Prevention and management of thrombosis in hospitalised patients with COVID-19 pneumonia

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A proportion of people infected with SARS-CoV-2 develop moderate or severe COVID-19, with an increased risk of thromboembolic complications. The inflammatory response to SARS-CoV-2 infection can cause an acute-phase response and endothelial dysfunction, which contribute to COVID-19-associated coagulopathy, the clinical and laboratory features of which differ in some respects from those of classic disseminated intravascular coagulation. Understanding of the pathophysiology of thrombosis in COVID-19 is needed to develop approaches to management and prevention, with implications for short-term and long-term health outcomes. Evidence is emerging to support treatment decisions in patients with COVID-19, but many questions remain about the optimum approach to management. In this Viewpoint, we provide a summary of the pathophysiology of thrombosis and associated laboratory and clinical findings, and highlight key considerations in the management of coagulopathy in hospitalised patients with severe COVID-19, including coagulation assessment, identification of thromboembolic complications, and use of antithrombotic prophylaxis and therapeutic anticoagulation. We await the results of trials that are underway to establish the safety and benefits of prolonged thromboprophylaxis after hospital discharge.

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Introduction

Infection with SARS-CoV-2 causes mainly asymptomatic disease, or mild symptoms similar to those of influenza infection, often with loss of taste or smell; a proportion of patients develop more severe disease. In the early stages of the pandemic, more severe forms of disease were initially considered by clinicians as a form of community-acquired pneumonia, often evolving into the acute respiratory distress syndrome (ARDS). As it became apparent that organs other than the lungs could also be involved, the concept that COVID-19 is a more generalised disease, a viral sepsis,[1] became accepted, with important implications for patient management.

A common pathophysiological alteration across organs has been proposed, specific for SARS-CoV-2 and involving the endothelium. The virus directly infects endothelial cells, as shown by the presence of viral particles in endothelial cells of different organs in biopsies from patients,[2] leading to endothelial cell perturbation, with so-called endotheliopathy or endotheliitis.[3,4] One impact of these endothelial changes, alongside the prothrombotic changes of the acute-phase response, is an increased risk of thrombotic events in patients with COVID-19 pneumonia, and autopsy studies have confirmed the presence of macrovascular and microvascular thrombi in the lungs[2,5,6] and other organs[4,7] of non-survivors of COVID-19.

In this Viewpoint, we briefly summarise the pathophysiological changes associated with thrombosis in COVID-19. We discuss laboratory findings and clinical consequences of coagulopathy in patients with COVID-19, and outline current prophylactic and therapeutic approaches, based on the available evidence.

Pathophysiology of thrombosis in COVID-19

COVID-19 pneumonia is associated with a profound inflammatory response within the lungs, including infiltrating lymphocytes and macrophages, resulting in the release of inflammatory cytokines, such as interleukin-1 (IL-1) and IL-6 (figure).[3,8] IL-6 is responsible for generating an acute-phase response, with increased production of fibrinogen, factor VIII, and von Willebrand factor (vWF). Endothelial cells represent a central interface for the bidirectional interaction

Key messages

- Patients with moderate or severe COVID-19 develop a pro-coagulant state known as COVID-19-associated coagulopathy (CAC); although CAC shares some features with sepsis-related forms of disseminated intravascular coagulation (DIC), it has distinct features that set it apart from DIC, including near-normal activated partial thromboplastin time and prothrombin time, and elevated fibrinogen concentrations
- CAC reflects a combination of endothelial and acute-phase changes, and results in an increased risk of thromboembolic complications, with a clinical picture of predominantly venous thromboembolic events
- Antithrombotic prophylaxis should be applied in all patients hospitalised with COVID-19; whether thromboprophylaxis should continue after discharge remains unclear
- Therapeutic anticoagulation is of benefit in certain patients, but should not be given routinely to all critically ill patients with COVID-19
- Coagulopathy improves as patients recover from COVID-19, but D-dimers can remain elevated for months; long-term morbidity associated with CAC-induced thrombotic events requires post-discharge follow-up
- Recent randomised controlled trials have provided information about optimum doses of heparin for inpatient thromboprophylaxis in subgroups of patients with COVID-19; trials are underway to establish whether post-discharge thromboprophylaxis is safe and beneficial

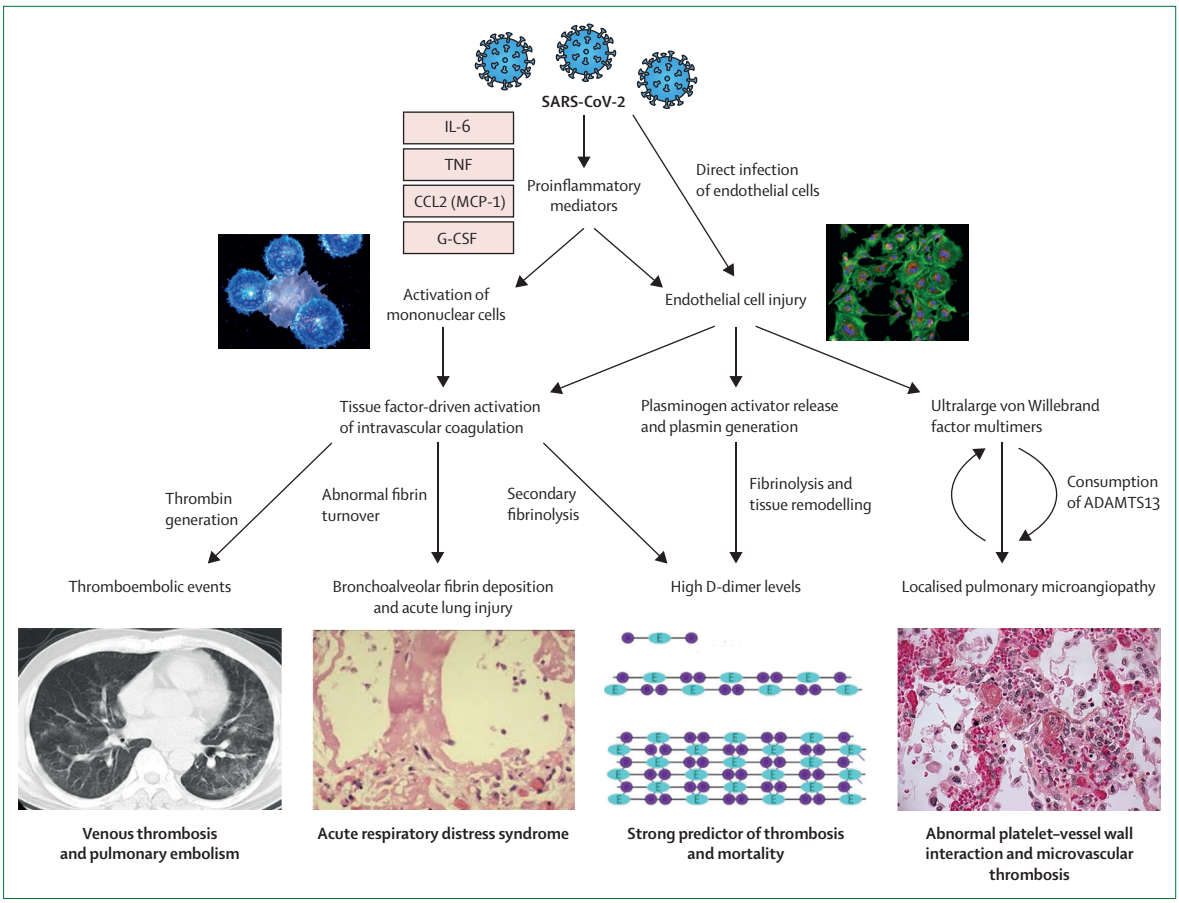

Figure: **Pathogenetic pathways of coagulopathy in COVID-19 and associated clinical manifestations**
SARS-CoV-2 elicits a strong inflammatory response orchestrated by various inflammatory mediators, such as interleukin-6 (IL-6), tumour necrosis factor (TNF), C-C motif chemokine 2 (CCL2 or monocyte chemoattractant protein 1 [MCP-1]), and granulocyte-colony stimulating factor (G-CSF), which leads to activation of mononuclear cells. These cells express tissue factor on their surface, leading to thrombin generation and subsequent fibrinogen-to-fibrin conversion. Simultaneously, SARS-CoV-2 can directly infect and damage endothelial cells, causing massive release of endothelial cell constituents, such as plasminogen activators and von Willebrand factor (vWF). Plasminogen activator release can contribute to fibrinolysis, but might also affect tissue remodelling (eg, increasing vascular permeability and contributing to pulmonary oedema) through plasmin-mediated activation of matrix metalloproteinases. Massive release of high-molecular-weight vWF overwhelms a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13, the cleaving protease of vWF multimers), causing even higher levels of ultralarge multimeric forms of this factor, mediating strong platelet–vessel wall interaction. Clinically, thrombin generation, fibrin formation, and fibrinolysis result in a high risk of venous thromboembolism, very high levels of D-dimer (a strong marker for adverse outcomes), and abnormal turnover of fibrin in the lung (a pathological hallmark of acute respiratory distress syndrome). The resulting elevated levels of ultralarge multimeric vWF might cause thrombotic microangiopathy and microvascular platelet thrombi. Adapted from Levi and Thachil,[8] by permission of Georg Thieme Verlag KG.

between inflammation and coagulation in COVID-19. Binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 receptor on the endothelium elicits a complex inflammatory response that results in endothelial cell activation.[9,10] Endothelial involvement in COVID-19 is illustrated by high levels of the platelet adhesion molecule vWF, and low levels of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which cleaves high-molecular-weight vWF,[11] resulting in an abnormal ratio of vWF to ADAMTS-13. SARS-CoV-2 can also increase the expression of tissue factor, and simultaneously decrease the expression of tissue factor pathway inhibitor. In addition, the regulatory activated protein C pathway is impaired in COVID-19.[12]

Plasma concentrations of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor 1 (PAI-1) are markedly elevated in patients with COVID-19.[13,14] This elevation is not only a marker of coagulation activation after clot formation (thrombin stimulates the release of t-PA from the endothelium), but also a reflection of the intensity of the inflammatory response, because proinflammatory cytokines, such as tumour necrosis factor and IL-1β, induce the endothelial production of both. The resulting plasmin effects on tissue metalloproteinases can cause extracellular matrix modification, expediting capillary leakage and lung oedema.

Coronavirus infections are also associated with a distinct fibrinolytic profile,[15–17] and fibrin deposits have been

reported in lung tissue in COVID-19 autopsy studies.[6,18] In the lung inflammation seen in COVID-19 and other causes of ARDS, microvascular fibrin deposition can be regarded as the effector system of the immune response (phylogenetically one could consider that fibrin deposition would wall-off invading organisms).[19] Physiologically, the fibrinolytic agents t-PA and urokinase-type plasminogen activator (uPA) act to prevent fibrin accumulation, but the raised levels of PAI-1 and thrombin-activatable fibrinolysis inhibitor in COVID-19 outbalance the effects of t-PA and uPA, with resultant fibrinolysis.[17] The extremely high levels of D-dimers seen in COVID-19 reflect this increased fibrinolytic activity.

The production of autoantibodies might contribute to the thrombotic process in COVID-19.[20] The so-called two-hit model of thrombosis that is associated with antiphospholipid syndrome proposes that after a first-hit injury to the endothelium, antiphospholipid antibodies potentiate thrombus formation as a second hit. An early study indicated that the majority of critically ill patients with COVID-19 were positive for lupus anticoagulant;[21] however, unfortunately, the authors did not take into account the fact that a high concentration of C-reactive protein can interfere with the assay, giving a false positive result. Subsequently, there have been no further publications suggesting that critically ill patients with COVID-19 and apparent antiphospholipid antibodies have persistent antibodies—ie, a positive assay 3 months later.

Histopathology from autopsies of non-survivors of COVID-19 shows typical microvascular platelet-rich thrombotic depositions in the small vessels of various organs—in particular, the lungs—next to local haemorrhage and accumulation of neutrophils.[18] These features are suggestive of pulmonary thrombotic microangiopathy and might be a consequence of local inflammation or, possibly, the result of increased platelet adhesion to the vascular endothelium in association with platelet aggregation.

Laboratory findings and clinical consequences of COVID-19-associated coagulopathy

The coagulopathy associated with COVID-19 has similarities with other sepsis-related forms of disseminated intravascular coagulation (DIC), but it also has distinct features, so it is usually referred to specifically as COVID-19-associated coagulopathy or CAC. COVID-19-associated coagulopathy is characterised by very elevated D-dimer concentrations, which are directly related to outcome.[22] Other characteristics include high levels of fibrinogen—two to four times baseline levels—factor VIII, and vWF, in keeping with the IL-6-driven acute-phase response.[23,24] These elevated levels of coagulation factors do not cause prolongation of the activated partial thromboplastin time (aPTT) or prothrombin time in COVID-19-associated coagulopathy[25]—in contrast to classic DIC, in which they are prolonged. DIC is rarely seen in active COVID-19 infection, except in patients who are terminally ill with multiorgan failure.[25] Many patients with COVID-19 have a slightly low platelet count (between 100×10^9 and 150×10^9 per L); more severe thrombocytopenia is seen rarely, in less than 5% of patients.[26] Thrombocytopenia is related to a higher risk of severe disease.[27,28] Guidelines published early in the pandemic recommended measurement of D-dimers, prothrombin time, and platelet count in all hospitalised patients with COVID-19, with regular monitoring of these parameters and, additionally, fibrinogen to evaluate worsening coagulopathy.[29] However, although initial D-dimer levels are recognised as a useful prognostic marker in COVID-19,[30] experience suggests that repeated measurement might be of limited value unless DIC is suspected. Thromboelastography can be used to document the hypercoagulopathy of COVID-19,[31] but whether it could be used to direct therapy remains unclear.

The hypercoagulable state and endothelial perturbation, in combination with patient immobility, can explain the increased occurrence of thromboembolic complications seen in COVID-19, including microvascular thrombosis, venous and pulmonary thromboembolism,[24,32] and (to a lesser extent) acute arterial thrombosis, primarily stroke.[33,34] The main mechanisms of stroke specific to COVID-19 are purported to be the hypercoagulable state, endothelial activation, and cardiomyopathy.[34] In view of the high incidence of pulmonary embolism, it might be assumed that embolisation of clots through a patent foramen ovale results in ischaemic stroke in a small proportion of these patients.

A recent meta-analysis estimated that venous thromboembolic events (VTEs) occur in about 17% of hospitalised patients with COVID-19, increasing to about 28% of those treated in the intensive care unit (ICU).[35] However, the interpretation of these results is not straightforward, as events were usually determined by changes detected on imaging, including CT pulmonary angiogram, and many segmental and subsegmental pulmonary changes might actually be the result of severe local inflammation leading to local microvascular thrombosis, sometimes called immunothrombosis, associated with ARDS. Nevertheless, thrombotic changes seen on CT pulmonary angiogram—both pulmonary embolism and immunothrombosis—in patients with COVID-19 and ARDS who require extracorporeal membrane oxygenation (ECMO) are more extensive than those seen in patients receiving ECMO for other viral pneumonias over the past 8 years.[36]

Prevention and management

General measures

As for all hospitalised patients, the increased risk of VTE in immobilised patients with a severe infectious and inflammatory condition is a major concern. Pharmacological and mechanical methods of prevention should be used according to recommended practice,[37] and early mobilisation should be promoted whenever possible.

Heparin

The severe coagulopathy of COVID-19 might require a greater degree of anticoagulation, as pharmacological thromboprophylaxis has been shown to be of benefit in hospitalised patients with COVID-19. Early in the pandemic, it was suggested that the dose of thromboprophylaxis should be escalated to empirical therapeutic-dose anticoagulation, or to intermediate-dose anticoagulation (generally 0·5 mg/kg of enoxaparin twice daily or 1 mg/kg of enoxaparin once daily, or an equivalent) in an attempt to better balance thrombotic and bleeding risks. However, recent clinical studies do not support this approach in critically ill patients with COVID-19,[38–40] suggesting an increased risk of bleeding in more severely ill patients. INSPIRATION[38] was a randomised controlled trial (RCT) of intermediate-dose (1 mg/kg enoxaparin daily) compared with standard-dose (40 mg enoxaparin daily) thromboprophylaxis in critically ill patients with COVID-19. Among the 562 patients who were included in the primary analysis, there was no significant difference in benefit or safety between the two groups.[38] A recent cohort study[39] of more than 1300 adults hospitalised with COVID-19 from 30 US hospitals indicated that receiving any dose of anticoagulation (compared with no anticoagulation) was associated with significantly lower in-hospital mortality; however, only prophylactic-dose anticoagulation was associated with lower mortality at 60 days. The ATTACC, ACTIV-4a, and REMAP-CAP investigators evaluated the effects of therapeutic-dose anticoagulation in more than 1000 critically ill patients with COVID-19 in an open-label, adaptive multiplatform RCT.[40] The primary endpoint was a combination of in-hospital mortality and days free of cardiovascular or respiratory organ support. The majority of those assigned to therapeutic heparin (89%) received low-molecular-weight heparin (LMWH). Those who received unfractionated heparin were generally monitored with a target aPTT of 1·5 to 2·5 times the upper limit of normal or, in a few centres, with anti-factor Xa monitoring. Therapeutic-dose anticoagulation did not improve clinical outcome, but was associated with major bleeding in 3·8% of patients compared with 2·3% of those assigned to usual care pharmacological thromboprophylaxis. Interestingly, the same group of investigators studied more than 2200 moderately ill patients with COVID-19 (hospitalised but not requiring ICU-level care at enrolment).[41] The probability that therapeutic anticoagulation would increase the number of organ support-free days compared with usual care pharmacological thromboprophylaxis was 98·6% (adjusted odds ratio 1·27, 95% credible interval 1·03–1·58). In these less severely ill patients, major bleeding occurred less frequently, in 1·8% and 0·9% of participants randomised to therapeutic-dose anticoagulation and thromboprophylaxis, respectively.[41] To explain the dichotomy in outcomes between severely ill and moderately ill patients with COVID-19, some authors have suggested that the benefit seen in moderate COVID-19 is related more to heparin's anti-inflammatory and, theoretically, antiviral effects[42] than to its anticoagulant effect.

In critically ill patients with COVID-19, therapeutic-dose heparin therapy is therefore only indicated for documented thromboembolic complications.[43,44] Prophylaxis against VTE can be achieved using prophylactic doses of LMWH in all patients. Some clinicians prefer unfractionated heparin infusion for the treatment of VTE in patients with renal failure (preferably guided by anti-factor Xa levels, because the aPTT is unreliable in those with COVID-19 owing to elevated factor VIII levels). Fondaparinux, argatroban, and bivalirudin are alternative treatment options for patients with heparin-induced thrombocytopenia.

Direct oral anticoagulants

ACTION[45] was a pragmatic, multicentre RCT in which more than 3300 adult patients hospitalised with COVID-19 in Brazil, with symptoms for up to 14 days and elevated D-dimer concentrations, were randomly assigned to in-hospital prophylactic (enoxaparin or unfractionated heparin) or therapeutic (oral rivaroxaban, or enoxaparin followed by rivaroxaban continued to day 30) anticoagulation. The therapeutic regime did not improve clinical outcomes compared with routine prophylactic anticoagulation and caused increased bleeding.[45] Therefore, use of therapeutic-dose rivaroxaban and other direct oral anticoagulants is not recommended in patients with COVID-19.

Antiplatelet agents

Considering the central role of platelets in the pathogenesis of COVID-19, use of antiplatelet agents has been considered in addition to heparin.[46] Investigators from the RECOVERY trial platform recently assessed the effect of usual care plus 150 mg aspirin daily compared with usual care alone in patients hospitalised with COVID-19.[47] The results showed shorter hospital stays among patients who received aspirin, but no effects on 28-day mortality. The REMAP-CAP investigators have recently stopped a trial of aspirin or a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) in nearly 1500 critically ill patients with COVID-19 due to lack of efficacy.[48]

The platelet aggregation inhibitor dipyridamole might have additional antiviral properties,[49] and a clinical trial is currently underway (ClinicalTrials.gov NCT04391179) to evaluate the effects of dipyridamole in patients with COVID-19.

Experimental therapies

Nebulised heparin to direct treatment more specifically to the lungs has already been tested in patients with ARDS unrelated to COVID-19, with some promising exploratory results on lung function,[50] and is also being tested in COVID-19.[51,52]

***Panel:* Considerations in the management of coagulopathy in hospitalised patients with severe COVID-19**

- Initial coagulation assessment should include measurements of D-dimer, fibrinogen, prothrombin time, activated partial thromboplastin time, and platelet count; repeated measurement is only of value if disseminated intravascular coagulation is suspected
- Viscoelastic tests, including rotational thromboelastometry and thromboelastography, can be used to document hypercoagulopathy, but whether or how these measurements could guide management in COVID-19 remains unresolved
- Thromboembolic complications can be identified using different techniques, including CT pulmonary angiogram, but point-of-care ultrasonography of the venous system should be encouraged to avoid unnecessary patient transfer; if confirmation or exclusion of pulmonary embolism is crucial for clinical decision making, a CT pulmonary angiogram is the first choice, and the chest CT scan should be carefully examined to identify possible silent thromboembolism
- Thromboembolic prophylaxis should be applied routinely; treatment can include low-molecular-weight heparin, unfractionated heparin, or fondaparinux, argatroban, or bivalirudin for those with heparin-induced thrombocytopenia
- Full therapeutic-dose anticoagulation should be limited to documented thromboembolism; its use as thromboprophylaxis should be avoided in critically ill patients
- The use of direct oral anticoagulants in severe COVID-19 is not supported by clinical studies
- The use of antiplatelet agents is still experimental; trials with thienopyridine derivatives, platelet glycoprotein IIb/IIIa inhibitors, and dipyridamole are ongoing
- Patients should be mobilised as soon as possible in the hospital or intensive care unit setting
- Patients with a documented thrombotic event should continue therapeutic anticoagulation for 3 months post-event and need appropriate post-discharge follow-up; the role of post-hospital antithrombotic prophylaxis for patients after admission for COVID-19 is unclear and not currently recommended

Search strategy and selection criteria

We searched PubMed for original research papers, reviews, editorials, and commentaries published between Jan 1, 2020, and Sept 27, 2021, using the following terms: "coronavirus disease 2019", "COVID-19", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "coagulopathy", "coagulation", "embolism", "thrombosis", "heparin", and "platelet". Only English language manuscripts were selected; studies in children were not included. One preprint that was relevant to the main aim of this Viewpoint—to provide an overview of approaches to the prevention and management of thrombosis in patients with COVID-19—was selected, and final publication details were added when the peer-reviewed paper was published. Reference lists of retrieved articles were checked for any articles that had been missed in the original search. Published guidelines for management of thrombosis in patients with COVID-19 were also reviewed. Clinical trial databases (ClinicalTrials.gov and the ISRCTN registry) were searched for new and ongoing studies in this field.

Recognition of sepsis-related endotheliopathy has generated renewed interest in the administration of pharmacological doses of physiological anticoagulants, including activated protein C[53] or thrombomodulin.[54] Unfortunately, these molecules have not been assessed in COVID-19.

Duration of therapy and outpatient treatment

The risk of VTE among hospitalised patients lasts from admission to about 90 days post-discharge.[55] There are contrasting observational data on the risk of post-discharge VTE after admission with COVID-19.[56,57] Trials are in progress to determine whether extended thromboprophylaxis is effective and safe in these patients. There is some evidence—in particular, in those patients with persistent respiratory problems after SARS-CoV-2 infection—that there are lasting pulmonary thrombotic abnormalities.[58] It is not known whether these patients would benefit from prolonged anticoagulation. The potential benefits of antithrombotic prophylaxis in non-hospitalised patients with COVID-19 have not yet been established; prophylaxis in these patients might be harmful because the prothrombotic changes seen in patients with moderate and severe COVID-19 are not seen in those with mild disease. In patients with documented VTE during COVID-19, current guidance indicates that this can be viewed as provoked thrombosis, so a treatment duration of 3 months post-COVID-19 should be sufficient.[37,43]

Conclusions

Moderate and severe COVID-19 are associated with an inflammatory response that causes an acute-phase response and endothelial dysfunction, resulting in a pro-coagulant state referred to as COVID-19-associated coagulopathy or CAC. Data relating to the optimum approach to prevention and management are scarce and many questions remain, but from the available literature discussed in this Viewpoint, we have drawn together some perspectives for the management of coagulopathy in hospitalised patients with severe COVID-19 (panel). Antithrombotic prophylaxis should be applied in all patients; therapeutic anticoagulation is of benefit in those requiring supplementary oxygen outside the ICU setting and in those with documented thrombotic complications, but should not be applied in all critically ill patients.

Further research is needed to clarify the place of pre-hospital and post-hospital antithrombotic prophylaxis, to examine the potential benefits of other prophylactic and therapeutic agents, including antiplatelet drugs, and to address the question of whether anti-inflammatory drugs such as steroids and IL-6 receptor antagonists can reduce coagulopathy and rates of thrombosis.

Contributors
JLV wrote the first draft of this Viewpoint; ML and BJH revised the article for critical content. All authors read and approved the final version.

Declaration of interests
The authors declare no competing interests.

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