19 induced endotheliitis was attributed to the impairment in microcirculation occurring in various vascular beds. The risk for endothelial damage was higher with pre-existent risk factors such as smoking, hypertension, diabetes, obesity, and chronic cardiovascular illness.

A similar study by Menter et al. [13] showed signs of thrombotic microangiopathy in three out of 21 autopsy reports of COVID-19 patients. Microthrombi were found in glomerular capillaries accompanying signs of disseminated intravascular coagulation (DIC) leading to shock. They found that coagulopathies were predominantly associated with blood group A. ABO alleles may elevate the Von-Willebrand factor by 20 % and increase the risk of venous thrombosis [14,15]. The coronavirus responsible for SARS was seen to interact with blood group A antigen and viral S proteins, allowing for virus and ACE2 receptor interaction and viral entry [16]. These coagulopathies are consistent with complement-mediated microvascular damage to the lungs and skin, resulting in DAD from microthrombi and florid vasculitis of small veins and capillaries. However, vasculitis could have developed independently from bronchopneumonia as vascular changes in other organs were not found.

Lax et al. [17] examined both lungs of COVID-19 patients and found DAD and thrombosis in small and mid-sized pulmonary arteries associated with infarction and bronchopneumonia. They concluded that death might be due to thrombosis in segmental and subsegmental pulmonary arterial vessels despite prophylactic anticoagulation.

Simultaneously, several studies highlighted the effects of COVID-19 infection on platelets [4, 6, 7, 18–20]. Platelet count was significantly lower in non-survivors compared with survivors [18]. Guan et al. [4] reported thrombocytopenia in 36.2 % of patients on admission and 57.7 % with severe disease amongst 1099 COVID-19 patients. Another large study with 1476 patients in Wuhan, China showed a significantly higher rate of thrombocytopenia in non-survivors than survivors (72.7 % vs. 10.7 %, $p<0.001$) [20]. DAD by the virus could entrap megakaryocytes and hinders the release of platelets [20]. However, decreased platelet count could cause a reactive elevation in thrombopoietin levels, resulting in a hypercoagulable state [21].

Likewise, the incidence and characteristics of venous thromboembolic disease in COVID-19 patients have been the subject of numerous studies. During the initial stage of the pandemic, a COVID-19 positive patient with cerebral venous sinus thrombosis was treated successfully with low molecular weight heparin (LMWH), [22] which suggested the possibility of a thrombotic event as the initial presentation in COVID-19.

Studies have approximated 20 % risk of venous thromboembolism (VTE) and 3 % risk of stroke, especially in the severely ill and those admitted to intensive care units (ICU) 23–28]. Furthermore, COVID-19 patients were twice as likely to develop pulmonary embolism (PE) when compared to the control group. 29 While the risk of VTE

appears higher in patients requiring ICU compared to those on general wards, thromboembolic events also contribute to morbidity and mortality in the ambulatory setting [30,31].

Current evidence suggests that elevated D-dimer measurements are a predictor of coagulopathy in COVID-19, [4–9] and higher D-dimer levels are directly linked to increased mortality [5,6,18]. A prospective Italian study [9] showed elevated procoagulant factors and higher D-dimer levels at baseline in all patients. Notably, a study including 1099 COVID-19 patients revealed that patients with severe infection had higher D-dimer levels [4]. A level of 0.5 mg/L or more was seen more commonly in patients with severe presentations than in those with non-severe illness (59.6 % vs. 43.2 %; P=0.002) [4]. Furthermore, D-dimer levels in ICU patients were 2.5 to 5 times higher than in non-ICU patients [6,7].

Moreover, a retrospective analysis of the coagulation function of 303 patients with COVID-19 was performed to compare the coagulation trends of the mild and severe infection [10]. The majority of patients in the severe groups were males (76.9 % vs. 49.8 %), elderly (median age: 65 vs. 50), and had underlying diseases (73.1 % vs. 36.1 %). There were abnormal coagulation parameters in 69 % of patients on admission (100 % severe group vs. 66.1 % mild group). International normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and fibrinogen degradation products, and D-dimer were higher in the severe group. Fibrinogen and APTT returned to normal as the disease improved.

However, COVID-19 patients also have an added bleeding risk [32,33]. A multicentre retrospective study [32] of 400 patients admitted to hospital with COVID-19 (144 critically ill) has shown 4.8 % overall and 2.3 % major bleeding rates. Among the critically ill patients, major bleeding rates were 5.6 % [32]. Deep muscle (23 %), gastrointestinal (14 %), central venous catheter (14 %), and otorhinolaryngological (14 %) haemorrhages have been reported [33].

Pregnant women, children and COVID 19

Pregnant women with COVID-19 are found to have increased APTT, fibrinogen, D-dimer, PT, and platelet [34]. Unfortunately, there are reports of increased stillbirth during the current COVID-19 crisis [35,36]. However, it is yet early to implicate these findings to the vascular complications without accessing the impact of disruptions in health services and reduced access to medical care during the ongoing pandemic [37].

COVID-19 positive or exposed children have displayed symptoms consistent with pediatric inflammatory conditions, known as Multisystem Inflammatory Syndrome in Children (MIS-C) [38]. This syndrome closely resembles Kawasaki disease and show elevated inflammatory markers at the time of admission with signs of coagulopathy, elevated D-dimer, and PT [38]. Most of the patients suffered from neurological and/or coagulopathic complications, requiring anticoagulation [38–41].

Mechanism of coagulopathies

SARS-CoV-2 activates coagulation, inducing procoagulant factors and proinflammatory cytokines that predispose to atherosclerotic plaque rupture, ischemia, and thrombosis [18,42]. High levels of proinflammatory cytokines/interleukins (IL) (IL2, IL7, etc.) have been observed in COVID-19 patients admitted to ICU [43]. Furthermore, coagulation abnormalities due to an inflammatory response to the virus resulting in inflammation-induced thrombosis are more apparent in those with severe disease, and those developing sepsis-induced coagulopathy and DIC [44].

The aetiology of the procoagulant response is complex and has been thought to result from specific interactions between host defense mechanisms and coagulation systems, including microangiopathy, local thrombus formation, and a systemic coagulation defect that leads to large vessel thrombosis and major venous and arterial thromboembolic complications [45,46]. Fogarty et al. [19] suggested the 'double hit' hypothesis for COVID-19 pulmonary manifestations, which targeted both ventilation and perfusion; the latter in the form of pulmonary vasculopathy that causes what is now known as 'pulmonary intravascular coagulation' or 'PIC'.

Furthermore, Bowles et al. [47] found 31 out of 34 COVID-19 patients tested positive for lupus anticoagulant assays; dilute Russell's viper-venom time, and lupus anticoagulant-sensitive aPTT. All patients with a positive lupus anticoagulant assay had a prolonged aPTT. However, 91 % of patients with prolonged aPTT were lupus anticoagulant positive, the majority of those having a related factor XII deficiency. The presence of lupus anticoagulant could be linked with a thrombotic tendency within the antiphospholipid syndrome. However, the role of lupus anticoagulant in the pathophysiology of COVID-19 is not yet clear.

Serological analysis has also shown the presence of anticardiolipin IgA antibodies as well as anti–β2-glycoprotein I IgA and IgG antibodies in COVID-19 patients admitted to ICU [48]. While these antibodies are central for the diagnosis of antiphospholipid syndrome, they can be positive in critically ill patients who may suffer from other causes of thrombosis, such as DIC.

Lillicrap [49] explained that the pathophysiology of DIC and the bleeding tendency in COVID-19 is complex and multifactorial, involving an interplay between cellular and plasmatic elements of the haemostatic system and components of the immune response towards the pathogen causing the infection. A dysregulated thrombin generation occurs both systemically and locally in the lungs of COVID-19

patients, resulting in the deposition of fibrin. This leads to tissue damage and microangiopathic pathology. Evolving evidence suggests that the cause of this pathophysiology is initiated by the exposure of endothelium, platelets, and leukocytes to the pathogen. This is further exacerbated by inhibition of fibrinolysis and impairment of normal anticoagulant mechanisms. However, treatment of DIC up to this publication had been primarily focused on targeting the responsible pathogen with supportive care to maintain critical organ function.

Anticoagulation therapy

Understanding the pathogenesis, epidemiology, management, and outcomes of patients with COVID-19 who develop venous or arterial thrombosis and those with a pre-existing thrombotic disease who develop COVID-19 provided a supplement for clinical-decision making in terms of antithrombotic therapy in COVID-19 patients [50].

There is a recommendation to strictly apply VTE screening, and thrombosis prophylaxis or early therapeutic anticoagulation in all COVID-19 patients admitted to ICU with severe COVID-19 infection [51,52].

There is a narrow therapeutic index between preventing and treating venous and arterial thrombotic events and the risk of bleeding in COVID-19 patients. Watson et al. [53] stated that it is reasonable to continue outpatient anticoagulation in COVID-19 confirmed or suspected patients. However, bridging should not be offered in patients with a low risk of thrombosis due to the risk of bleeding. Routine use of aspirin increases the bleeding risk and benefits should be carefully assessed. Similarly, they suggested that prolonged dual antiplatelet therapy (DAPT) beyond six months in COVID-19 after stenting and beyond a year for the acute coronary syndrome (ACS) should be weighed, balancing risks and benefits. Furthermore, warfarin-based triple therapy for COVID-19 patients with atrial fibrillation is inferior to a direct oral anticoagulant-based regimen with P2Y12 receptor blockers and short-duration aspirin [53].

Questions have been asked about a possible role for thromboprophylaxis after hospital discharge and in selected non-hospitalised COVID-19 if immobilised or they have other prothrombotic factors [54]. However, a COVID-19 positive patient has been documented to develop superior mesenteric arterial thrombosis after cessation of LMWH [55]. Khan et al. [56] suggested maintaining full anticoagulation for at least one to two months post-hospital discharge with LMWH due to its anti-inflammatory effects. Analytical parameters such as high D-dimer and IL-6 levels should also be taken into account and treatment individualised.

Recent recommendations from the International Society on Thrombosis and Hemostasis suggest that all hospitalised patients with COVID-19 should receive thromboprophylaxis or full therapeutic anticoagulation if indicated [54]. Their interim guidance on recognising and managing coagulopathy in COVID-19 called for careful reconsideration of anticoagulation, mainly focusing on the proposed approach for the use of heparin [57]. They also called for an expeditious randomised control trial of COVID-19 coagulopathy to evaluate unfractionated heparin (UH) and LMWH at therapeutic and prophylactic doses. This is with the hope of answering the critical questions surrounding anticoagulation in these patients due to the advanced form of COVID-19 showing evidence of DIC with a thrombotic phenotype. However, drug-drug interactions between antiplatelet and anticoagulant agents should be considered with investigational COVID-19 therapies [50].

Extracorporeal membrane oxygenation (ECMO)

ECMO has been tried in COVID-19 patients with respiratory failure following futile mechanical ventilation efforts. However, ECMO has been associated with thrombotic events due to activation of the coagulation cascade from non-endothelial surface contact in the extracorporeal circuit [58,59].

Extracorporeal Life Support Organization (ELSO) Registry showed significantly higher in-hospital mortality in patients who used ECMO for circulatory support (HR 1·89); however, COVID-19 patients on respiratory venovenous ECMO with concurrent ARDS had less than 40 % estimated cumulative in-hospital mortality at 90 days [60].

Higher thromboembolic risk in patients on ECMO favours the routine anticoagulation use [59, 61]. ELSO COVID-19 Interim Guidelines support implementing the standard ELSO anticoagulation guidelines in COVID-19 patients [62]. Systemic anticoagulation with bivalirudin on venovenous ECMO had lower circuit-related thrombotic events [63]. However, Parzy et al. [64] reported that all their patients with SARS-CoV2 infection and ARDS, who were on venovenous ECMO, suffered from venous thromboembolism despite receiving the anticoagulation.

Anticoagulation strategy in COVID-19 patients on ECMO is further complicated by the co-existence of thrombocytopenia and thromboembolism [65,66]. Therefore, the innate thrombotic potential of ECMO within the emerging evidence of higher thrombotic complications seen in COVID-19 makes it challenging, necessitating a large scale study to establish its clinical utility [67,68].

Risk stratification

There is a need to determine the role of biomarkers and/or scoring systems to stratify patients' risk in COVID-19 [23]. Older age, high 'Sequential Organ Failure Assessment' (SOFA) score, and D-dimer greater than one ug/mL were

associated with poor prognosis [18]. Patients who died were more likely to be elderly, have more pre-existing morbidities, dyspnoea, low oxygen saturation, increased white blood cell count, decreased lymphocytes, and elevated C-reactive protein (CRP) levels [69]. Furthermore, complications such as ARDS, acute cardiac injury, acute kidney injury, shock, and DIC were more commonly seen in non-survivors [69].

Fibrinolysis shutdown evident by elevated D-dimer levels and complete failure of clot lysis at 30 min on thromboelastography predicts thromboembolic events and the need for haemodialysis in critically ill patients with COVID-19 [70].

Khan et al. [56] suggested that D-dimer levels and renal function should guide the anticoagulation in the ICU. For patients with D-dimer levels >1000ug/mL, enoxaparin 1.5 mg/kg once daily was initiated. If the patient's creatinine clearance was <30mL/min, 1 mg/kg was used until the D-dimer level was <1000ug/mL. However, this treatment was continued if there was clinical evidence of deep venous thrombosis (DVT), PE, or other thrombotic events regardless of D-dimer level. D-dimer levels were evaluated daily to assess the VTE risk, and clinical examinations were performed to look for any signs. They reported no instances of PE and one case of DVT.

Although D-dimer is a valuable tool in categorizing the risk of developing VTE in patients with novel coronavirus pneumonia (NCP), a higher threshold D-dimer is suggested for the detection of PE [28,71]. In the presence of clinical signs and/or suspicion of VTE, compression ultrasonography and echocardiography should be performed irrespective of disease stage [72]. Furthermore, patients with severe COVID-19 may have associated PE, and thus, the use of contrast computerized tomography (CT) rather than routine non-contrast CT is encouraged [73].

Discussion

COVID-19 can lead to severe illness with accompanying multiorgan failure. Inflammatory cytokine release mediating atherosclerosis results in hemodynamic changes and causes induction of procoagulant mediators. It is believed that a storm of inflammatory mediators triggered by SARS-CoV-2 results in irreversible multisystem inflammation that can partially present as abnormal haemostasis and coagulopathy, further aggravating organ injury [74]. Similarly, the virus targets ACE-2 receptors present on vascular muscle membrane and endothelial cells [75].

The pathogenesis of thrombotic events induced by COVID-19 could occur due to host cell aggression [47,76]. An excessive immune-response induced cytokine storm is followed by inflammatory response activation and hypercoagulability, ultimately resulting in systemic thrombosis formation. Complications could include DIC, although not common. Similarly, pulmonary micro-thrombosis can induce COVID-19 related ARDS. Monitoring critically ill patients includes evaluating PT, fibrinogen, platelet, and D-dimer levels. Elevated D-dimer and fibrinogen levels suggest a hypercoagulable and inflammatory state. High D-dimer levels are also a predictor of ARDS, which leads to increased mortality.

Blood clots can, to some degree, act as a barrier to pathogen invasion, referred to as immunothrombosis. However, this immunothrombosis concept is affected by COVID-19 [77]. Haemostatic components initially operate in a chemotactic fashion, which stimulates the immune system. As SARS-CoV-2 targets, the lungs, bronchoalveolar haemostasis activation attempts to combat the infection by recruiting immune cells [77]. This can be observed by elevated acute phase reactants such as platelets, fibrinogen, and CRP. When examining post-mortem reports, the presence of pulmonary microthrombi also points to hypercoagulability induced by SARS-CoV-2. Among those patients with mild-moderate disease, the microthrombi are broken down, presenting as an elevation in D-dimer levels. In severe disease, marked activation of the coagulation system could lead to thrombosis in limbs, intestines, and the brain.

Unfortunately, those vulnerable to thrombotic events are more likely to have severe COVID-19 illness [77]. Elevations in platelet count and acute phase reactants, such as fibrinogen, lead to hypercoagulability in these patients. Microthrombi formation, as a result of this hypercoagulable state, is linked to patient deterioration. In mild illness, microthrombi are broken down by the fibrinolytic function of the lungs. Alternatively, in severe infection, the pulmonary coagulation system is highly activated, leading to possible systemic thrombosis in limbs, intestine, and brain with resultant multiorgan damage.

Complement-mediated thrombotic microangiopathy (TMA) in severe infection is possible [78]. TMA is characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and organ damage such as neurological, renal, and cardiac dysfunction. However, reports of schistocytes to confirm microangiopathic haemolytic anaemia is lacking, and little is known about the nature of cardiac dysfunction in COVID-19 patients. As such, the pathophysiology of TMA is described in a two-hit hypothesis. The first hit is a germline mutation in complement regulatory protein, and the second hit could be due to pregnancy, inflammation, surgery, or autoimmunity.

Diurno et al. [79] treated four severe COVID-19 patients with eculizumab (one of the two FDA-approved complement inhibitors: eculizumab in 2007 and ravulizumab in 2019) resulting in immediate improvement and successful disease outcomes. This highlights a need for more extensive prospective trials to examine complement inhibitors in patients with severe COVID-19 infection. Furthermore, the concern

of thromboembolic risk and microvascular thrombosis in patients with COVID-19 suggests a need for RCT to examine the possible benefit of prophylactic anticoagulation or using increased anticoagulation doses in inpatients or long-term anticoagulation following discharge [80].

Conclusions

Current evidence indicates dysfunctional coagulation pathways in COVID-19 patients; however, specific studies concerning vascular complications are lacking. It is crucial to have large-scale multicentre studies to establish and ascertain the vascular complications in COVID-19 to formulate management strategies with optimal patient outcomes.

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Declarations

Conflict of interest The Authors declare that there is no conflict of interest.

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