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REVIEW ARTICLE

Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad

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Abstract

The pathogenesis of Coronavirus disease 2019 (COVID-19) is gradually being comprehended. A high number of thrombotic episodes are reported, along with the mortality benefits of heparin. COVID-19 can be viewed as a prothrombotic disease. We overviewed the available evidence to explore this possibility. We identified various histopathology reports and clinical case series reporting thromboses in COVID-19. Also, multiple coagulation markers support this. COVID-19 can be regarded as a risk factor for thrombosis. Applying the principles of Virchow's triad, we described abnormalities in the vascular endothelium, altered blood flow, and platelet function abnormalities that lead to venous and arterial thromboses in COVID-19. Endothelial dysfunction, activation of the renin-angiotensin-aldosterone system (RAAS) with the release of procoagulant plasminogen activator inhibitor (PAI-1), and hyperimmune response with activated platelets seem to be significant contributors to thrombogenesis in COVID-19. Stratifying risk of COVID-19 thromboses should be based on age, presence of comorbidities, D-dimer, CT scoring, and various blood cell ratios. Isolated heparin therapy may not be sufficient to combat thrombosis in this disease. There is an urgent need to explore newer avenues like activated protein C, PAI-1 antagonists, and tissue plasminogen activators (tPA). These should be augmented with therapies targeting RAAS, antiplatelet drugs, repurposed antiinflammatory, and antirheumatic drugs.

Key Points

- *Venous and arterial thromboses in COVID-19 can be viewed through the prism of Virchow's triad.*
- *Endothelial dysfunction, platelet activation, hyperviscosity, and blood flow abnormalities due to hypoxia, immune reactions, and hypercoagulability lead to thrombogenesis in COVID-19.*
- *There is an urgent need to stratify COVID-19 patients at risk for thrombosis using age, comorbidities, D-dimer, and CT scoring.*
- *Patients with COVID-19 at high risk for thrombosis should be put on high dose heparin therapy.*

Keywords Antiphospholipid antibodies · Blood flow · Comorbidities · COVID-19 · Cytokine storm · Endothelial dysfunction · Platelets · Pregnancy · Thrombosis · Virchow's triad

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Introduction

Coronavirus disease 2019 (COVID-19) has swept through the world in the last 6 months with 6,194,533 confirmed cases, including 376,320 deaths, being reported to the World Health Organization (WHO) by the 3rd of June, 2020 [1]. COVID-19 is caused by the SARS-CoV-2 virus, a member of the Coronaviridae family that include the SARS-CoV and the MERS-CoV viruses that were responsible for outbreaks of severe respiratory illnesses. Initially recognized as an acute respiratory distress syndrome (ARDS) [2], it was soon realized that heart, brain, and kidney involvement was also common in COVID-19 [3–5]. A hyperimmune response referred to as cytokine release syndrome is associated with high mortality [6]. Interestingly, a larger than expected number of thrombotic events were being reported in COVID-19 patients. Advanced age and comorbidities are predictors of increased mortality in COVID-19 [7], which may be associated with susceptibility to thrombosis in these individuals.

Though several viruses are linked to haemorrhagic fevers [8], there are few viruses known to cause thrombosis. Cytomegalovirus has been implicated in thrombosis while varicella-zoster has been linked to both thrombosis and haemorrhage [9]. There is a minimal risk of thromboembolism linked to respiratory viral illnesses in the community [10].

Initial autopsies from COVID-19 patients showed microthrombi in the lung vasculature [11]. The report of heparin having a mortality benefit in a subgroup of patients drew attention to the thrombosis prevalent in COVID-19 [12]. COVID-19 patients are reported to suffer from hypoxemia, particularly in conditions associated with high glycosylated haemoglobin [13]. In the early stages of the disease, lung compliance is not reduced during mechanical ventilation [14]. The lung compliance of 16 patients had been studied and found atypical for ARDS [15]. Thus the hypoxia at the initial stage may be more due to other factors than ARDS. The loss of oxygen transfer capacity of haemoglobin and impaired gas exchange in alveoli with microthrombi can explain this. The microthrombi may cause altered lung perfusion and hypoxic vasoconstriction, worsening the hypoxemia [16]. Prone positioning may help by improving ventilation-perfusion ratio by changing vascular flow distribution in the pulmonary vessels, and not by recruitment as in the case of ARDS [17].

Elevated troponins, indicating cardiac damage, are common findings during the pandemic [18]. These raised troponins are also a predictor of mortality [19]. The cardiomyopathy seems to be an immune or hormone-driven pathology rather than due to direct invasion of the SARS-CoV-2 virion in the myocardium [20].

Venous thromboembolism is frequent in COVID-19. Deep vein thrombosis was detected by Doppler ultrasound in 15% of COVID-19 patients with pneumonia and elevated D-dimer [21]. Some patients present with resistance to conventional heparin therapy [22]. Patients with diabetes who develop COVID-19 seem to be at a higher risk of thrombosis [23]. Other evidence for the role of thrombosis is the presence of chilblain-like lesions in the periphery of COVID-19 patients that might be explained by vasculopathy [24]. Also, an atypical Kawasaki-like syndrome reported in COVID-19 may again be evidence of medium vessel vasculopathy [25].

In this article, we aim to overview thrombosis as an integral part of COVID-19 and characterize systemic features of thrombosis through the prism of Virchow's triad. Additionally, we explore therapeutics most likely to be effective in this prothrombotic disease.

Search strategy

We performed comprehensive searches through the Scopus and MEDLINE/PubMed databases which were restricted to English sources. No time limitation was set since items on COVID-19 accumulate on a daily basis. Although all article types were processed, preference was given to items with higher evidence base. The following main keywords were employed: "COVID-19", "SARS-CoV-2", "thrombosis", "rheumatic disease", "immunity", and "antithrombotic agents". Overall, we adhered to the recommendations on writing narrative biomedical reviews [26].

COVID-19 as a risk factor of thromboembolism

Autopsies have been performed in a very limited number of COVID-19 cases [27]. Various studies reporting histopathology from autopsies or other sources in COVID-19 are analysed in Table 1 [28–38]. Most of these studies demonstrate venous thromboembolism and microthrombi in arterioles and venules.

There are numerous reports of patients with COVID-19 presenting with both arterial (stroke, myocardial infarction) and venous thrombosis (deep vein thrombosis, pulmonary thromboembolism, venous sinus thrombosis). Many of these patients had traditional risk factors for thrombosis. Perhaps the most important risk factors in the context of COVID-19 are obesity and poorly controlled diabetes mellitus that may aggravate physiological processes such as pregnancy and result in venous and arterial thromboses [39, 40].

Interestingly, pregnancy in women infected with the coronavirus may also increase the risk of placental thrombosis. A case series of 20 pregnant women with COVID-19 reported foetal vascular malperfusion or foetal vascular thrombosis in 10 mainly because of intravascular fibrin deposition, though clinical significance of this placental phenomenon remained uncertain [41].

Table 1 Histopathological studies in COVID-19

Reported in	No of patients	Procedure	Main findings	Remarks
Wuhan, China [28]	2	Lung (lobectomy specimen)	Oedema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells. Hyaline membranes were not prominent.	Both patients had lung carcinoma and were asymptomatic for COVID-19.
Beijing, China [29]	1	Autopsy	Bilateral diffuse alveolar damage with cellular fibro-myxoid exudates	"Early ARDS"
Hamburg, Germany [30]	12	Autopsy	Deep vein thrombosis in 7 out of 12 patients; Pulmonary thromboembolism caused death in 4 patients.	Coronary heart disease and bronchial asthma or chronic obstructive pulmonary disease were common comorbid conditions.
Graz, Austria [11]	11	Autopsy	Diffuse alveolar damage (DAD), oedema, hyaline membranes, and proliferation of pneumocytes and fibroblasts. Thrombosis of small and mid-sized pulmonary arteries was found in all 11 patients.	Ten of the 11 patients received prophylactic anticoagulant therapy; venous thromboembolism was not clinically suspected antemortem
Oklahoma, US [31]	2	Autopsy	Diffuse alveolar damage and chronic inflammation and mucosal oedema; acute bronchopneumonia	One had hypertension, post-splenectomy state; other obese with myotonic dystrophy
New York, US [32]	5 1	Skin biopsies Autopsy	Generalized thrombotic microvascular injury, haemorrhagic pneumonitis with complement C5a fraction deposition	Complement-associated microvascular injury
Wuhan, China [33]	4	Core needle biopsies taken postmortem	Injury to the alveolar epithelial cells, hyaline membrane formation, and hyperplasia of type II pneumocytes, all components of diffuse alveolar damage. Superimposed bacterial pneumonia	Immunocompromised status (chronic lymphocytic leukaemia and renal transplantation) or other conditions (cirrhosis, hypertension, and diabetes)
Wuhan, China [34]	26	Kidney biopsy	Diffuse proximal tubule injury with the loss of brush border, non-isometric vacuolar degeneration, and frank necrosis; erythrocyte aggregates obstructing the lumen of capillaries	Frank thrombosis not reported
São Paulo, Brazil [35]	10	Ultrasound-Guided Minimally Invasive Autopsy	Massive epithelial injury and microthrombi in pulmonary vessels. Microthrombi were less frequent in glomeruli, spleen, heart, dermis, testis, and liver sinusoids	Systemic thrombosis is common in COVID-19.
New York, US [36]	5	Postpartum placenta histology	Focal avascular villi and thrombi in larger foetal vessels with complement deposition.	All 5 had healthy, term deliveries
Switzerland [37]	21	Autopsy	Pulmonary thromboembolisms ($n = 4$), alveolar haemorrhage ($n = 3$), vasculitis ($n = 1$), generalised thrombotic microangiopathy	Patients were mostly elderly males, with arterial hypertension, obesity, and severe cardiovascular comorbidities.
Massachusetts, US [38]	7	Autopsy	Thromboses with microangiopathy. Alveolar capillary microthrombi were more prevalent in patients with COVID-19 than in those with influenza A (H1N1).	Established that angiopathy leading microthrombi are an integral part of COVID-19

COVID-19 Coronavirus-2019 disease; *ARDS* acute respiratory distress syndrome

We are summarising studies and case series (with at least three patients) demonstrating clinical thrombotic episodes in COVID-19 patients as Table 2 [42–57]. As apparent from Table 2, numerous thromboembolic episodes occurred despite prophylactic, or even therapeutic anticoagulation. The rate of pulmonary thromboembolism detected in the intensive care setting is above 20% while in nonCOVID-19 cases, it is usually less than 2% [58]. Besides conventional computerised tomography (CT), lung ultrasound was also able to detect peripheral pulmonary thrombosis confirmed by contrast-enhanced ultrasound [59]. Other lung ultrasounds have reported subpleural "consolidations" that might be microinfarcts of 3–5 mm size [60].

Virchow's triad in COVID-19

Virchow's triad (Fig. 1) comprises of vascular damage, altered blood flow, and hypercoagulability of blood. These factors are active in varying degrees in venous thrombosis [61, 62], atrial

Table 2 Evidence of thrombotic events in COVID-19

Reported in	Number of patients with events	Manifestation	Major findings	Remarks
Italy [42]	6	Stroke	Both ischemic (4) and haemorrhagic (2) strokes reported; median age 69 years	Five had pre-existing vascular risk factors
New York, US [43]	32	Ischemic stroke	Out of 3556 hospitalised patients with diagnoses of COVID-19 infection, 32 patients (0.9%) had imaging proven ischemic stroke	Most strokes were cryptogenic, possibly related to an acquired hypercoagulability, and mortality was increased
Sakarya, Turkey [44]	4	Ischemic stroke	All had symptomatic COVID-19 infection; Three patients have elevated D-dimer levels, and two of them had high C-reactive protein (CRP) levels	Stroke developed simultaneously with the diagnosis of COVID-19
London, UK [45]	6	Ischemic stroke	All had raised D-dimer and large vessel occlusion 3 had multi-territory infarcts, 2 had concurrent venous thrombosis	Ischemic strokes occurred despite therapeutic anticoagulation in two patients
New York, US [46]	33	Stroke patients detected to have COVID-19	28% (33/118) had COVID-19 related lung findings. RT-PCR was positive for COVID-19 in 93.9% (31/33) of these	Retrospective review of COVID-19 related findings in the lung apices of CTA done for stroke evaluation
New York, US [47]	4	Ischemic stroke	All large vessel thrombus	All had strokes during the early stages of COVID-19
Milan, Italy [48]	28	10 pulmonary thromboembolism; VTE 16; stroke 9; ACS 4	Thromboembolic events occurred in 28 (7.7%); VTE was confirmed in 16 (36%)	Overt DIC was present in 8 (2.2%)
Paris, France [49]	18	18 VTE including 6 pulmonary embolism	Out of 26 screened for VTE in 2 centres, 18 were positive. Most had hypertension, high BMI and were on mechanical ventilation.	High rate of thromboembolic events even in patients on therapeutic anticoagulation
Amsterdam, The Netherlands [50]	39	VTE	39 patients (20%) out of 75 admitted to intensive care had VTE despite routine thrombosis prophylaxis	Cumulative incidence of VTE at day 21 was 42% (95% CI 30–54)
The Netherlands [51]	75	65 pulmonary embolism; 5 ischemic strokes; 5 others	Out of 184 ICU patients, 75 had thromboembolic events and 41 died	Patients diagnosed with thrombotic complications were at higher risk of all-cause death, for an HR of 5.4 (95%CI 2.4–12)
Detroit, US [52]	72	Pulmonary embolism	Out of 337 COVID-19 patients who had CTA, 72(20%) had pulmonary embolism	In multivariate analysis, statins were protective while high BMI and D-dimer levels predicted pulmonary embolism
Brighton, UK [22]	21	VTE	21/274 (7.7%) COVID-19 patients were diagnosed with VTE. Most COVID-19 patients had elevated (> 0.5 μg/mL) D-dimers	Higher rates of VTE in patients who had turned PCR negative
Strasbourg, France [53]	64	25 pulmonary embolism; 4 strokes	Comparison with non-COVID-19 ARDS patients ($n = 145$) confirmed that COVID-19 ARDS patients ($n = 77$) developed significantly more thrombotic complications, mainly pulmonary embolisms (11.7 vs 2.1%, $p < 0.008$)	Many patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications despite anticoagulation
Besancon, France [54]	23	Pulmonary embolism	Out of 280 patients hospitalised for COVID-19, 100 had CTA of which 23 turned out to have pulmonary embolism	Pulmonary embolus was diagnosed at mean of 12 days from symptom onset
Paris, France [55]	32	Pulmonary embolism	137 CTA of COVID-1 positive cases revealed 32 cases of pulmonary embolism	Prophylactic anticoagulation did not avoid the occurrence of PE in hospitalised patients
New York, USA [56]	3	Pulmonary embolism	All had comorbidities; survived with enoxaparin/rivaroxaban	All had persistent hypoxemia
Strasbourg, France [57]	32	Pulmonary embolism	Thirty-two of 106 patients with COVID-19 infection were positive for acute pulmonary embolus on CTA	Rate higher than usually encountered in critically ill patients without COVID-19 infection

COVID-19 Coronavirus-2019 disease; *RT-PCR* real time-polymerase chain reaction; *CTA* computerized tomography with angiography; *DIC* disseminated intravascular coagulation; *VTE* venous thromboembolism; *ACS* acute coronary syndrome; *BMI* body mass index; *HR* hazard ratio; *PE* pulmonary embolism

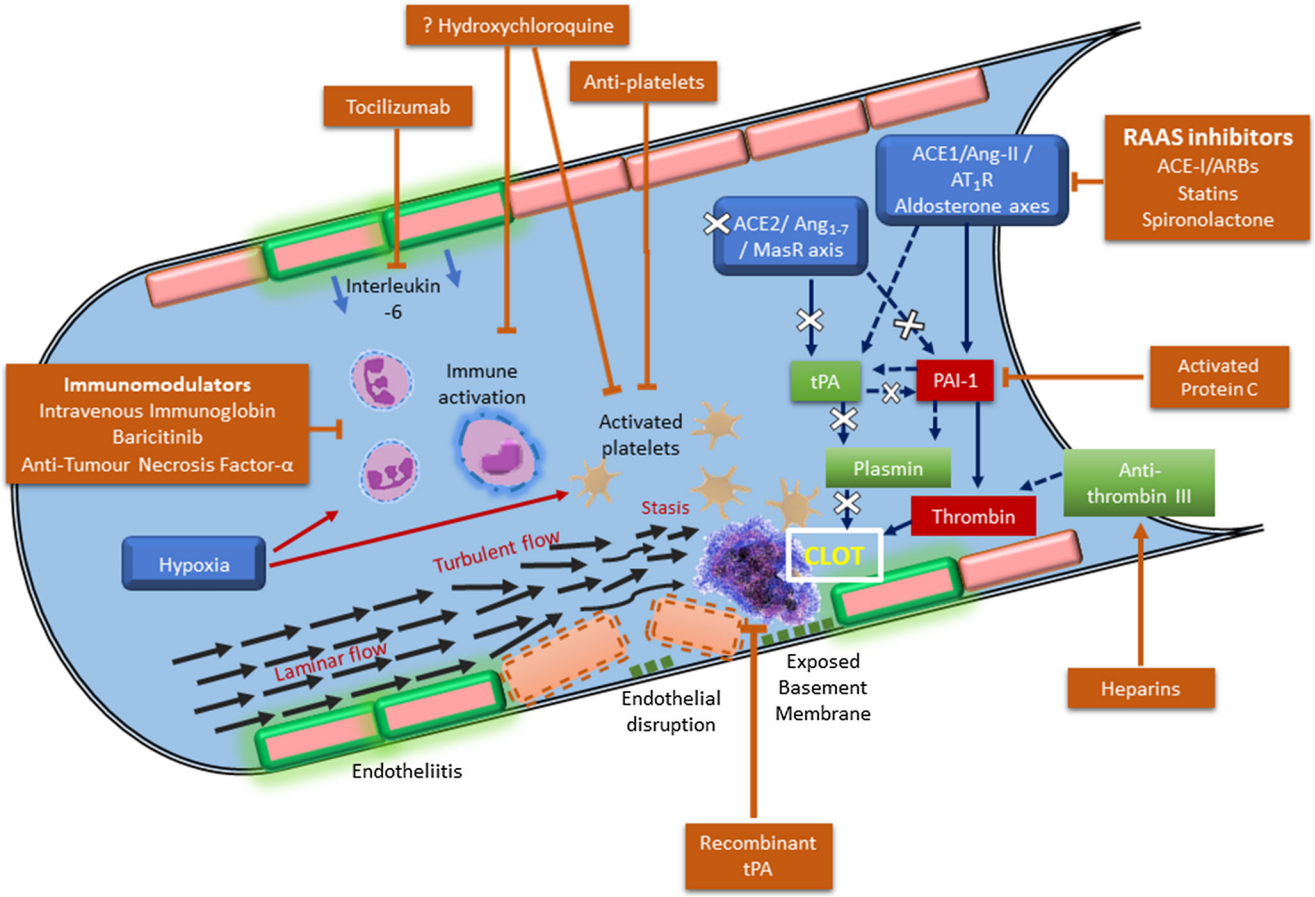

Fig. 1 Virchow's triad in the thrombogenesis in COVID-19. Virchow's triad consists of abnormal vessel wall (endotheliitis, endothelial dysfunction with loss of glycocalyx, endothelial disruption), abnormal flow (due to hyper-viscosity, immune activation, high fibrinogen, impaired microcirculation due to hypoxia and turbulent flow due to microthrombi), and hypercoagulable state (inhibition of plasminogen system due to unopposed canonical renin-angiotensin pathway, platelet dysfunction, complement activation (not shown), and hyperimmune response)

fibrillation [63], myocardial infarction [64], and stroke [65]. The significance of this triad is that it unifies the inflammatory and the coagulation pathways in the genesis of clotting [63–65]. One classic example of Virchow's triad explaining thrombosis in vascular disease is the case of Behcet disease where abnormalities in the vessel wall and in the blood flow, as well as of hypercoagulability have been described [66]. Each of these components is explored in the context of COVID-19.

The primary function of the endothelium is the maintenance of nonturbulent blood flow with homeostatic mechanisms to prevent thrombosis and inflammation [67, 68]. The structure of endothelium is different in different tissue as required for specialised function as determined by local need [69]. The endothelium can undergo considerable proliferative changes as well as plastic changes [70]. Most diseases, including viral infections, affect the vascular endothelium and lead to endothelial dysfunction [71].

Vessel wall abnormalities in COVID-19

The endothelium has a glycocalyx layer and secretes tPA (tissue plasminogen activator) that prevents binding of platelets or initiation of the coagulation cascade [67, 72]. Previous, in the SARS outbreak, SARS-CoV virion was detectable in endothelial cells [73]. The ACE2 receptor for SARS-CoV-2 is present in endothelial cells [74]. With this background in mind, initial electron microscopy studies were done, and these studies have demonstrated SARS-CoV-2 like virion in endothelial cells [75, 76]. The seminal study exhibiting intussusceptive angiogenesis in COVID-19 has also demonstrated endothelial invasion by SARS-CoV-2, with subsequent severe endothelial injury and associated disruption of cellular membranes [38]. The endothelial dysfunction leads to the loss of the fibrinolytic function of these cells, predisposing to thrombus formation [77]. Endothelial disruption leads to massive release on von-Willebrand factor (vWF) from Weibel-Palade

bodies that have been reported in COVID-19 [78]. All these endothelial factors can initiate thrombosis.

The propagation of thrombosis can be aided by the inflammation induced by endothelial dysfunction. Endothelial cells release interleukin-6 (IL-6) in response to the virus invasion that amplifies the host immune response, even to the state of cytokine storm syndrome [79]. Though immune complex vasculitis has been postulated as a pathological mechanism for COVID-19, the evidence is limited at present [80]. Severe COVID-19 leads to a cytokine storm and coagulopathy is a known consequence of acute sepsis [81]. This underlying coagulation cascade activation predisposes to sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) [82].

Abnormal blood flow

COVID-19 has been linked to hyperviscosity [83]. In a study of 15 patients, all had blood viscosity exceeding 95th percentile of normal, and the plasma viscosity correlated with the sequential organ failure score (SOFA). Hyperviscosity not only directly predisposes to thrombosis but also induces endothelial injury and dysfunction [84]. Fibrinogen is a major determinant of blood viscosity, and high levels have been reported in COVID-19 [85–87]. Fibrinogen-to-albumin ratio (FAR) has been shown to be a predictor of disease progression in multivariate Cox analysis [85].

Another critical area for turbulent blood flow is the microcirculation. The presence of microthrombi and reactionary angiogenesis can lead to impaired microcirculation in COVID-19 [88]. The presence of arterial and venous occlusion has already been discussed (Tables 1 and 2), and the presence of such thrombus acts as a perpetrator of abnormal blood flow and further thrombosis.

Though there is no known association between COVID-19 and aneurysm formation, there may be accelerated thrombus formation in preexisting aneurysms. At least two cases of aortic aneurysm rupture during active COVID-19 infections have been reported [89, 90]. A similar report exists for thrombosis in a popliteal aneurysm [91]. This can be due to the hypercoagulable state of COVID-19 superimposed on the turbulent flow in the aneurysm.

Hypercoagulable state

The loss of the protective endothelium with its glycocalyx layer, low levels of tPA, and the inhibition of the clot-lysing system lead to a prothrombotic state. This can be augmented by platelet dysfunction, complement activation, and systemic immune reactions.

Inhibition of the plasminogen system

When SARS-CoV-2 enters a susceptible cell via the ACE2 (angiotensin converting enzyme-2) receptor, there is an internalisation of ACE2 and degradation in the lysosome [92]. ACE2 is a negative regulator of the canonical renin-angiotensin-aldosterone system (RAAS). The loss of the protective ACE2/angiotensin$_{1–7}$/Mas receptor axis leads to unopposed action of angiotensin II via the angiotensin type 1 receptor (AT_1R) that is further augmented by angiotensin IV [93].

Blockade of the angiotensin$_{1–7}$/Mas by receptor knock-out [94] or pharmacological blockade [95] in murine experiments has accentuated thrombus formation. Directly blocking ACE2 increases thrombus size in animal models while amplifying its function can have antithrombotic effects [96]. ACE2 contributes by activation of tissue plasminogen activator (tPA). Angiotensin II and AT_1R activation lead to the formation and release of plasminogen activator inhibitor-1 (PAI-1) from endothelial and smooth muscle cells [97, 98]. Thus the loss of ACE2 alters the PAI-1/tPA balance to a prothrombotic state. There is evidence from a cohort of 44 patients with COVID-19 that the plasminogen pathway is dysfunctional with the complete lack of lysis of clot at 30 min seen in 57% [99].

Platelet dysfunction

The platelet-to-lymphocyte ratio (PLR) is an established marker of inflammation and can predict immune suppression and thrombosis in neoplastic diseases [100]. PLR is raised in COVID-19 and predicts severe disease therein [101, 102]. Both thrombocytosis and thrombocytopenia can occur in COVID-19. A multivariate analysis from China had shown that platelet counts of more than $135x10^9$/L predicted nonsevere disease [85]. Interestingly, bleeding manifestations are rare even in the presence of DIC with thrombocytopenia [103]. Absence of bleeding is more indicative of thrombotic microangiopathy [104].

Platelet activation can take place via the angiotensin II/AT_1R pathways. Platelets have AT_1R that cause increased adherence in response to angiotensin II [105]. AT_1R activation causes the release of PAI-1 from platelet alpha-granules, smooth muscle cells, hepatocytes, and adipocytes [106]. Moreover, the loss of the protective angiotensin$_{1–7}$/Mas pathway can increase platelet aggregation. Platelets have Mas receptor that modulates thrombosis via the release of nitric oxide (NO) [107].

Another pathway for platelet activation in COVID-19 is via the altered ACE1/ACE2 function. Bradykinin is cleaved by ACE1 into metabolites such as vasoactive bradykinin (1–8) and des-Arg9-bradykinin that are further degraded by ACE2. In the absence of ACE2, des-Arg9-bradykinin accumulation can activate both neutrophils and platelets into an

inflammatory phenotype [108]. The activated platelets have a greater tendency to attach to the vascular endothelium [109]. COVID-19 patients have both increased clot strength as well as platelet contribution to clots [87]. Thus platelet activation has a specific role in COVID-19-induced thrombosis.

Complement activation

Complement activation has been demonstrated in COVID-19 skin biopsies, and autopsy and has been shown to be associated with microthrombosis [32]. Complement activation is an integral part of thrombogenesis at its various stages [110, 111]. It may be difficult to delineate cause-effect relationships. However, targeting complement in COVID-19 has been proposed [112, 113]. Four patients with severe COVID-19 have been successfully treated by eculizumab, a monoclonal antibody that targets complement protein C5 [114].

Another possibility is immune complex vasculitis. If the immune complex deposition reported in COVID-19 is due to immune complex vasculitis, it will be more likely to respond to a complement inhibitor eculizumab. The Kawasaki-like syndrome reported in children with COVID-19 may be due to this immune phenomenon [25]. COVID-19 can mimic a variety of vasculitides [115].

Hyperimmune response and thrombosis

DIC is often presented in the later stages of severe sepsis and is characterized by thrombosis in the microcirculation [116]. Presence of only laboratory abnormalities in various coagulation tests without evidence of thrombosis or bleeding manifestation has been termed SIC. This nomenclature attempts at detection and correction of these abnormalities before DIC sets in irreversibly. It has been recognized that SIC and DIC are an invariable component of the hyperimmune response. Thus, they are included in the diagnosis of the macrophage activation–like syndrome (MALS) [117]. Severe COVID-19 has a similar hyperimmune syndrome referred to by various names [6]. It is rational to suggest that the hyperimmune activation itself has a role in perpetuating the widespread thrombosis in this disease. Both activated platelets and leucocytes can activate complement and augment the coagulation cascades.

Antiphospholipid antibodies

A study of antiphospholipid antibodies in three patients with severe COVID-19 spawned interest if SARS-CoV-2 was precipitating antiphospholipid syndrome and related thrombogenesis [118]. Antiphospholipid antibodies are not uncommon in situations of severe sepsis and often do not have any pathological role [119]. Furthermore, a prospective cohort study of 24 patients with COVID-19 who had venous thromboembolism revealed weakly positive anticardiolipin IgM and antiβ2-glycoprotein I IgM in only 2 patients [120]. Another retrospective cohort study of 56 COVID-19 patients pointed to an independent association of anticardiolipin IgG with low oxygen saturation and other severe disease manifestations [121]. Only 1 patient with anticardiolipin IgG had a stroke in that study. There are no studies specifically examining shifts in titres of antiphospholipid antibodies in patients with lupus and other prothrombotic rheumatic diseases overlapping with COVID-19. Available retrospective analyses may suggest that antiphospholipid antibodies alone rarely lead to thromboses even in the course severe inflammatory and immune disturbances due to the virus. Overall, the role of antiphospholipid antibodies and antiphospholipid syndrome in the thrombogenesis due to COVID-19 remains uncertain [122].

Targeting thrombosis in severe COVID-19

It is apparent that thrombosis plays a major role in the pathogenesis of severe COVID-19. Thrombogenesis in such a critical condition should be targeted at multiple levels since only anticoagulation seems insufficient.

Heparin

The initial evidence for mortality benefit with heparin was found in patients with a SIC score ≥ 4 or D-dimer > 6-fold of the upper limit of normal [12]. A larger retrospective study with the data of 17 Spanish hospitals has also confirmed the mortality benefit of heparin after adjusting for age and gender [123]. Beyond the benefit of anticoagulation, heparin also has antiarrhythmic properties [124] and can even oppose classical RAAS activation [125].

The International Society of Thrombosis and Hemostasis (ISTH) have suggested that patients with raised D-dimers (defined as three- to fourfold above the upper range of normal), should be admitted even in the absence of other features because this signifies increased thrombin generation. They have also recommended low-molecular-weight heparin (LMWH) for all admitted patients, including noncritically ill patients [126]. The problem, however, lies in that several studies have shown that thrombosis occurs in patients with severe COVID-19 despite LMWH therapy at therapeutic doses (Table 2).

Overall, clinicians utilizing anticoagulation therapy COVID-19 should also carefully weigh risks of thrombosis and bleeding, particularly in patients with low platelet counts [127].

Tissue plasminogen activator

Thrombolysis can be life-saving in myocardial infarction, ischemic stroke, and pulmonary thromboembolism. One prospective study of 24 patients in intensive care (without COVID-19 or cardiac disease) revealed that tissue factor and PAI-1 rise with the development of ARDS [128].

There are two case series encompassing a total of eight cases of ARDS due to COVID-19 who benefitted from tPA administration [129, 130]. After tPA infusion, oxygen requirements improves, allowing to avoid intubation [130]. An in silico model has also demonstrated mortality benefit with the use of tPA [131]. There is a proposal to use nebulised tPA for ADRS due to COVID-19 [132].

PAI-1 antagonists

Thrombosis can be initiated due to high levels of PAI-1 after the loss of ACE2/angiotensin$_{1–7}$/Mas pathway. As such, PAI-1 antagonists may offer some benefits. Angiotensin-converting enzyme inhibitors (ACE-I), insulin-sensitizing agents (including metformin and thiazolidinediones), and hormone-replacement therapy in women can have mild to moderate reduction of PAI-1 levels [133]. There are direct PAI-1 antagonists known, but none has been cleared for human use yet [134, 135].

Activated protein C (APC) was initially shown to have benefit in severe sepsis in the protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial [136]. Later trials did not support the results of this study, and APC went into disuse [137]. It may be worthwhile to try APC to maintain the plasminogen pathway in severe COVID-19.

Antiplatelet drugs

Antiplatelet drugs can potentiate the action of anticoagulation. In a proof-of-concept study, five COVID-19 patients with pulmonary infiltrates and D-dimer > 3 times the upper limit of normal were given oral clopidogrel and infusions of acetylsalicylic acid and tirofiban, on a background of fondaparinux. After 48 h of infusion, the patients had better PaO2/FiO2 ratio as compared with controls that persisted till 7 days [138].

RAAS inhibitors

There was some controversy regarding the use of ACE1-inhibitors (ACE-I) and angiotensin II-receptor blockers (ARBs) in patients with COVID-19 since both are known to increase ACE2 level that is the receptor for SARS-CoV-2 [139]. However, since the primary pathology is due to the loss of ACE2, it stands to reason that ACE-I and ARBs can be helpful [140].

At least two metaanalyses have shown that the use of ACE-I/ARBs is not associated with more severe disease but lead to decreased mortality [141, 142]. However, both these reviews had included a study that has been retracted [143]. A third metaanalysis that has not included this retracted study has also reported mortality benefit of ACE-I/ARBs [144].

There is evidence from cardiology that RAAS inhibitors can reduce thrombosis [145]. Even in animal models, the use of ACE-I and ARBs have been shown to abrogate thrombosis [146, 147]. Both losartan and ramipril have synergistic antiplatelet action when given with dual antiplatelet drugs given postmyocardial infarction [148]. Thus, ACE-I/ARBs can potentiate other antithrombotic therapies in COVID-19.

Targeting complement

Eculizumab can be successfully used in COVID-19 [114]. Complement activation has been demonstrated in COVID-19 patients, but it is difficult to discern whether this is a cause or effect of the pathogenesis [149]. Murine models of various coronavirus infections do not support the therapeutic inhibition of complement factors C3 or C4 [150].

Immune therapy

Timely use of various modalities of immune therapies may decrease viral load and improve survival rates in COVID-19 [151]. While interventions such as intravenous immunoglobulin (IVIg) therapy may save lives of patients with Kawasaki-like syndrome, its use may also increase thrombosis risk [152]. This risk may be due to increased blood viscosity [153] or due to factor (F) XI in substantial quantities in the IVIg products [154].

A Cochrane living systematic review has identified 32 patients across eight studies reporting low evidence of the effectiveness of convalescence plasma therapy in the middle of May 2020 [155]. However, these data are preliminary, and outcomes of clinical trials are awaited [156]. Transfusion-related acute lung injury (TRALI) is a rare complication of IVIg therapy [157], and it has even been reported with convalescence plasma therapy, too [158].

Antirheumatic drugs for preventing thrombosis

The use of various disease-modifying antirheumatic drugs (DMARDs) has been suggested for COVID-19 [159–161]. There is controversy about the utility of hydroxychloroquine (HCQ) in COVID-19. The prolonged use of HCQ in systemic lupus erythematosus and rheumatoid arthritis proved effective for reducing cardiovascular risk [162]. HCQ has been shown to reduce levels of tissue factor and related thrombotic pathways in antiphospholipid syndrome [163].

Colchicine exerts some cardiovascular protective effects in neutrophilic disease entities and in other clinical conditions [164]. It is also viewed as a drug candidate for repurposing therapies and using in COVID-19 [165]. Interleukin-1 and interleukin-6 are potential targets in COVID-19 and both can be attenuated by colchicine [166]. Beyond reducing antiinflammatory cytokines, colchicine also has favourable effects on peptides associated with vascular health such as oxidized low-density lipoprotein receptor and phosphodiesterase 5A [167]. In this randomized controlled trial, colchicine had antithrombotic effects in the sera of obese patients [167].

Baricitinib is another repurposed antirheumatic drug [168]. Patients on baricitinib may be at risk for venous thromboembolism [169]. This risk may be amplified in COVID-19. Similarly, there is a theoretical risk of thrombosis with tocilizumab since it alters the lipid profile. However, metaanalysis has shown that it may have better cardiovascular safety as compared with other biological DMARDs [170].

Interestingly, a recent description of mild cases of COVID-19 in 3 different patients with Behçet disease with history of venous thromboses, ankylosing spondylitis and rheumatoid arthritis pointed to positive effects of previously prescribed antiTNF therapies which possibly protected from cytokine storm and related vascular events [171].

Glucocorticoids are associated with an increased risk of thrombosis. Although confounding effect cannot be eliminated, there is a pathobiological basis for this association [172]. The initial report of the COVID-19 Global Rheumatology Alliance has demonstrated an association of prednisolone doses of more than 10 mg with hospitalisation due to COVID-19 [173].

Conclusion

Available evidence points to a propensity for thrombosis in COVID-19. Bleeding is rare even in the setting of thrombocytopenia and DIC [103]. Thrombosis can occur despite prophylactic and therapeutic use of heparin. Manifestations such as ARDS and cardiac compromise are better explained by microthrombi and RAAS activation than by isolated immune activation. These provide compelling reasons to augment anticoagulation with other synergistic therapies such as immune therapies, DMARDs, antiplatelet drugs, RAAS antagonists, statins, and activators of the plasmin system (active thrombolysis therapy).

There is an urgent need to stratifying patients at high risk of thrombosis, particularly the elderly, those with comorbidities, high D-dimer, high chest CT (computed tomography) scores, and shifted blood cell ratios, high ferritin, PAI-1, and IL-6.

Targeting COVID-19 is inchoate without reducing the risk for thrombosis. Thrombotic risk reduction must take into account each facet of Virchow's triad. The endothelial dysfunction leading to PAI-1/tPA imbalance can be corrected by APC and PAI-1 antagonists. Blood flow abnormalities and microthrombi can be prevented by high dose heparin and RAAS inhibitors including ACE-I/ARBs and statins. Platelet activation and hyperinflammation leading to hyperviscosity can be dealt with by antiinflammatory and antiplatelet drugs.

Authors' contributions The conception and design of the study–SA, AYG; acquisition of data, analysis, and interpretation of data–SA, OZ, AYG. Drafting the article–SA, AYG; revising it critically for important intellectual content–OZ, AYG. Final approval of the version to be submitted–SA, OZ, AYG. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved–SA, AYG, OZ.

Compliance with ethical standards

Disclosures None.

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