Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 and immunothrombosis: Pathophysiology and therapeutic implications

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ABSTRACT

The coagulopathy of COVID-19 is characterised by significantly elevated D Dimer and fibrinogen, mild thrombocytopenia and a mildly prolonged PT/APTT. A high incidence of thrombotic complications occurs despite standard thromboprophylaxis. The evidence to date supports immunothrombosis as the underlying mechanism for this coagulopathy which is triggered by a hyperinflammatory response and endotheliopathy. A hypercoagulable state results from endothelial damage/activation, complement activation, platelet hyperactivity, release of Extracellular Neutrophil Traps, activation of the coagulation system and a "hypofibrinolytic" state. Significant cross-talk occurs between the innate/adaptive immune system, endothelium and the coagulation system. D dimer has been shown to be the most reliable predictor of disease severity, thrombosis, and overall survival. In this context, targeting pathways upstream of coagulation using novel or repurposed drugs alone or in combination with other anti-thrombotic agents may be a rational approach to prevent the mortality/morbidity due to COVID-19 associated coagulopathy.

1. Introduction

The emergence of coronavirus 2019 (COVID-19), a new disease entity caused by the severe acute respiratory syndrome coronavirus 2 (SARS−COV2) virus has led to an unprecedented global health crisis. It was first declared a global pandemic by the World Health Organisation on 11 March 2020 and as of 10 September 2021, over 223 million cases have been reported worldwide, with 4.6 million deaths attributed to this devastating disease. The clinical spectrum ranges from asymptomatic carriers to a critical illness manifested by acute respiratory distress syndrome which occurs in about 5% of patients typically around day 10 of the onset of illness and can progress to respiratory failure, multiorgan failure and death (Berlin et al., 2020). While the reasons that predispose some individuals to a more severe illness are poorly understood, severe disease has been associated with a hypercoagulable state. Indeed, the coagulopathy associated with COVID-19 characterised by elevated D-dimer and fibrin degradation products (FDPs) has been shown to correlate with disease severity and increased mortality (Tang et al., 2020a). In addition, COVID-19 is associated with an increased rate of thrombotic complications including microvascular, venous thromboembolism and arterial thrombosis (McFadyen et al., 2020). Further, the incidence of thrombotic complications associated with COVID-19 appears to be higher in intensive care unit (ICU) patients with COVID-19 than Non−COVID-19 ICU patients and other respiratory viruses such as Middle East respiratory syndrome (MERS) coronavirus and influenza viruses (Nopp et al., 2020). Various mechanisms have been proposed to explain the coagulopathy caused by COVID-19, although immunothrombosis, an interplay between the immune system and the coagulation pathway is believed to be the primary underlying mechanism. In this narrative review we discuss the pathophysiology, clinical, laboratory and therapeutic implications of COVID-19 coagulopathy. A summary of the pathophysiology is shown in Fig. 1.

2. Pathophysiology of COVID-19 coagulopathy

2.1. Entry of SARS-Cov-2 via ACE2

SARS−COv-2 enters the host cell by binding to the transmembrane Angiotensin Converting Enzyme 2 (ACE2) receptor via the S1 subunit of its spike protein. This receptor is widely expressed in a variety of cell types and organs throughout the body including the lungs, cardiovascular system, gut, kidneys, central nervous system, and adipose tissue. In addition to ACE2, SARS−COV-2 also binds to heparan sulphate, a cell surface glycosaminoglycan via the receptor binding domain on S1 which

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induces a conformational change in of S1, thus enhancing its interaction with ACE2 (Clausen et al., 2020). Fusion of the S2 subunit with the host membrane is facilitated by a serine protease, Transmembrane protease serine 2 (TMPRSS2) which primes this step by proteolytic cleavage of the S2 binding site. Binding of SARs−COV-2 to ACE2 leads to subsequent downregulation of surface ACE2 expression which may be mediated by proteolysis and ectodomain shedding of ACE-2 by A Disintegrin And Metalloproteinase-17 (ADAM-17) (Gheblawi et al., 2020). ACE-2 is an important mediator of the Renin-Angiotensin System, converting Angiotensin II to Angiotensin 1–7. Angiotensin II is a potent vasoconstrictor which has pro-inflammatory and pro-fibrotic effects while Angiotensin 1–7 is a vasodilator which negatively regulates the Renin Angiotensin system and has cardioprotective effects. Downregulation of ACE-2 therefore leads to unopposed angiotensin II effects, including proinflammatory, prothrombotic, and pro-oxidant risks. In addition, differences in tissue expression of ACE-2 receptor and activating proteases may contribute to unique aspects of the pathophysiology of different coronaviruses.

2.2. Systemic inflammatory response versus "cytokine storm"

Severe COVID-19, is characterised by a hyperinflammatory response with elevated levels of ferritin, CRP, and cytokines such as interleukin-2R (IL-2R), IL-6, IL-8, IL-10, and Tumour Necrosis Factor alpha (TNF-α) (Henry et al., 2020; Chen et al., 2020). In particular, IL-6 has been shown to be selectively induced by SARS-CoV-2 and circulating IL-6 levels are closely associated with the severity of COVID-19 (Tang et al., 2020b). The release of proinflammatory cytokines is believed to be triggered by pathogen-associated molecular patterns (PAMPs) and host derived damage-associated molecular patterns (DAMPs) leading to activation of the immune system (Iba et al., 2020a) of which macrophages and monocytes are believed to play a key role (Merad and Martin, 2020). This is supported by the detection of macrophage/monocyte attracting chemokines such as monocyte chemotactic protein 1 (MCP-1), interferon-inducible protein-10, macrophage inflammatory protein-1α in the Bronchial Alveolar Lavage Fluid (BALF) obtained from COVID-19 patients (Xiong et al., 2020) and similarities in the cytokine profile of patients with severe COVID-19 pneumonia and other hyperinflammatory syndromes such as macrophage activation syndrome or secondary haemophagocytosis lymphohistiocytosis (McGonagle et al., 2020a; Mehta et al., 2020).

In children, a delayed hyperinflammatory syndrome has also been recognised which typically occurs 2–6 weeks after SARS-CoV-2 infection. This rare but serious condition has been termed multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) or paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) although it has also been reported in adolescents (Jiang et al., 2020). It shares similar clinical features with Kawasaki disease, but affects older children and more often presents with intestinal involvement, myocardial failure and shock (Brodin, 2021).

Although the hyperinflammatory response has been referred widely in the literature as "cytokine storm syndrome", use of this term in COVID-19 is controversial. Critics have argued that to date there has been no standard definition for the "cytokine storm syndrome" and that compared to non−COVID-19 acute respiratory distress syndrome (ARDS), levels of IL-6 and other cytokines in severe COVID-19 patients are significantly lower (typically 10–200 fold) (Sinha et al., 2020; Kox et al., 2020). Further, distinguishing an appropriate from a dysregulated

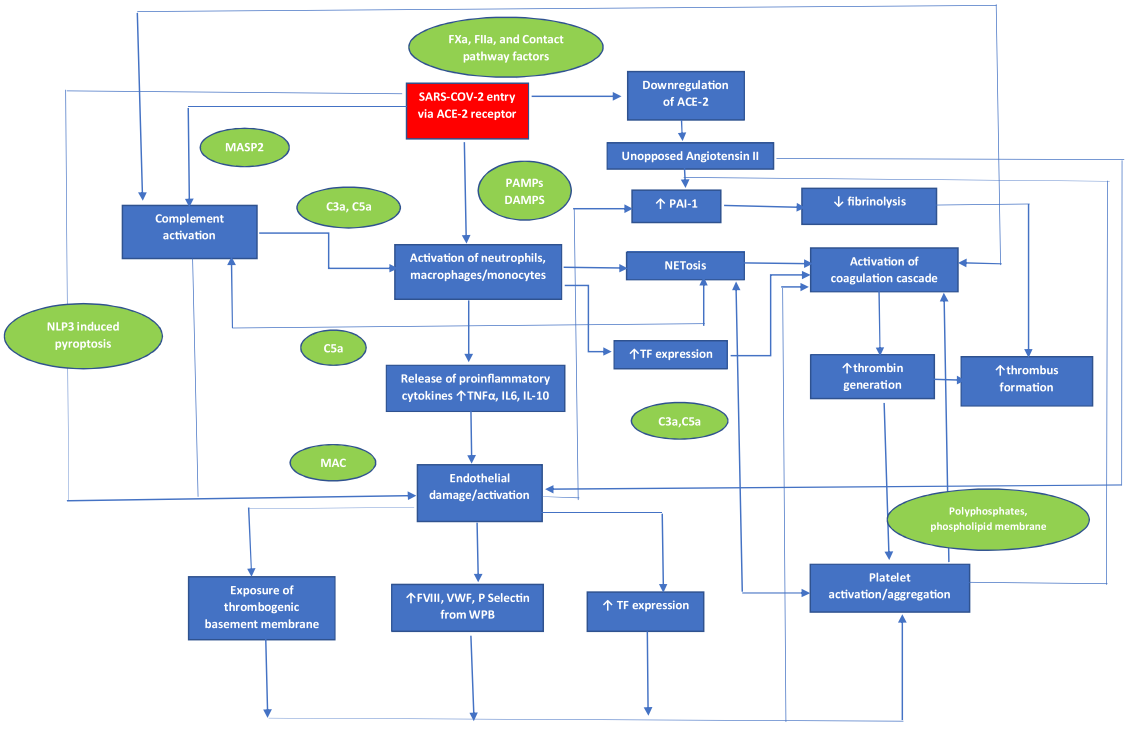

Fig. 1. Pathophysiology of COVID-19 associated coagulopathy. SARS-CoV2 triggers the release of cytokines from monocytes, macrophages and neutrophils leading to a cytokine storm. This results in activation of monocytes, macrophages and neutrophils with upregulation of tissue factor and release of NETs. The endothelium is damaged/activated due to pyroptosis induced by direct viral invasion, release of cytokines, complement activation and downregulation of ACE2. This leads to exposure of the thrombogenic basement membrane, upregulation of tissue factor and release of factor VIII, VWF and P-Selectin from WPB resulting in activation of platelets and coagulation factors. Fibrinolysis is also suppressed due to inhibition of PAI-I further contributing to the procoagulant state. In addition, there is significant cross talk between the immune, complement, and coagulation systems leading to a positive feedback loop, thus amplifying this response. ACE-2, angiotensin converting enzyme 2; C, complement; COVID-19, coronavirus disease 2019; IL, interleukin; NET, neutrophil extracellular trap; MASP2, Mannan-binding lectin serine protease 2; MAC; membrane attack complex; NLP3, NLR pyrin domain containing 3; PAI-1, plasminogen activator inhibitor 1; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TF, tissue factor; TNF, tumour necrosis factor; WPB, Weibel Palade body.

inflammatory response in the pathophysiology of critical illness is challenging and this has implications for the use of anti-cytokine therapies such as IL-6 inhibitors and high dose corticosteroids which may block pathways critical to host immune response. This has led to the proposal to use the alternative term "systemic inflammatory response syndrome" which has historically been described in patients with sepsis (Sinha et al., 2020).

While severe COVID-19 is associated with an excessive inflammatory response, it should be noted that immunosuppression or immune-paralysis occurs concurrently in patients with severe COVID-19. This manifests as progressive lymphopenia, with a decrease in lymphocytes, predominantly CD4+ and CD8 + T cells, resulting in a decrease in numbers as well as IFN-γ production by CD4 + T cells which may correlate with disease severity (Chen et al., 2020; Kiselevskiy et al., 2020; Triggle et al., 2021).

An association between hyperinflammation characterised by elevated cytokine levels and coagulopathy is supported by work by Ranucci et al. who demonstrated a correlation between IL-6 and fibrinogen levels in patients with COVID-19 acute respiratory distress syndrome (Ranucci et al., 2020). A few mechanisms have been postulated to explain how this hyperinflammatory response leads to thrombosis (Iba et al., 2020b) which include: (1) increased expression of tissue factor (TF) on monocytes/macrophages and vascular endothelial cells stimulated by pro-inflammatory cytokines such as Tumour necrosis factor-α, IL-1β, IL-6 thus promoting coagulation via the extrinsic pathway (MacKman et al., 2020) (2) suppression of the fibrinolytic system by decreased activity of urokinase-type plasminogen activator and increased release of plasminogen activator inhibitor-1 (3) platelet activation by various proinflammatory cytokines and (4) endothelial damage by the inflammatory reaction. Conversely, thrombin generation enhances the release of pro-inflammatory cytokines such as IL-6 and TNF-a by monocytes through protease-activated receptors (PARs). Thus there is significant cross-talk between inflammation and coagulation which leads to a vicious cycle. (Levi and Hunt, 2020).

2.3. Endotheliopathy/endotheliitis

The intact endothelium plays an important role in maintaining haemostasis under physiological conditions by providing a protective glycocalyx barrier to the thrombogenic subendothelial basement membrane, as well as regulating tight junctions, adhesion molecules and vascular tone. It also has antithrombotic properties through the expression of antiplatelet (e.g. nitric oxide and prostacyclin) and anti-coagulant (e.g. antithrombin, thrombomodulin, Endothelial protein C receptor (EPCR), and heparin-like proteoglycans) mediators (Yau et al., 2015). SARs-Cov-2 infection results in endothelial damage/activation which can be mediated via direct or indirect mechanisms. Evidence for direct viral infection of the endothelial cell is supported by a study by (Varga et al. (2020)) who showed that direct viral infection was associated with diffuse endothelial inflammation and apoptosis. Several mechanisms for this have been described of which activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome (Freeman and Swartz, 2020), leading to pyroptosis, an inflammatory form of programmed cell death usually seen in infections by intracellular pathogens is believed to play a major role (Manolis et al., 2020; Price et al., 2020). The endothelium can also be activated by indirect mechanisms including pro-inflammatory cytokines, downregulation of ACE2, hypoxia, complement activation, and Neutrophil Extracellular Traps (NET) osis (O'Sullivan et al., 2020). This in turn leads to activation of the coagulation system through a number of mechanisms (Teuwen et al., 2020) such as (1) exposure of the thrombogenic basement membrane (2) release of factor VIII (FVIII), von Willebrand factor (VWF) and P-selectin from Weibel-Palade bodies (WPB) and (3) release of Vascular Endothelial Growth factor (VEGF), from activated platelets which causes upregulated expression of TF.

Evidence for endothelial activation/dysfunction leading to coagulopathy is supported by biomarker and postmortem studies in COVID-19 patients. Goshua et al. showed that markers of endothelial cell activation, including VWF antigen/antibody, FVIII activity, and thrombin antithrombin (TAT) complexes were significantly higher in intensive care unit (ICU) patients with severe COVID-19 compared to non-ICU patients (Goshua et al., 2020). In addition, a post-mortem study by Ackermann et al. demonstrated that alveolar capillary microthrombi were nine times as prevalent in patients who died from respiratory failure caused by SARS-CoV-2 infection as in patients with influenza, thus supporting the hypothesis of endothelial injury-mediated microvascular thrombosis in COVID-19 (Ackermann et al., 2020).

2.4. Platelet hyperactivity

While platelets have an established role in haemostasis and thrombosis, their role in the immune response to pathogens is also increasingly being recognised (Koupenova et al., 2018). Thrombocytopenia occurs in 5–40 % of patients with COVID-19(Larsen et al., 2020) and is associated with severe disease and increased mortality.(Lippi et al., 2020) Recent studies have also demonstrated that COVID-19 is associated with platelet hyperreactivity, (Manne et al., 2020; Hottz et al., 2020; Zaid et al., 2020) thus suggesting that platelets may contribute to COVID 19 coagulopathy. Unlike sepsis induced coagulopathy/disseminated intravascular coagulopathy (SIC/DIC) however, the coagulopathy associated with COVID-19 is characterised by significantly elevated D Dimer levels and fibrinogen and only mild thrombocytopenia. The exact mechanisms for how platelets may contribute to coagulopathy in COVID-19 have yet to be elucidated although several possible mechanisms have been discussed in recent reviews (McFadyen et al., 2020; Koupenova, 2020). One leading hypothesis is internalisation of the SARs-CoV2 virus by platelets which has been previously described in studies of patients infected with influenza, a single stranded RNA virus similar to SARs-CoV-2. This leads to activation of the Toll-like receptor TLR-7 resulting in the release of complement C3 from platelet alpha granules which in turn stimulates the release of NETs, a scaffold and potent activator of coagulation via multiple mechanisms. While there is ongoing debate as to whether internalisation of SARS-CoV-2 by platelets occurs and whether ACE2 the main receptor for SARS-CoV2 is expressed on platelets, platelets can also be activated by other mechanisms such as the release of tissue factor, platelet activating factor (PAF) and binding of platelet GP (Glycoprotein) VI to collagen. Coagulation is subsequently triggered by platelet degranulation and aggregation, chemokine induced leucocyte-platelet aggregates, as well as release of platelet derived inorganic polyphosphate and tissue bearing microvesicles.

2.5. Neutrophil extracellular traps: scavenger and scaffold

As a first-line host defence against foreign microbes, neutrophils release NETs, web-like structures composed of Deoxyribonucleic acid (DNA) filaments coated with histones and granule proteins. However, in addition to its immune function, NETs also provide a scaffold for platelet, red blood cells, TF bearing extracellular vesicles and pro-coagulant molecules (e.g. VWF, fibronectin, fibrinogen, FXII, and TF), thus leading to activation of platelets and the coagulation system. The pro-coagulant effect of NETs is perpetuated by cross-talk between the endothelium, platelets and neutrophils/NETs resulting in a vicious circle which leads to further thrombus formation (Laridan et al., 2019). Of note, studies on respiratory viral infections have demonstrated a key role for neutrophils in clearing viruses in the lung by phagocytosing viral particles and by releasing NETs (Tate et al., 2009; Camp and Jonsson, 2017). In keeping with this, high levels of markers of NETs (cell-free DNA, myeloperoxidase-DNA complexes, and citrullinated histone H3) are found in the plasma of patients with COVID-19 which have been shown to corelate with disease severity (Middleton et al., 2020; Leppkes et al., 2020; Zuo et al., 2020a). Further, in lung tissue obtained from autopsies of COVID-19 patients, NETs were associated with

microthrombi and platelet deposition (Middleton et al., 2020; Leppkes et al., 2020; Nicolai et al., 2020). Interestingly, NETosis can be induced by plasma from COVID-19 patients (Middleton et al., 2020; Nicolai et al., 2020) which can be successfully blocked by a NET-inhibitory peptide (Middleton et al., 2020). In clinical studies, markers of NETs were associated with higher risk of morbid thrombotic events despite prophylactic anticoagulation in hospitalised COVID-19 patients (Zuo et al., 2020b). Taken together, this suggests that NETosis plays an important role in COVID-19 associated coagulopathy/thrombosis.

2.6. Complement activation: friend or foe

The complement system is a key mediator of the innate immune response that can be activated by three pathways (classical, lectin, and alternative) of which binding of the lectin pathway of complement component mannan-binding lectin (MBL) via the SARS CoV-1 spike protein is believed to be the likely mechanism of systemic activation of complement in COVID-19 (Gralinski et al., 2018). C3a and C5a anaphylatoxins recruit and/or activate neutrophils, monocytes, endothelial cells and platelets resulting in the release of proinflammatory cytokines which promotes coagulation as previously described. Significant interaction occurs between the complement and coagulation systems. C5a upregulates TF expression on neutrophils and endothelial cells and stimulates secretion of VWF from endothelial cells. In addition, C5a also impairs fibrinolysis by increasing the release of plasminogen activator inhibitor 1 (PAI-1) from mast cells and basophils (Foley and Conway, 2016). Coagulation factors FXa, FXIa and plasmin in turn cleave both C5 and C3, to generate C5a and C3a while thrombin cleaves C5 to generate C5a (Amara et al., 2008). The complement system is also activated by Contact pathway factors, such as FXIIa which activates complement C1, leading to activation of the classical pathway of complement (Ghebrehiwet et al., 1983), and kallikrein which cleaves both C3 and factor B (Irmscher et al., 2018). In addition, indirect activation of coagulation by the complement system occurs via C5a induced NETosis while neutrophils themselves can activate the complement system. Finally, there is also reciprocal activation between platelets and the complement system (Peerschke et al., 2006).

Excessive complement activation leading to widespread microvascular thrombosis is known to occur in a number of pathological settings. The classic example is atypical haemolytic-uremic syndrome (aHUS), a rare disorder of uncontrolled complement activation characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal failure. (Sakari Jokiranta, 2017). Evidence that the complement system may play a role in the coagulopathy of COVID-19 in at least a subset of patients was demonstrated in a case series of 5 patients with severe COVID-19. Autopsies of these patients showed evidence of deposition of C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL)-associated serine protease (MASP)2 in the microvasculature of their lungs and skin. In addition, two of these patients also had co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in the interalveolar septa and the cutaneous microvasculature (Magro et al., 2020). In this context, studies of complement inhibition in murine models of SARS−COV and MERS−COV, coronaviruses similar to SARS−COV-2, have demonstrated improved outcomes (Gralinski et al., 2018; Jiang et al., 2018) suggesting a role for complement inhibitors in COVID-19.

2.7. Antiphospholipid antibodies epiphenomenon or pathogenic

Antiphospholipid syndrome is an acquired thrombophilia characterised by thrombotic events or pregnancy morbidity and the presence of persistently positive antiphospholipid antibodies. Evidence for an association between antiphospholipid antibodies and COVID-19 coagulopathy/thrombosis emerged from an early report of three COVID-19 ICU patients with multiple cerebral infarcts who tested positive for IgA anticardiolipin antibodies and IgA/G anti-Beta 2-glcoprotein antibodies (Zhang et al., 2020a). This was followed by reports of a high incidence of positive Lupus anticoagulant (45–87 %) among non-ICU and ICU patients with COVID-19 (Harzallah et al., 2020; Helms et al., 2020). Subsequently, the presence of antiphospholipid antibodies and/or lupus anticoagulant in COVID-19 patients was confirmed in other studies (Xiao et al., 2020; Zhang et al., 2020b; Amezcua-Guerra et al., 2020; Bertin et al., 2020) with one study demonstrating a correlation between IgG anticardiolipin antibodies and severity of disease (Bertin et al., 2020). This has been tempered by counter-arguments that antiphospholipid antibodies often appear transiently during critical illness and infections, the use of heparin and marked elevation of C-Reactive Protein (CRP) in most of these patients which can cause false positive lupus anticoagulant tests, the inclusion of non-criteria antiphospholipid antibodies and the baseline high incidence of thrombosis in the patient populations studied (Connell et al., 2020). Indeed, several subsequent studies have shown that the detection of lupus anticoagulant was not associated with an increased risk of thrombosis. In addition, cases of triple positive antibodies were rare, and the antibodies were transient in most cases (negative on repeat testing) (Devreese et al., 2020; Siguret et al., 2020; Gatto et al., 2020) suggesting that antiphospholipid antibodies are an epiphenomenon rather than pathogenic in COVID-19 coagulopathy. Interestingly, however, a recent Ex-vivo study by (Zuo et al. (2020c)) demonstrated that IgG fractions purified from COVID-19 patient serum positive for antiphospholipid antibodies (anti--beta2-glycoprotein, anti-phosphatidylserine/prothrombin) promoted NET release similar to Immunoglobulin G (IgG) isolated from individuals with established antiphospholipid syndrome. Further, when injected into mice, thrombosis was stimulated, suggesting that these auto-antibodies are potentially pro-thrombotic. Further studies are therefore required to clarify the presence, temporal association and role of antiphospholipid antibodies in COVID-19 patients.

2.8. Fibrinolytic system shutdown or consumption

Suppressed fibrinolysis due to elevated levels of PAI-1 has been described in acute lung injury and SIC/DIC (Idell, 2003; Iba and Levy, 2020). This has led to the suggestion that abnormalities in the fibrinolytic system may play an important role in acute lung injury caused by COVID-19 associated coagulopathy. Indeed, in a mouse model of acute lung injury by SARS-CoV infection, levels of Serpine1, a urokinase inhibitor were elevated, while Serpine1 knockout mice demonstrated increased fibrinolytic activity and haemorrhage in the lungs thus highlighting the role of the urokinase pathway in the pathogenesis of SARS-CoV induced acute lung injury (Gralinski et al., 2013). In humans, impaired fibrinolysis has also been reported in SARS-CoV2 infected patients which was mainly associated with high PAI-1 levels (Nougier et al., 2020). In addition, fibrinolysis shutdown was reported in a significant proportion of COVID-19 ICU patients using viscoelastic testing and this was associated with a higher incidence of thrombotic complications (Wright et al., 2020). While the exact mechanisms for suppressed fibrinolysis in Covid-19 are uncertain, plausible mechanisms include activation of Thrombin Activable Fibrinolysis Inhibitor (TAFI) by high concentrations of thrombin due to a hypercoagulable state and increased release of PAI-1 from endothelial cells and activated platelets secondary to inflammation (Nougier et al., 2020). Another possible mechanism is overactivation of the Renin-Angiotensin system due to SARS-CoV-2 mediated downregulation of ACE2, leading to unopposed Angiotensin II effects which increases the expression of PAI-1 (Lazzaroni et al., 2020; Hanff et al., 2020). Of note, however, significantly elevated D dimer, a breakdown product of fibrin is a common feature of late, severe disease, suggesting that the fibrinolytic system is still functional. This has led to the alternative hypothesis that “consumptive fibrinolysis”, a failing attempt of the fibrinolytic system to remove fibrin and necrotic tissue from the lung parenchyma, with the fibrinolytic system being consumed or overwhelmed in the process occurs rather than “fibrinolytic shutdown” per se (Medcalf et al., 2020). The same authors

propose a "plasmin paradox" in which anti-fibrinolytics may be protective in the early stages of COVID-19 through an anti-viral effect, whereas exogenous plasmin(ogen) or plasminogen activators may be useful in later stages to enhance fibrinolysis (Medcalf et al., 2020).

3. Role of biomarkers in COVID-19 coagulopathy

COVID-19 associated coagulopathy is characterised by significantly elevated D Dimer and fibrinogen, mild thrombocytopenia and mildly prolonged prothrombin (PT) and activated partial thrombin time (APTT). This laboratory pattern is distinct from DIC/SIC and other coagulopathies (Iba et al., 2020a) although progression to DIC can also occur. DIC typically occurs between 7–10 days after admission, but can occur as early as 4 days and may be due to secondary causes independent of COVID-19 effects, such as prolonged hospitalization, mechanical ventilation, superinfection, and other typical ICU aetiologies (Connors and Levy, 2020). D Dimer is the most well-studied biomarker and consistent predictor of outcome in COVID-19 patients. Studies have shown that levels of D Dimer correlate with disease severity (Lippi and Favaloro, 2020) and can be used to predict the risk of venous thromboembolism, (Nopp et al., 2020) need for ventilatory support, (Berger et al., 2020) and mortality.(Gungor et al., 2020) Interim guidelines from the International Society on Thrombosis and Haemostasis (ISTH) recommend performing D Dimer, prothrombin (PT), platelet count and fibrinogen on admission as a risk stratification tool (Thachil et al., 2020). It has also been suggested that D Dimer, PT, and platelet count should be repeated every 2–3 days to monitor for the development of coagulopathy (Levi et al., 2020).

4. Thrombotic complications

A high incidence of thrombotic complications occurs in COVID-19 patients with venous or arterial thrombotic complications reported in one-third of ICU patients despite pharmacological thromboprophylaxis (Klok et al., 2020). VTE accounts for the majority of thrombotic events although arterial thrombosis such stroke and acute myocardial infarction also occurs (Cheruiyot et al., 2020). Diagnosis of VTE is challenging and may be underestimated for various reasons including the need to limit patient contact with health personnel, limited resources in hospitals overwhelmed by high caseloads, and inability to perform diagnostic imaging in unstable patients (e.g. inability to perform Computer Tomography Pulmonary Angiogram (CTPA) in ventilated patients lying prone). The reported incidence of venous thromboembolism varies depending of disease severity (ICU versus Non-ICU patients) and whether screening of asymptomatic DVT cases was performed. A meta-analysis reported an overall VTE prevalence estimate of 14.1 % (95 % confidence interval [CI], 11.6–16.9) with a higher incidence in those who underwent ultrasound screening (40.3 % 95 % CI, 27.0–54.3) compared to those without screening (9.5 % 95 % CI, 7.5–11.7). The VTE prevalence was also higher in ICU 22.7 % (95 % CI, 18.1–27.6) versus non-ICU patients 7.9 % (95 % CI, 5.1–11.2) (Nopp et al., 2020). In another meta-analysis, VTE occurred in 24 % (95 % PI, 5%–66 %), PE in 19 % (95 % PI, 6%–47 %), and DVT alone in 7% (95 % PI, 0%–69 %) of ICU patients (Porfidia et al., 2020). Taken together, this suggests a higher incidence of VTE in patients with severe COVID-19 compared to historical cohorts of ICU patients (5%–15%) (Nopp et al., 2020). Interestingly, the prevalence of pulmonary embolism (PE) appears to be disproportionately high relative to deep venous thrombosis (DVT) with one study reporting PE accounting for up to 80 % of all thrombotic events in ICU patients (Klok et al., 2020) suggesting that the underlying mechanism is primary in-situ thrombosis (pulmonary arterial thrombosis) rather than embolism. This has led to the use of new terminology such as 'diffuse pulmonary intravascular coagulation' or 'microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome' (MicroCLOTS) to describe this phenomenon (McGonagle et al., 2020b; Ciceri et al., 2021). In keeping with this theory, an autopsy series of 11 patients with COVID-19 found thrombosis predominantly affecting small and mid-sized (subsegmental/segmental) pulmonary arteries (Lax et al., 2020).

5. Therapeutic implications

5.1. Institutional guidelines

Most societal guidelines recommend thromboprophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) in all hospitalised patients unless contraindicated (Thachil et al., 2020; Bikdeli et al., 2020a; Spyropoulos et al., 2020; Moores et al., 2020). However, there is no consensus regarding the optimal risk stratification, intensity and duration of anticoagulation or whether post-hospital discharge should be given (Flaczyk et al., 2020). In brief, whereas guidelines by the American College of Chest physicians (ACCP) suggest standard dose thromboprophylaxis only in hospitalised patients with COVID-19 (Moores et al., 2020), ISTH Scientific and Standardisation Committee (SSC) goes beyond this to suggest intermediate dose low molecular weight heparin be considered in severe or high risk patients (Spyropoulos et al., 2020). In addition, ISTH SCC and the American College of Cardiology (ACC) also suggest consideration of post hospital discharge thromboprophylaxis for approximately 14 days in patients at high risk of thrombosis with a low risk of bleeding (Bikdeli et al., 2020a; Spyropoulos et al., 2020). Therapeutic anticoagulation is not currently recommended for primary prevention although ISTH SSC suggest consideration of increased intensity of anticoagulation (i.e., from standard or intermediate intensity to therapeutic intensity) in patients without confirmed VTE or PE but with deteriorating pulmonary status or acute respiratory distress syndrome (ARDS). In this context, a number of randomised controlled trials comparing intermediate/therapeutic vs standard prophylactic dose UFH/LMWH in hospitalised COVID-19 patients are currently underway/have been completed which will further inform guidelines (see Table 1) (Tritschler et al., 2020). Recently, results from the ACTIV-4 clinical trial (NCT04505774), part of an international collaboration of 3 linked studies (ACTIV-4, ATTAC and REMAP-CAP) using a multi-platform trial design have been published. This demonstrated that therapeutic anticoagulation is superior to standard care thromboprophylaxis in terms of reduced need for organ-support for moderate but not severe COVID-19 without a significant rate of bleeding (Investigators et al., 2021a, b). A recent randomised trial comparing standard to intermediate dose enoxaparin for thromboprophylaxis in COVID-19 patients admitted to ICU also did not show any significant difference in the composite outcome of arterial or venous thrombosis, need for extracorporeal membrane oxygenation or 30-day mortality (INSPIRATION Investigators et al., 2021). Taken together, these preliminary results do not support the use of higher intensity anticoagulation in unselected ICU patients with COVID-19. In terms of confirmed PE, most societies suggest the use of established guidelines. However, LMWH may be preferred in the inpatient setting over vitamin K antagonists (VKA), unfractionated heparin or direct oral anticoagulants (DOACs) for a number of reasons. For example, DOACs and warfarin may be limited by drug-drug interactions (e.g. interaction with antiviral agents such as lopinavir/ritonavir and other immunomodulatory investigational COVID-19 therapies). The limited experience and availability of specific reversal agents for DOACs may be also be a concern. Another concern is the need for monitoring with warfarin and unfractionated heparin which may increase health care worker exposure due to frequent blood draws. Finally, heparin resistance due to acute phase reactants may be an issue with unfractionated heparin.

5.2. Selected potential/experimental therapies

The high incidence of thrombosis in COVID-19 patients despite standard prophylaxis and association of thrombosis with increased mortality (Malas et al., 2020) has led to the search for novel approaches

Table 1
Clinical trials of potential therapeutic agents targeting immunothrombosis in COVID-19.

Study	Design	Target sample size	Population	Intervention	Control	Primary Outcome	Established/ postulated mechanisms for investigational agent
Systemic heparin/low molecular weight heparin							
COVID-HEP NCT04345848	Randomised, open-label, multicentre, clinical trial	200	1) Non-ICU patients with D-dimer >1000 μg/L or 2) ICU patients	Therapeutic LMWH or UFH	Prophylactic LMWH or UFH (augmented dose for ICU patients)	Composite outcome of arterial or venous thrombosis, DIC, and all-cause mortality (30 days)	Anticoagulant Anti-inflammatory Antiviral
HEP-COVID NCT04367831	Randomised, open-label, multicentre, clinical trial	308	Patients with D-dimer >4 × ULN or SIC score ≥4 stratified by ICU vs non- ICU stay	Therapeutic LMWH	Prophylactic or intermediate dose LWMH or UFH	Composite outcome of arterial thromboembolic events, venous thromboembolic events, and all-cause mortality (30 days)	Anticoagulant Anti-inflammatory Antiviral
IMPACT NCT04406389	Randomised, open-label, clinical trial	186	Non-ICU or ICU patients requiring supplemental oxygen and D-dimer >3× ULN	Therapeutic LMWH, UFH, fondaparinux, or argatroban	Intermediate dose LMWH, UFH, or fondaparinux	Mortality (30 days)	Anticoagulant Anti-inflammatory Antiviral
X-Covid 19 NCT04366960	Randomised, open-label, multicentre, clinical trial	2712	Non-ICU patients	Intermediate-dose LMWH	Prophylactic LMWH	Objectively confirmed venous thromboembolism (30 days)	Anticoagulant Anti-inflammatory Antiviral
IMPROVE-COVID NCT04367831	Cluster randomised, open-label, single-centre, adaptive trial	100	ICU patients	Intermediate-dose LMWH or UFH	BMI- and weight-adjusted prophylactic dose LMWH	Clinically relevant venous or arterial thrombotic events in ICU (30 days)	Anticoagulant Anti-inflammatory Antiviral
ACTIV-4 NCT04505774	Randomized, open label, adaptive platform trial	2000	Hospitalised patients with confirmed COVID-19	Therapeutic dose UFH or LMWH	Prophylactic dose UFH or LMWH	Organ Support (respiratory or vasopressor) Free Days	Anticoagulant Anti-inflammatory Antiviral
ATTACC NCT04372589	Randomized, open-label, multicentre, adaptive clinical trial	Adaptive with maximum of 3000	Patients with COVID-19 requiring hospitalisation or hospitalised not on mechanical ventilation	Therapeutic dose UFH or LMWH	Local standard care thromboprophylaxis	Mortality and days free of organ support	Anticoagulant Anti-inflammatory Antiviral
REMPA-CAP NCT02735707	Randomised, embedded, multifactorial, adaptive platform trial	Estimated enrolment 7100	Patients admitted to an ICU for severe CAP within 48 h of hospital admission	Therapeutic dose UFH or LMWH	Local standard care thromboprophylaxis	Mortality and days free of organ support	Anticoagulant Anti-inflammatory Antiviral
RAPID COVID COAG NCT04362085	Randomised, pragmatic, open-label, multicentre, adaptive clinical trial	462	Hospitalised, Non-ICU patients with D Dimer ≥2 times ULN or above ULN and Oxygen saturation ≤93 %	Therapeutic dose UFH or LMWH	Local standard care thromboprophylaxis	Composite outcome of ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation, or all-cause death up to 28 days	Anticoagulant Anti-inflammatory Antiviral
Nebulised heparin							
NEBUHEPA NCT04530578	Randomised, open-label, clinical trial	200	Patients with suspected COVID-19 and severe acute respiratory syndrome	Nebulised unfractionated heparin and prophylactic dose LMWH	Prophylactic LMWH	Requirement for mechanical ventilation	Anticoagulant Anti-inflammatory Antiviral
CHARTER-MT NCT04545541	Randomised, open label and blinded placebo controlled, multicentre, clinical trials (Meta-trial)	202	Mechanically ventilated COVID-19 patients	Nebulised unfractionated heparin and prophylactic dose LMWH	Standard care and nnebulised 0.9 % sodium chloride (5 mL) in placebo-controlled studies	Alive and Ventilator Free Score	Anticoagulant Anti-inflammatory Antiviral
Fibrinolytic therapy							
NCT04357730	Randomised, open-label, multicentre, clinical trial (phase 2a)	60	Patients with known/suspected COVID-19 and ARDS	IV Alteplase 50 mg +/- re-bolus in patients who shown initial transient response	Standard care	PaO2/FiO2 improvement from pre-to-post intervention	Fibrinolytic
PACA NCT04356833	Non-randomised, open-label, single-centre	24	Patients with COVID-19 and ARDS	Nebulised recombinant tissue-Plasminogen	Standard care	Percentage change in PaO2/FiO2 ratio from baseline and to day 5	Fibrinolytic

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Target sample size	Population	Intervention	Control	Primary Outcome	Established/ postulated mechanisms for investigational agent
	clinical trial (phase 2)			Activator (rt-PA) every 6 h for 66 h		(96 h ± 2 h) post treatment and day 7 (144 h ± 4 h) in the groups receiving rt-PA	
Dipyridamole							
TOLD NCT04424901	Randomised, open-label, single-centre clinical trial	100	Hospitalized patients with moderate to severe COVID-19	Dipyridamole 100 mg, 3 times daily for 7 days.	Standard care	D-dimer and platelet count	Anti-platelet Antiviral Inhibition of NETs
ATTAC-19 NCT04410328	Randomised, open-label, single-centre clinical trial	132	Patients with SARS-CoV-2 infection and symptoms consistent with COVID-19.	Dipyridamole ER 200 mg/ Aspirin 25 mg orally/ enterally, 2 times daily starting on the day of enrolment for a total of 2 weeks.	Standard care	Change in composite COVID ordinal scale at day 15.	Anti-platelet Antiviral Inhibition of NETs
DICER NCT04391179	Randomised, Placebo-controlled, clinical trial	160	Non-severe hospitalised COVID-19 patients	Dipyridamole 100 mg 4 times a day for 14 days while in hospital	Placebo 4 times a day for 14 days while in hospital	Change in D Dimer	Anti-platelet Antiviral Inhibition of NETs
Complement inhibitors							
CORIMUNO19-ECU NCT04346797	Randomised, open-label, clinical trial (cohort multiple RCT design)	120	1) Non-ICU patients with moderate or severe COVID-19 pneumonia 2) ICU patients	Eculizumab	Standard care	1) Survival without intubation at day 14 2) Change in organ failure at day 3, defined by the Sequential Organ Failure Assessment score	C5a inhibition
NCT04570397	Randomised, open-label, single-centre clinical trial	120	COVID-19 patients with acute kidney injury and clinical diagnosis of TMA (D dimer >100 % of upper limit and >25 % increase in Cr above normal range or baseline)	Ravulizumab	Standard care	50 % improvement in eGFR compared to conventional therapy within 30 days of treatment	C5a inhibition
NCT04369469	Randomised, open-label, multicentre, clinical trial (phase 3)	270	Patients With COVID-19 Severe Pneumonia, Acute Lung Injury, or ARDS	Ravulizumab	Standard Care	Survival (based on all-cause mortality) at Day 29	C5a inhibition
TACTIC-R NCT04390464	Randomised, parallel arm, open-label platform trial	1167	Pre-ICU Patients admitted with Covid-19 who are at risk as defined by specific risk count criteria	Patients randomised in a 1:1:1 ratio to Ravulizumab, Baricrintinb or standard care	NA	Time to incidence of the composite endpoint of: Death, Mechanical ventilation, ECMO, Cardiovascular organ support, or Renal failure	C5a inhibition
SAVE NCT04395456	Randomized, placebo-controlled, single-blind clinical trial (phase 2)	144	Patients with ARDS due to COVID-19	AMY-101	Placebo	1) Survival without evidence of ARDS. 2) COVID-19 ordinal scale	C3 inhibition
NCT04402060	Phase 1 Single arm, open label Phase 2 Randomized, Double-Blinded, Vehicle-Controlled, Multicentre, Parallel-Group Study	66	Adults with mild to moderate ARDS Due to COVID-19	APL-9	No comparator (phase 1) Vehicle control and standard of care (phase 2)	Cumulative incidence of treatment-emergent serious adverse events and treatment-emergent adverse events	C3 inhibitor
ZILU-COV NCT04382755	Randomized controlled, open-label, multicentre clinical trial (phase 2)	81	Patients with suspected/confirmed COVID-19 with acute hypoxic respiratory Failure	Zilucoplan® for 14 days	Placebo and standard of care	Mean change in oxygen as defined by Pa02/FiO2 at room air, P(Aa)O2 gradient and a/A pO2 ratio	C5 inhibitor

Aa, alveolar-arterial; ARDS, acute respiratory distress syndrome; BMI, body-mass index; C, complement; CAP, Community Acquired Pneumonia; COVID-19, coronavirus disease 2019; Cr, creatinine; DIC, disseminated intravascular coagulation; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; ER,

extended release; IV, intravenous; eGFR, estimated glomerular filtration rate; FiO2, fraction of inspired oxygen; NET, neutrophil extracellular trap; LMWH, Low Molecular Weight Heparin; PaO2, partial pressure of oxygen; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SIC, sepsis-induced coagulopathy; TMA, thrombotic microangiopathy; UFH, unfractionated heparin, ULN; upper limit of normal.

to prevent thrombosis driven by an overactive immune response beyond traditional anticoagulation strategies alone. For example, immune modulators or immunosuppressive therapy such as hydroxychloroquine, corticosteroids and IL-6 inhibitors have been used in clinical trials to target pathways upstream of the coagulation cascade. In addition, a number of antithrombotics have been repurposed which in addition to their direct antithrombotic effects may also have other potential mechanisms of action such as antiviral or anti-inflammatory effects. An extensive discussion of potential pharmacological agents targeting immunothrombosis is beyond the scope of this review and for this the reader is referred to a recent review article prepared by the Global COVID-19 Thrombosis Collaborative Group (Bikdeli et al., 2020b). However, a few selected candidate therapies are briefly discussed here. In addition, Table 1 gives a summary of a number of clinical trials investigating the use of these potential therapeutic agents in COVID-19 associated immunothrombosis.

5.2.1. Nebulised heparin

Nebulised heparin has been proposed as one of the potential therapeutic agents for COVID-19 induced ARDS and pneumonia. Besides its anticoagulant properties, unfractionated heparin may also have other advantages through off-target effects. Heparan sulphate is used as a co-receptor for some coronaviruses (including SARS−COV-2) for host cell attachment. Nebulised heparin may thus have an anti-viral effect by competitive binding to the SAR−COV-2 surface protein S1 thus inhibiting viral entry. In addition, there is evidence that heparin also has anti-inflammatory and mucolytic properties. The benefits of nebulised heparin in acute lung injury have been demonstrated in previous pre-clinical and clinical studies (Van Haren et al., 2020) and a number of clinical trials in COVID-19 patients are also currently underway (Table 1).

5.2.2. Fibrinolytic (thrombolytic) agents

Fibrinolytic therapy is another potential treatment for thrombotic complications and ARDS in COVID-19 patients. ARDS develops in about 5% of COVID-19 patients and is characterised by a diffuse inflammatory reaction, progressing through 3 phases – exudative, proliferative and fibrosis. The hallmark of ARDS is diffuse alveolar damage and fibrin deposition, leading to hyaline membrane formation and subsequent alveolar fibrosis. This, coupled with association of a hypofibrinolytic state in ARDS due to upregulation of PAI-1 has provided a rationale for the use of fibrinolytic therapy in COVID-19 patients. Indeed, use of fibrinolytics such as urokinase or tissue plasminogen activator has been shown to prevent ARDS in porcine models (Hardaway et al., 1990) and results of a phase 1 clinical trial to treat ARDS in critically ill patients has been promising with improvements in oxygenation (Hardaway et al., 2001). To date, only a small case series for the use of fibrinolytic therapy in COVID-19 patients has been reported (Wang et al., 2020). The main concern is the risk of bleeding, especially intracranial bleeding which is reported to occur in 1–3 % of patients given systemic thrombolysis (Chatterjee et al., 2014; Goldhaber et al., 1999). In this context, viscoelastic testing may be of value to identify patients with fibrinolytic shutdown who may benefit most from fibrinolytic therapy (Wright et al., 2020). The use of nebulised plasminogen activator to promote local fibrinolysis in the lungs while minimising the risk of systemic bleeding has also been proposed and the results of an ongoing phase 2 clinical trial using nebulised fibrinolysis in COVID-19 patients (NCT04356833) are eagerly awaited.

5.2.3. Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor that inhibits platelet aggregation by increasing the intracellular concentration of cyclic adenosine monophosphate. Pre-clinical studies have shown that dipyridamole is able to inhibit NETosis and thrombosis in anti-phospholipid syndrome by activation of adenosine A_{2A} receptors (Ali et al., 2019). In addition, Dipyridamole has a broad-spectrum activity to a wide range of viruses and is able to inhibit positive-stranded RNA viruses in vitro (Fata-Hartley and Palmenberg, 2005). A recent study showed that dipyridamole has specific affinity to the human coronavirus (HCoV-19) protease Mpro using in silico data and suppresses HCoV-19 replication in vitro. Further, Dipyridamole was shown to induce type 1 interferon response and prolong survival in a mouse model of viral pneumonia. The study also provided early data suggesting a clinical benefit of dipyridamole in a small group of severely ill COVID-19 patients (n = 31) who were treated with concomitant antiviral drugs. Compared to controls, patients treated with Dipyridamole had decreased D-dimer levels, improvements in platelet and lymphocyte counts and a trend towards improved clinical outcomes including clinical cure and discharge rates (Liu et al., 2020). While this data is encouraging, further high-quality studies are needed for confirmation.

5.2.4. Complement inhibitors

A potential role for complement inhibition in COVID-19 is supported by studies showing efficacy of this approach in murine models of SARS-CoV (Gralinski et al., 2018) and MERSCoV (Jiang et al., 2018), as well as autopsy evidence of complement deposition in organs of patients with severe COVID-19 (Magro et al., 2020). Eculizumab, a C5 inhibitor has already been used successfully in the treatment of atypical haemolytic uraemic syndrome, a complement mediated disease. The use of eculizumab (Diurno et al., 2020) and IFX-1, another anti-C5a monoclonal antibody (Vlaar et al., 2020) has recently been reported in a small number of patients with COVID-19 although further studies are currently underway. Another promising target is C3 which is positioned at the convergence of all three activation pathways, upstream of C5. Inhibition of C3 simultaneously blocks both C3a and C5a thus leading to more potent inhibition of the complement cascade. In addition, inhibition of C3 can also prevent IL-6 release from cells such as macrophages expressing the C3aR (Mastellos et al., 2019). One such drug compound is Compstatin (AMY-101), a C3 inhibitor which is currently undergoing investigation in phase 2 clinical trials of COVID-19 patients with ARDS (NCT04395456). A third potential target is the lectin pathway. MASP-2 an activator of the lectin pathway has been shown to bind to the nucleocapsid protein of coronaviruses such as MERSCoV, SARS-CoV, and SARS-CoV2 (Gao et al., 2020). Suppression of this pathway can be achieved using the anti-MASP2 antibody narsoplimab (Elhadad et al., 2020).

6. Summary and conclusions

In summary, the coagulopathy associated with COVID-19 is the consequence of a complex interplay between the immune, endothelium and coagulation system, with bidirectional interactions, resulting in a procoagulant milieu. The observation of a high incidence of thrombotic event despite routine thromboprophylaxis suggests a different approach is required. In particular, targeting pathways upstream of coagulation using novel or repurposed drugs alone or in combination with other antithrombotic agents may be a rational approach to reduce the mortality and morbidity associated with Covid-19 coagulopathy. Further studies are required to determine the optimal agent or combinations, dose, timing of intervention, efficacy and safety of such an approach.

Contributions

M. S. Lim wrote the first draft of the manuscript. S. Mcrae contributed to critical revision of the manuscript. Both authors approved the

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Ethical standards

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