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.

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

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.
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]. Proximal 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 cardiac myopathy 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].
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 Ischemic stroke | 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 3 had multi-territory infarcts, 2 had concurrent venous thrombosis | 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/ivaroxaban | 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.
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 Behçet 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 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/angiotensin1-7/Mas receptor axis leads to an opposed action of angiotensin II via the angiotensin type 1 receptor (AT1R) that is further augmented by angiotensin IV [93].

Blockade of the angiotensin1-7/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 AT1R 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 nonsenvere 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/AT1R pathways. Platelets have AT1R that cause increased adherence in response to angiotensin II [105]. AT1R activation causes the release of PAI-1 from platelet alpha-granules, smooth muscle cells, hepatocytes, and adipocytes [106]. Moreover, the loss of the protective angiotensin1-7/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 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 ARDS due to COVID-19 [132].

**PAI-1 antagonists**

Thrombosis can be initiated due to high levels of PAI-1 after the loss of ACE2/angiotensin1–7/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 ACE1/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.

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**Compliance with ethical standards**

**Disclosures** None.

**Disclaimer** All views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any institution or association.

**References**

1. COVID-19 situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 3 Jun 2020

2. Cohen J, Normile D (2020) New SARS-like virus in China triggers alarm. Science 367:234–235. https://doi.org/10.1126/science.367.6475.234

3. Huang C, Wang Y, Li X et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet Lond Engl 395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

4. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

5. Garaci F, Di Giuliano F, Picchi E et al (2020) Venous cerebral thrombosis in COVID-19 patient. J Neurol Sci 414:116871. https://doi.org/10.1016/j.jns.2020.116871

6. Moore JB, June CH (2020) Cytokine release syndrome in severe COVID-19. Science 368:473–474. https://doi.org/10.1126/science.abb8925

7. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

8. Paessler S, Walker DH (2013) Pathogenesis of the viral hemorrhagic fevers. Annu Rev Pathol 8:411–440. https://doi.org/10.1146/annurev-pathol-020712-164041

9. Geijtenbeek M, van Wissen M, van de Weg C, Jong E, Gerdes VEA, Meijers JCM, Brandjes DPM, van Gorp ECM (2012) Review: viral infections and mechanisms of thrombosis and bleeding. J Med Virol 84:1680–1696. https://doi.org/10.1002/jmv.23354

10. Smeeth L, Cook C, Thomas S et al (2006) Risk of deep vein thrombosis and pulmonary embolism after acute infection in a
community setting. Lancet Lond 367:1075–1079. https://doi.org/10.1016/S0140-6736(06)68474-2
11. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koebbling C, Vander K, Bergfrieder U, Trauner M (2020) Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, Clinicopathologic Case Series. Ann Intern Med. https://doi.org/10.1011/jh.14817
12. Tang N, Bai H, Chen X et al (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. https://doi.org/10.1111/jth.14817
13. Wang Z, Du Z, Zhu F (2020) Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. Diabetes Res Clin Pract 164:108214. https://doi.org/10.1016/j.diabres.2020.108214
14. Beloncle FM, Pavlovsky B, Desprez C, Fage N, Olivier PY, Asfar P, Richard JC, Mercat A (2020) Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. Ann Intensive Care 10:55. https://doi.org/10.1186/s13613-020-00675-7
15. Gattoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiennello D (2020) COVID-19 does not Lead to a “typical” acute respiratory distress syndrome. Am J Respir Crit Care Med 201:1299–1300. https://doi.org/10.1164/rccm.202003-0817LE
16. Dunham-Snary KJ, Wu D, Sykes EA, Thakrar A, Parlow LRG, Mewburn JD, Parlow JL, Archer SL (2017) Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest 151:181–192. https://doi.org/10.1016/j.chest.2016.09.001
17. Sklar MC, Patel BK, Beilir JR, Piraino T, Goligher E (2019) Optimal ventilator strategies in acute respiratory distress syndrome. Semin Respir Crit Care Med 40:81–93. https://doi.org/10.1055/s-0039-1683896
18. Fan H, Zhang L, Huang B, Zhu M, Zhou Y, Zhang H, Tao X, Cheng S, Yu W, Zhu L, Chen J (2020) Cardiac injuries in patients with coronavirus disease 2019: not to be ignored. Int J Inf Secur. https://doi.org/10.1016/j.jinf.2020.05.022
19. Zhou R (2020) Does SARS-CoV-2 cause viral myocarditis in COVID-19 patients? Eur Heart J. https://doi.org/10.1093/eurheartj/ehaa392
20. Demelo-Rodriguez P, Cervilla-Muñoz E, Ordieres-Ortega L, Parra-Virto A, Toledano-Macias M, Toledano-Samaniego N, Garcia-Garcia A, Garcia-Fernández-Bravo I, Ji Z, de-Miguel-Diez J, Álvarez-Sala-Walther LA, del-Toro-Cervera J, Galeano-Valle F (2020) Incidence of asymptomatic deep vein thrombosis in COVID-19 patients with acute respiratory distress syndrome and elevated D-dimer levels. Thromb Res 192:23–26. https://doi.org/10.1016/j.thromres.2020.05.018
21. Stoneham SM, Milne KM, Nuttal E, Frew GH, Sturrock BR, Sivaloganathan H, Ladikou EE, Drage S, Phillips B, Chevassut TJT, Eziefula AC (2020) Thrombotic risk in COVID-19: a case series and case-control study. Clin Med Lond.clinmed.2020–cclinmed.0228. https://doi.org/10.7861/clinmed.2020-0228
22. (2020) Analysis on 54 mortality cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020. J Korean Med Sci 35. https://doi.org/10.3346/jkms.2020.35.e132
23. Galván Casas C, Catalá A, Carretero Hernández G et al (2020) Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. https://doi.org/10.1111/bjd.19163
24. Licciardi F, Prucelli G, Deninga M, Parodi E, Taglietto M, Rosati S, Montin D (2020) SARS-CoV-2-induced Kawasaki-like Hyperinflammatory syndrome: a novel COVID phenotype in children. Pediatrics.e20201711. https://doi.org/10.1542/peds.2020-1711
25. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417. https://doi.org/10.1007/s00296-011-1999-3
26. Salerno M, Sessa F, Pisopo A et al (2020) No autopsies on COVID-19 deaths: a missed opportunity and the lockdown of science. J Clin Med 9. https://doi.org/10.3390/jcm9051472
27. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY (2020) Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 15:704–704. https://doi.org/10.1111/jto.14070
28. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8:420–422. https://doi.org/10.1016/S2213-2600(20)30076-X
29. Wichmann D, Sperhake J-P, Lütgheitsmann M, Steurer S, Eddler C, Heinemann A, Heinrich F, Mushumba H, Kneip I, Schröder AS, Burdelski C, de Heer G, Nierhaus H, Frings D, Pfeiferle S, Becker H, Bredereke-Wielding H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S (2020) Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med. https://doi.org/10.7326/M20-0203
30. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S (2020) COVID-19 Autopships, Oklahoma, USA. Am J Clin Pathol 153:725–733. https://doi.org/10.1093/ajcp/aqaa062
31. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Hap, Baxter-Stoltzfus A, Laurence J (2020) Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Trans R Soc 220:1–13. https://doi.org/10.1098/rsbl.2020.04.007
32. Tian S, Xiong Y, Liu H, Niu L, Guo J, Liu M, Xiao SY (2020) Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem biopsies. Pathol. Meth 33:1007–1014. https://doi.org/10.1038/s41379-020-0536-x
33. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X, Zhang C (2020) Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 98:219–227. https://doi.org/10.1016/j.kint.2020.04.003
34. Nunes Duarte-Neto A, de Almeida Monteiro RA, da Silva LFF, Malheiro DMAC, de Oliveira EP, Theodoro Filho J, Pinho JRR, Soares Gomes-Gouvêa M, Salles APM, de Oliveira IRS, Maud T, de Nascimento Saldiva PH, Dolinhoff M (2020) Pulmonary and systemic involvement of COVID-19 assessed by ultrasound-guided minimally invasive autopsy. Histopathology. https://doi.org/10.1111/his.14160
35. Mulvey JJ, Magro CM, Ma LX, Nuovo GJ, Baergen RN (2020) Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol 46:151530. https://doi.org/10.1016/j.anndiagpath.2020.151530
36. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deignendesch N, Frank S, Turek D, Willi N, Pargger H, Bassetti S, Leuppi JD, Cathommas G, Tolyan M, Mertz K, Danovski A (2020) Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variated findings of lungs and other organs suggesting vascular dysfunction. Histopathology. https://doi.org/10.1111/his.14134
37. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D (2020) Pulmonary vascular
endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. https://doi.org/10.1056/NEJMoa2105432
39. Martinelli I, Ferrazzi E, Ciavarella A, Erra R, Iurlaro E, Ossola M, Lombardi A, Blasi F, Mosca F, Peyvandi F (2020) Pulmonary embolism in a young pregnant woman with COVID-19. Thromb Res 191:36–37. https://doi.org/10.1016/j.thromres.2020.04.022
40. Ahmed I, Azhar A, Eltaweel N, Tan BK (2020) First Covid-19 maternal mortality in the UK associated with thrombotic complications. Br J Haematol 190:e37–e38. https://doi.org/10.1111/bjh.16849
41. Baergen RN, Heller DS (2020) Placental pathology in Covid-19. Semin Thromb Hemost. https://doi.org/10.1055/s-0041-1771684
42. Morassi M, Bagatto D, Cobelli M, D’Agostini S, Gigli GL, Bnà C, Vogrig A (2020) Stroke in patients with SARS-CoV-2 infection: case series. J Neurosci. https://doi.org/10.1007/s00134-020-06085-4
43. Yaghi S, Ishida K, Torres J et al (2020) SARS2-CoV-2 and stroke in a New York healthcare system. Stroke: STROKEAHA.120.030335. https://doi.org/10.1161/STROKEAHA.120.030335
44. Tunç A, Unlubay Y, Alemdar M, Akvitez E (2020) Coexistence of COVID-19 and acute ischemic stroke report of four cases. J Clin Neurosci. https://doi.org/10.1016/j.jocn.2020.05.018
45. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, Humphries F, Jäger HR, Losset NF, Perry RJ, Shah S, Simister RJ, Turner D, Chandratheva A, Werring DJ (2020) Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry.jnnp-2020-323586. https://doi.org/10.1136/jnnp-2020-323586
46. Kihira S, Schefflein J, Chung M et al (2020) Incidental COVID-19 related lung apical findings on stroke CTA during the COVID-19 pandemic. J Neurointerv Surg. https://doi.org/10.1136/jnns-2020-161188
47. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, Glaser A, Elsayegh D (2020) COVID-19 presenting as stroke. Brain Behav Immun 87:115–119. https://doi.org/10.1016/j.bbi.2020.04.077
48. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Alexia B, Sandri MT, Barco S, Humanitas COVID-19 Task Force (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 191:9–14. https://doi.org/10.1016/j.thromres.2020.04.024
49. Llitjos J-F, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Avray M, Merouani K (2020) High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. https://doi.org/10.1111/jth.14869
50. Middeldorp S, Coppens M, van Haaps TF, Poppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N (2020) Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. https://doi.org/10.1111/jth.14888
51. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H (2020) Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 191:148–150. https://doi.org/10.1016/j.thromres.2020.04.041
52. Povijadli N, Cormier P, Patel PY et al (2020) Acute pulmonary embolism and COVID-19. Radiology 201955:201955. https://doi.org/10.1148/radiol.2020201955
53. Helms J, Taucaud C, Severac F et al (2020) High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 46:1089–1098. https://doi.org/10.1007/s00134-020-06062-x
71. Rajendran P, Renganaray T, Thangavel J et al (2013) The vascular endothelium and human diseases. Int J Biol Sci 9:1057–1069. https://doi.org/10.7150/ijbs.7502

72. Urano T, Suzuki Y (2012) Accelerated fibrinolysis and its propagation on vascular endothelial cells by secreted and retained tPA. J Biomed Biotechnol 2012:208108. https://doi.org/10.1155/2012/208108

73. Ye J, Zhang B, Xu J et al (2007) Molecular pathology in the lungs of severe acute respiratory syndrome patients. Am J Pathol 170: 538–545. https://doi.org/10.2353/apath.2007.060469

74. Hamming I, Timmens W, Bulthuis MLC et al (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203:631–637. https://doi.org/10.1002/path.1570

75. Zhu N, Zhang D, Wang W, Li X, Yang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W, China Novel Coronavirus Investigating and Research Team (2020) A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382:727–733. https://doi.org/10.1056/NEJMoa2001017

76. Varga Z, Flammer AJ, Steiger P et al (2020) Endothelial cell infection and endothelitis in COVID-19. Lancet 395:1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5

77. Suzuki Y, Yasui H, Bzroska T, Mogami H, Urano T (2011) Surface-retained tPA is essential for effective fibrinolysis on vascular endothelial cells. Blood 118:3182–3185. https://doi.org/10.1182/blood-2011-05-353912

78. Escher R, Breakey N, Lännmle B (2020) Severe COVID-19 infection associated with endothelial activation. Thromb Res 190:62. https://doi.org/10.1016/j.thromres.2020.04.014

79. McGonagle D, Sharif K, O'Regan A, Bridgewood C (2020) The role of cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 102537. https://doi.org/10.1016/j.autrev.2020.102537

80. Roncati L, Ligabue G, Fabbiani L, Malagoli C, Gallo G, Lusenti B, Naselli V, Manenti A, Maioruta A (2020) Type 3 hypersensitivity in COVID-19 pneumonia patients. Clin Immunol Orlando Fla 108487: 108487. https://doi.org/10.1016/j.clim.2020.108487

81. Semeraro N, Ammollo CT, Semeraro F, Colucci M (2015) Angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis: a potential target for treating thrombotic diseases. Thromb Haemost 108:1089–1096. https://doi.org/10.1160/TH12-06-0396

82. Fang C, Stavrou E, Schmaier AA et al (2013) Angiotensin II-1 and mas decrease thrombosis in Bdkrb2/− mice by increasing NO and prostacyclin to reduce platelet spreading and glycoprotein VI activity. Blood 121:3023–3032. https://doi.org/10.1182/blood-2012-09-495156

83. Fraga-Silva RA, Da Silva DG, Montecucco F et al (2012) The angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis promotes antithrombotic activity. Mol Med Camb Mass 16:210–215. https://doi.org/10.2119/molmed.2009.00160

84. Nishimura H, Tsuji H, Masuda H, Nakagawa K, Nakahara Y, Kitamura H, Kasahara T, Sugano T, Yoshizumi M, Sawada S, Nakagawa M (1997) Angiotensin II increases plasminogen activator inhibitor-1 and tissue factor mRNA expression without changing that of tissue type plasminogen activator or tissue factor pathway inhibitor in cultured rat aortic endothelial cells. Thromb Haemost 77:1189–1195

85. van Leeuwen RT, Kol A, Andreotti F, Kluft C, Maseri A, Sperti G (2004) Thrombophilia? Lancet Lond. https://doi.org/10.1016/S0140-6736(04)68015-X
134. Gong L, Proulle V, Fung C, Hong Z, Lin Z, Liu M, Xue G, Yuan C, Lin L, Furie B, Flaumenhaft R, Andreassen P, Furie B, Huang M (2016) A specific plasminogen activator inhibitor-1 antagonist derived from inactivated urokinase. J Cell Mol Med 20:1851–1860. https://doi.org/10.1111/jcm.12875

135. Yu B, Zhang G, Jin L et al (2017) Inhibition of PAI-1 activity by Toddalolactone as a mechanism for promoting blood circulation and removing stasis by Chinese herb Zanthoxylum nitratum var. tomentosum. Front Pharmacol 8:489. https://doi.org/10.3389/fphar.2017.00489

136. Bernard GR, Vincent JL, Laterre PF, LaRosa S, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helderbrand JD, Ely EW, Fisher CJ Jr. Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709. https://doi.org/10.1056/NEJMoa005107

137. Ikzeoe T (2015) Thrombomodulin-activated protein C system in septic disseminated intravascular coagulation. J Intensive Care 3: 1. https://doi.org/10.1186/s40560-014-0050-7

138. Viecca M, Radovanovic D, Forleo GB, Santus P (2020) Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res. https://doi.org/10.1016/j.phrs.2020.104950

139. Thomas G (2020) Renin-angiotensin system inhibitors in COVID-19. Cleve Clin J Med. https://doi.org/10.3949/ccjm.87a.ccc009

140. Madzivire MN, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD (2020) Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 382:1653–1659. https://doi.org/10.1056/NEJMUs2005760

141. Zhang X, Ju Y, Pan L-Y, Jiang H-Y (2020) ACEI/ARB use and decreased mortality of COVID-19: a systematic review and meta-analysis. Pharmacol Res 158:104927. https://doi.org/10.1016/j.phrs.2020.104927

142. Pirola CJ, Sookoian S (2020) Estimation of RAAS-inhibitor effect on the COVID-19 outcome: a meta-analysis. J Inf Secur. https://doi.org/10.1016/j.jisc.2020.05.052

143. Mehra MR, Desai SS, Kuy J, Patel AN (2020) Retraction: cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. N Engl J Med 382:2582. https://doi.org/10.1056/NEJMz2021225

144. Guo X, Zhu Y, Hong Y (2020, 1979) Decreased mortality of COVID-19 with renin-angiotensin-aldosterone system inhibitors therapy in patients with hypertension: a meta-analysis. Hypertension. https://doi.org/10.1161/HYPERTENSIONAHA.120.15572

145. Sury V, Zhang Z, Fu H, Zhang Y, Yuan M, Wang Y, Goudis CA, Tse G, Liu T, Li G (2018) Inhibition of renin-angiotensin axis reduces the risk of thrombus formation in the left atrial appendage in patients with hypertension complicated by atrial fibrillation. J Renin-Angiotensin Aldosterone Syst 19:19. https://doi.org/10.1177/1470320318782623

146. Schmaier AH (2016) A novel antithrombotic mechanism mediated by the receptors of the Kallikrein/Kinin and renin-angiotensin systems. Front Med 3:61. https://doi.org/10.3389/fmed.2016.00061

147. Düsing R (2016) Pharmacological interventions into the renin-angiotensin system with ACE inhibitors and angiotensin II receptor antagonists: effects beyond blood pressure lowering. Ther Adv Cardiovasc Dis 10:151–161. https://doi.org/10.1177/175394716644130

148. Marinsek M, Sinković A (2016) Ramipril and losartan exert a similar long-term effect upon markers of heart failure, endogenous fibrinolysis, and platelet aggregation in survivors of ST-elevation myocardial infarction: a single centre randomized trial. Biomed Res Int 2016:9040457–9040457. https://doi.org/10.1155/2016/9040457

149. Cugno M, Meroni PL, Gualtierotti R, Griffini S, Grovetti E, Torri A, Panigada M, Aliberti S, Blasi F, Tedesco F, Peyvandi F (2020) Complement activation in patients with COVID-19: a novel therapeutic target. J Allergy Clin Immunol. https://doi.org/10.1016/j.jaci.2020.05.006

150. Maglakelidze N, Manto KM, Craig TJ (2020) A review: does complement or the contact system have a role in protection or pathogenesis of COVID-19? Pulm Ther. https://doi.org/10.1007/s41030-020-00118-5

151. Gasparay AY, Misra DP, Yessirkepov M, Zimba O (2020) Perspectives of immune therapy in coronavirus disease 2019. J Korean Med Sci 35:e176. https://doi.org/10.3346/jkms.2020.35.e176

152. Branch DR (2019) Serologic problems associated with administration of intravenous immune globulin (IVIg). Immunohematology 35:13–15

153. Bentley P, Rosso M, Sadnicka A, Israeli-Korn S, Laflan M, Sharma P (2012) Intravenous immunoglobulin increases plasma viscosity without parallel rise in blood pressure. J Clin Pharm Ther 37:286–290. https://doi.org/10.1111/j.1365-2710.2011.01287.x

154. Drellich DA, Bray PF, Herman JH (2012) Immunoglobulin therapy and thrombosis: coincidence or causation? Transfusion (Paris) 52:2075–2077. https://doi.org/10.1111/j.1537-2995.2012.03868.x

155. Valk SJ, Piechotta V, Chai KL et al (2020) Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. Cochrane Database Syst Rev 5:CD013600. https://doi.org/10.1002/14651858.CD013600

156. Bloch EM, Shoham S, Casadevall A et al (2020) Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 130:2757–2765. https://doi.org/10.1172/JCI138745

157. Baudel JL, Vigneron C, Pras-Landrie V, Joffre J, Marjot F, Ait-Outella H, Bigé N, Maury E, Guidet B, Fain O, Mekinian A (2020) Transfusion-related acute lung injury (TRALI) after intravenous immunoglobulins: French multicentre study and literature review. Clin Rheumatol 39:541–546. https://doi.org/10.1007/s10067-019-04832-7

158. Chun S, Chung CR, Ha YE, Han TH, KI KS, Kang ES, Park JK, Peck KR, Cho D (2016) Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. Ann Lab Med 36:393–395. https://doi.org/10.3343/alm.2016.36.4.393

159. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, Mekinian A, Anunciacion-Llunell A, Miró-Mur F (2020) Immunomodulatory therapy for the management of severe COVID-19. J Autoimmun 111:2077. https://doi.org/10.1016/j.jautrev.2020.102569

160. Misra DP, Agarwal V, Gasparay AY, Zimba O (2020) Rheumatologists’ perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol 39:2055–2062. https://doi.org/10.1007/s10067-020-05073-9

161. Perricone C, Triggianese P, Bartoloni E, Cafaro G, Bonifacio AF, Bursi R, Perricone R, Gerli R (2020) The anti-viral facet of antirheumatic drugs: lessons from COVID-19. J Autoimmun 111:2055. https://doi.org/10.1016/j.jauto.2020.102468

162. Gasparay AY, Ayvazyan L, Cocco G, Kitas GD (2012) Adverse reactions of intravenous immunoglobulin (IVIg). Dermatol Online J 18:4. https://doi.org/10.1159/000338919

163. Schreiber K, Breen K, Parmar K, Rand JH, Wu XX, Hunt BJ (2018) The effect of hydroxychloroquine on haemostasis, complement, inflammation and angiogenesis in patients with COVID-19. Clin Rheumatol 39:2529–2543
antiphospholipid antibodies. Rheumatol Oxf Engl 57:120–124. 
https://doi.org/10.1093/rheumatology/kex378

164. Gasparyan AY, Ayvazyan L, Yessirkepov M, Kitas GD (2015) 
Colchicine as an anti-inflammatory and cardioprotective agent. 
Expert Opin Drug Metab Toxicol 11:1781–1794. https://doi.org/ 
10.1517/17425255.2015.1076391

165. Deftereos S, Giannopoulos G, Vrachatis DA et al (2020) 
Colchicine as a potent anti-inflammatory treatment in COVID-19: can we teach an old dog new tricks? Eur Heart J Cardiovasc 
Pharmacother. https://doi.org/10.1093/ehjcvp/pva033

166. Piantoni S, Patroni A, Toniati P, Furloni R, Franceschini F, 
Andreoli L, Scarsi M (2020) Why not to use colchicine in COVID-19? An old anti-inflammatory drug for a novel auto-
inflammatory disease. Rheumatol Oxford 59:1769–1770. https:// 
doi.org/10.1093/rheumatology/keaa217

167. Demidowich AP, Levine JA, Apps R et al (2005) Colchicine’s 
effects on metabolic and inflammatory molecules in adults with 
obesity and metabolic syndrome: results from a pilot randomized 
controlled trial. Int J Obes 2020:1–7. https://doi.org/10.1038/ 
e41366-020-0598-3

168. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, 
Rawling M, Savory E, Stebbing J (2020) Baricitinib as potential 
treatment for 2019-nCoV acute respiratory disease. Lancet 395: 
e30–e31. https://doi.org/10.1016/S0140-6736(20)30304-4

169. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, 
Dougdos M, van Vollenhoven R, McInnes IB, Bijlsma JW, 
Burmester GR, de Wit M, Falzon L, Landewé R (2020) Safety 
of synthetic and biological DMARDs: a systematic literature 
review informing the 2019 update of the EULAR recommendations 
for the management of rheumatoid arthritis. Ann Rheum Dis 
79:760–770. https://doi.org/10.1136/annrheumdis-2019-216653

170. Castagné B, Viprey M, Martin J, Schott AM, Cucherat M, 
Soubrier M (2019) Cardiovascular safety of tocilizumab: a 
systematic review and network meta-analysis. PLoS One 14: 
e0220178. https://doi.org/10.1371/journal.pone.0220178

171. Brito CA, Paiva JG, Pimentel FN, Guimarães RS, Moreira MR 
(2020) COVID-19 in patients with rheumatological diseases treated 
with anti-TNF. Ann Rheum Dis. https://doi.org/10.1136/annrheumdis-2020-218171

172. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, Cannegieter 
SC, Jørgensen JOL, Ehrenstein V, Vandenbroucke JP, Pedersen 
L, Sørensen HT (2013) Use of glucocorticoids and risk of venous 
thromboembolism: a nationwide population-based case-control 
study. JAMA Intern Med 173:743–752. https://doi.org/10.1001/ 
jamainternmed.2013.122

173. Gianfrancesco M, Hyrich KL, Al-Adely S et al (2020) 
Characteristics associated with hospitalisation for COVID-19 in 
people with rheumatic disease: data from the COVID-19 Global 
Rheumatology Alliance physician-reported registry. Ann Rheum 
Dis 79:859–866. https://doi.org/10.1136/annrheumdis-2020- 
218781

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