

COVID Coagulopathy and Thrombosis: A Systematic Review

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Introduction: Since the onset of the SARS-CoV-2 pandemic, haematological laboratory abnormalities and thrombotic complications have been observed among infected patients. We aimed to highlight key pathophysiological mechanisms of COVID-19-associated coagulopathy and to summarize incidence rates of venous and arterial thrombotic events, comorbidities conferring risk, and current treatment guidelines including data from ongoing clinical trials. **Methods:** A systematic review was performed according to PRISMA recommendations of case-control studies, cohort studies, observational studies and randomized clinical trials (RCTs) published between 1 December 2019 and 30 September 2021 within PubMed and Web of Science. Inclusion criteria were English language, adult patients and at least one coagulation parameter described. **Results:** 2,554 records were screened, from which 59 studies were included. Abnormalities in several laboratory parameters were associated with worse clinical outcomes including elevations in prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen, von Willebrand factor antigen/activity and lupus anticoagulant antibodies. Rates of venous and arterial thromboembolism varied significantly among studies performed early in the pandemic and across different nations. Pathophysiological mechanisms included vascular endotheliopathy, increased inflammation and macrophage activation, neutrophil extracellular traps, antiphospholipid antibody production and obesity/adipose tissue signalling. Current recommendations for management of COVID coagulopathy from various societies include the use and dosing of systemic anticoagulation to prevent thrombotic sequelae in the outpatient, inpatient and critical care settings. The optimal anticoagulant dose for thromboprophylaxis in the inpatient and critical care settings is currently not well established. **Conclusions:** SARS-CoV-2 infection can cause a distinct form of coagulopathy, with thromboembolic complications leading to significant morbidity and mortality. The optimal treatment requires further refinement pending the results from key ongoing RCTs

Keywords

COVID-19, SARS-CoV-2, coronavirus, coagulopathy, thrombosis, thromboembolism, DVT, pulmonary embolism, thromboprophylaxis, anticoagulation

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In December 2019, an outbreak of pneumonia of unknown aetiology was observed in the Chinese city of Wuhan, capital of Hubei province. By January 2020, this outbreak was attributed to a novel virus classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the latest member of the coronaviridae family responsible for major infectious outbreaks, including severe acute respiratory distress syndrome (SARS) in 2002–2003, and Middle East respiratory syndrome (MERS).¹ Unlike the preceding outbreaks, coronavirus (COVID-19) rapidly spread throughout the world, reaching 11 million people by July 2020, with 570,000 associated deaths, with current incidence data (as of September 2021) of over 229 million cases and 4.7 million deaths worldwide.²

Clinically, COVID-19 displays a wide spectrum of illness, with most cases resulting in asymptomatic disease, while others require hospitalization or management in the intensive care unit (ICU) for acute respiratory distress and end-organ failure. Since the onset of the global pandemic, various reports of abnormal haematological parameters and clinical sequelae of thrombosis have been reported. Early reports of critically ill patients with severe COVID-19 showed a rate of pulmonary embolism (PE) as high as 40% of patients.³ Strikingly, rates of increased thromboembolism were also reported despite the widespread use of prophylactic and therapeutic anticoagulation in hospitalized patients.⁴ The unique pathobiology, as well as optimal prevention and treatment of thrombosis in COVID-19, remain largely uncertain and controversial at this time.

The aim of the current study was to highlight key pathophysiological mechanisms of COVID-19-associated coagulopathy and to summarize incidence rates of venous and arterial thrombotic events, comorbidities conferring risk and current treatment guidelines, including data from ongoing clinical trials.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) recommendations were followed for this review. An electronic search was performed of medical literature published between 1 December 2019 and 30 September 2021 within PubMed and Web of Science databases using the following Medical Subject Headings terms (including variations, synonyms and acronyms): 'COVID-19', 'COVID', 'SARS-CoV-2', 'coronavirus', 'coagulopathy', 'endothelial dysfunction', 'thrombosis', 'stroke', 'immunothrombosis'. References and citation lists of selected articles and reviews were also reviewed for any other relevant literature. Additionally,

Table 1: Abnormal haematological parameters observed in COVID-19 patients and associated clinical outcomes

Abnormal parameter	Clinical association
Slightly prolonged PT, aPTT ⁹⁻¹¹	Increased disease severity and mortality
Elevated D-dimer ^{6,8,10-12}	Increased disease severity, ICU admission and mortality.
Increased fibrinogen ^{8,13}	Increased disease severity, Increased thrombosis (DVT/PE) and mortality
Thrombocytopenia (platelet count <100 × 10 ⁹ cells/L) and/or thrombocytosis (mean 348 × 10 ⁹ cells/L) ¹⁰	Increased disease severity
Elevated vWF antigen and activity ^{14,15}	Increased thrombosis
Elevated factor VIII level and activity ¹⁶	Increased thrombosis
Positive lupus anticoagulant, elevated antiphospholipid antibodies (anticardiolipin/anti-β2-glycoprotein I/II) ^{17,18}	Increased thrombosis particularly stroke, increased disease severity, ICU admission

aPTT = activated partial thromboplastin time; DVT = deep venous thrombosis; ICU = intensive care unit; PE = pulmonary embolism; PT = prothrombin time; vWF = von Willebrand factor.

guidelines from relevant organizations and recent clinical trials were accessed as cited electronically to provide an up-to-date summary of recommendations.

Inclusion criteria were: 1) clinical and translational studies pertaining to coagulopathy in COVID-19 patients including case-control studies, cohort studies, observational studies and randomized clinical trials; 2) studies describing coagulation laboratory parameters or clinical outcomes.

Exclusion criteria were: 1) non-English literature; 2) non-human studies; 3) patient age <18 years; 4) non-original studies (i.e. reviews, commentaries). See Appendix 1 for the PRISMA flowchart illustrating the identification and selection of studies.

Haematological abnormalities

COVID coagulopathy describes the increased rate of localized and systemic coagulation defects and associated thrombotic events observed in infected individuals. Due to the unique pathobiology and clinical sequelae of COVID coagulopathy, some authors have termed this a new disorder: COVID-19-associated haemostatic abnormalities (CAHA).⁵ While coagulopathic features typical of disseminated intravascular coagulation are evident, hyperfibrinogenaemia typically seen in CAHA is a prominent feature of the disease.

Initial reports of abnormal coagulation parameters were first noted by treating physicians in Wuhan, China. One early retrospective epidemiological report analysed 99 hospitalized patients in January 2020, and identified defective coagulation parameters that manifested as mildly elevated prothrombin time (PT) in ~5% and activated partial thromboplastin time (aPTT) in ~6%, occurring in conjunction with elevated D-dimers in the larger subset (36%).³ This was followed by another retrospective cohort study that reviewed 191 patients from two main hospitals in Wuhan, identifying a subset with disordered haematological parameters and an increased mortality rate of 28% (54 patients).⁴ Haematological factors associated with increased mortality included: 1) elevated D-dimer >1 ug/mL (odds ratio [OR] of 18.42, 95% confidence interval [CI] 2.64–128.55; p=0.003); 2) an increased PT (OR 4.62, 95% CI 1.29–16.50; p=0.019); and 3) increased serum IL-6 (OR 1.12, 95% CI 1.03–1.23; p=0.008).⁶ Another retrospective chart review of a large cohort of 1099 hospitalized patients in mainland China further highlighted the frequent presence of increased D-dimer (>0.5 ug/mL) in 46.4% of patients, associated with the primary endpoint(s) of increased need for ICU admission, mechanical ventilation, severe COVID-19 infection and death.⁷ Thrombosis rate was not characterized in this study.⁷ A large retrospective cohort study enrolling 1643 patients admitted to one of

two ‘instant hospitals’ constructed in Wuhan also found that elevated fibrinogen (>420 mg/dL) was associated with a greater risk of developing critical illness (OR 2.16, 95% CI 1.05–4.46; p=0.038) and mortality (hazard ratio 4.79, 95% CI 1.14–20.20; p=0.033).⁸ Since these initial findings were reported, several other haematological defects have been observed in COVID-19 patients, as summarized in *Table 1*.⁸⁻¹⁸

Clinical thrombohaemorrhagic defects

Abnormalities in haematological laboratory parameters are associated with disease severity and mortality, and increased rates of thromboembolism reinforced the concept of a clinically distinct hypercoagulable state accompanying COVID-19 infection. Clinically relevant haemostatic defects are less frequent, and typically present with laboratory features usually seen in disseminated intravascular coagulation, such as hypofibrinogenaemia, severe consumptive coagulopathy and thrombocytopenia. Despite differences in study design, cohort selection and definable endpoints, numerous studies have identified increased rates of both venous thromboembolism (VTE) and arterial thromboembolism. VTE complications include deep venous thrombosis (DVT) and PE, while arterial thromboses include stroke, myocardial infarction (MI) or atypical thrombotic sites (e.g. iliac artery). A summary of the findings from reviewed reports is shown in *Table 2*.^{10, 17-25}

Rates reported in early experiences in Wuhan for critically ill patients in ICU approached 40% for PE and 28.8% for DVT.^{19,21} Subsequent studies focusing on hospitalized patients in the USA have shown much lower rates of PE (1.3%) and DVT (1.5%).²² A large meta-analysis by Jimenez et al. pooling data of 20 studies (aggregate 9350 non-ICU hospitalized patients) identified an overall VTE incidence of 7.1%.²⁶ Stroke was reported in 7.6% of patients in an early study from mainland China and Wuhan, although comparatively lower levels have been identified in the USA and Europe, with rates of 0.1–2.7%.^{17,18, 21-25}

Pathophysiology

Various mechanisms have been proposed as contributing to the development of the haemostatic abnormalities seen during COVID-19 infection. The findings are summarized in *Figure 1*.

Endotheliopathy (A in *Figure 1*)

Vascular endotheliopathy has been proposed to be of central importance in CAHA. The vascular endothelium plays an important role as a paracrine, autocrine and endocrine organ regulating vascular tone and homeostasis. Shifts in vascular endothelial tone due to infection result in increased vasoconstrictor activity, which may result in organ ischaemia, inflammation and ultimately a procoagulant state. COVID-19

Table 2: Incidence of thromboembolic complications observed in various reports

Study details	Study dates	Patient details			Outcomes						
		Patients (n)	Median age (years)	Disease severity/ setting	DVT	PE	CVA	MI	Arterial emboli	Anticoagulation use	
Chen et al. ¹⁹ China (Wuhan)	Jan–Feb 2020	25	65	Moderate (20%) Severe (80%)	NR	40% (10)	NR	NR	NR	NR	80% thromboprophylaxis
Xu et al.* ²⁰ China (Shanghai)	21 Jan–21 Feb 2020	138	52	Non-ICU (89.1%) ICU (10.1%)	2.9% (4)	NR	NR	NR	NR	NR	31% thromboprophylaxis
Cui et al. ¹⁰ China (Wuhan)	Jan–Mar 2020	81	59.9	ICU	25% (20)	NR	NR	NR	NR	NR	Unknown
Xiao et al. ²¹ China (Wuhan, Beijing)	Jan–Apr 2020	66	64	ICU	28.8% (19)	NR	7.6% (5)	1.5% (1)	NR	NR	60% thromboprophylaxis
Klok et al. ¹⁷ Netherlands	7 Mar–5 Apr 2020	184	64	ICU	1.6% (3)	35.3% (65)	2.7% (5)	0	1.0% (2)	NR	Thromboprophylaxis in all (LMWH) 9.2% therapeutic AC
Hill et al. ²² USA (Louisiana/ Mississippi)	1 Mar–1 May 2020	2748	61	Inpatient/ hospitalized	1.5% (42)	1.3% (35)	0.1% (3)	NR	0.1% (4)	NR	97% thromboprophylaxis (LMWH)
Hanif et al. ¹⁸ USA (New York City)	15 Mar–14 Apr 2020	921	62	Inpatient/ hospitalized	1.7% (16)		1.2% (11)	NR	0.2% (2)	NR	72% thromboprophylaxis 24% therapeutic AC
Yaghi et al. ²³ USA (New York City)	15 Mar–19 Apr 2020	3556	NR	Inpatient/ hospitalized	NR	NR	0.9% (32)	NR	NR	NR	Unknown
Bilaloglu et al. ²⁴ USA (New York City)	1 Mar–17 Apr 2020	3334	64	Inpatient (75%) ICU (25%)	3.9% (129)	3.2% (106)	1.6% (54)	8.9% (298)	1% (32)	NR	Unknown and dynamic through study period
Fournier et al. ²⁵ France (Paris)	1 Apr–30 Apr 2020	531	66.1	Inpatient Severe (13%)	NR	NR	1.5% (8)	1.6% (9)	2.4% (13)	NR	50.3% therapeutic AC

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AC = anticoagulation; CVA = cerebrovascular accident; DVT = deep venous thrombosis; ICU = intensive care unit; LMWH = low molecular weight heparin; MI = myocardial infarction; NR = not reported; PE = pulmonary embolism.

has been shown to infect engineered human blood vessels *in vitro*.²⁷ Clinicopathological autopsy series have demonstrated the presence of endotheliitis and intracellular viral inclusions across vascular beds of different organs (heart, small bowel, lung).²⁸ Of note, direct endothelial infection with SARS-CoV-2 is currently debated, with some studies showing low basal angiotensin-II (ACE-2) receptor expression *in vitro* via transcriptome and epigenetic data even with exposure to cytokines associated with SARS-CoV-2 infection.²⁹ Other studies, however, have shown localization of SARS-CoV-2 in the endothelium of infected mice and non-human primates at the RNA and protein level, as well as through immunogold labelling and electron microscopic examination.³⁰ Failure to identify ACE-2 localization in the endothelium *in vitro* may be explained by differences between the endothelial monolayer culture commonly used in the laboratory and the *in vivo* endothelial layer lining the blood vessels due to sheer stress activation by cytokine storm or tight contact with the epithelium in certain organ capillary beds such as the lungs.³¹

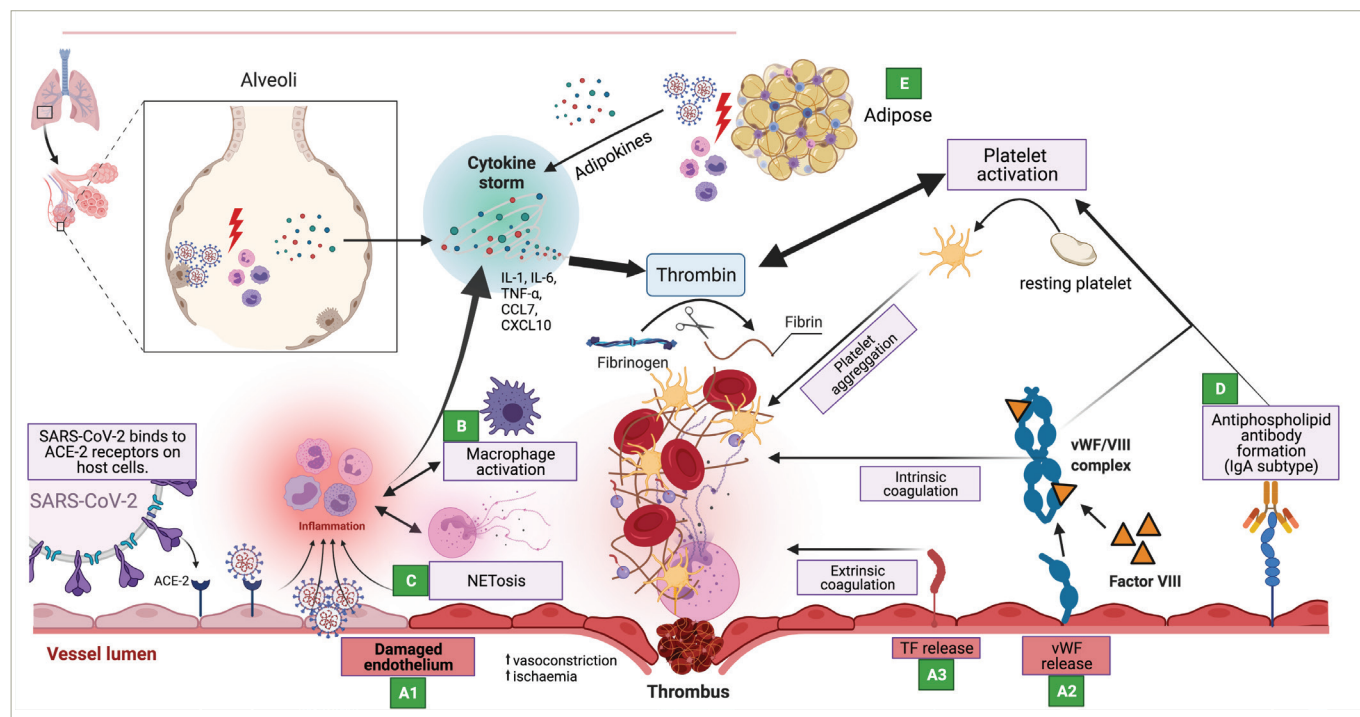
A cross-sectional study of 68 adult COVID patients (48 ICU, 20 non-ICU) compared with 13 non-hospitalized asymptomatic controls established that both ICU and non-ICU patients had elevations in plasminogen activator inhibitor-1 (PAI-1), a potent endothelial regulator of fibrinolysis. Additionally, elevations were noted in von Willebrand factor (vWF) antigen and functional activity, and factor VIII activity, with subsets of ICU patients having vWF activity above the upper limit of detection. Similarly, D-dimer and thrombin–antithrombin complexes were elevated in the aggregate cohort, with significantly higher values in the ICU subgroup.

P-selectin (a marker of endothelial and platelet cell activation) and soluble CD40 ligand were also increased in ICU patients compared with controls.³² These findings provide biochemical evidence towards the presence of endotheliopathy resulting in augmented vWF release and platelet activation as contributory mechanisms in the development of COVID coagulopathy.

Inflammation and the role of macrophage activation (B in Figure 1)

Hypercytokinemia and hyperferritinemia (500–3000 ng/mL) are prominent laboratory features of severe pulmonary disease (acute respiratory distress syndrome) seen in severely ill COVID-19 patients. These findings implicate both cytokine release syndrome and features of macrophage activation syndrome (or secondary haemophagocytic lymphohistiocytosis [HLH]) as prominent pathophysiological entities. Multiplex screening for 48 cytokines performed on 53 clinically moderate/severe patients have identified monocyte/macrophage-associated cytokines CXCL10 (IFNγ-inducible protein-10), CCL7 (monocyte chemoattractant protein-3), and IL-1 receptor antagonist to be at continuously high levels and associated with increased lung injury, viral load and fatal outcomes.³³ Predicated on these findings, the previously validated risk calculator (HScore) has been proposed as a means of deciding which patients should be diagnosed with and treated for HLH,³⁴ although its inadequate sensitivity and specificity in COVID-19 may be insufficient for defining the subsets requiring ICU admission or those at increased risk for death.³⁵ Ultimately many patients fail to fulfil diagnostic criteria for HLH, most commonly

Figure 1: Schema highlighting critical features of COVID coagulopathy



A1–A3. SARS-CoV-2 enters host tissues via initial interaction with the angiotensin-II (ACE-2) receptor in respiratory alveoli (upper left), followed by a viremic phase resulting in secondary infection and cytotoxicity of endothelial cells, which also express ACE-2 (A1). SARS-CoV-2-infected endothelium shifts from its normal anticoagulant properties to a prothrombotic state, with accompanying changes in vascular tone (vasoconstriction) resulting in organ ischaemia. Damaged endothelium also results in cell-surface tissue factor (TF) expression and activation of the extrinsic coagulation pathway (A3), while the increased release of endothelial cell von Willebrand Factor (vWF) and circulating vWF/factor VIII serve to accelerate the intrinsic coagulation pathway, platelet activation/aggregation and thrombus formation. Enhanced thrombin generation in conjunction with circulating hepatocyte-derived hyperfibrinogenaemia presumably accounts for the inordinately elevated D-dimers (fibrin degradation products) (A2). B. SARS-CoV-2-mediated endothelial inflammation promotes macrophage activation and release of proinflammatory cytokines (IL-1, IL-6, TNF- α) and chemokines (CCL7, CXCL10), further enhancing the procoagulant state by accelerated thrombin production. Widespread systemic tissue and organ infection with SARS-CoV-2 contribute to an elevated cytokine milieu (i.e. cytokine storm), promoting a systemic procoagulant state. C. Neutrophils activated by local and systemic inflammatory cytokines release extracellular traps composed of DNA and intercalated histones (NETosis), which capture red blood cells, platelets and other procoagulant molecules, thereby accelerating both intrinsic and extrinsic pathways of the coagulation cascade. D. Antiphospholipid antibodies (IgA subtype) produced as a result of severe viral infection contribute to arterial endothelial dysfunction and distant microthrombotic complications, such as cerebrovascular accidents or myocardial infarction. E. Obese patients may suffer more severe disease due to increased ACE-2 expression in adipocytes and subsequent increased release of cytokine mediators contributing to 'cytokine storm'. Created with BioRender.com.

due to inconsistencies related to cytopenias, hepatosplenomegaly or hypofibrinogenaemia. Furthermore, while not an obligate criterion for diagnosis of HLH, there appears to be a lack of haemophagocytosis involving bone marrow biopsies of investigated patients.³⁶ Nonetheless, recognition of a hyperinflammatory state in a subset of COVID-19 patients with severe illness has resulted in the investigation and use of certain immunosuppressant agents, including corticosteroids, intravenous immunoglobulin, IL-1 inhibition (anakinra), IL-6 inhibition (tocilizumab) and, more recently, Janus kinase inhibition (baricitinib, tofacitinib).³⁷⁻⁴¹

Neutrophil extracellular traps (C in Figure 1)

Recent studies have elucidated the role of activated neutrophils in the formation of arterial and venous thrombi. One key hallmark of the prothrombotic neutrophil is the release of web-like structures composed of DNA intercalated with histones and granule proteins (referred to as neutrophil extracellular traps [NETs]). Intravascular NETs have been characterized and isolated from the pulmonary vasculature, kidney and heart of COVID-19 patients. Elevated intravascular NETs were also found to correlate with severe disease. By providing a scaffold, NETs capture platelets, red blood cells and other procoagulant molecules and thereby activate both the intrinsic and extrinsic coagulation cascade.⁴² In a study by Nicolai et al., platelets from patients with severe COVID-19 showed increased adhesion to neutrophils and enhanced NET formation, supporting a mechanistic link for immunogenic platelets driving neutrophil activation.¹⁵

Antiphospholipid antibodies (D in Figure 1)

Antiphospholipid antibody syndrome is an autoimmune disorder characterized by the presence and persistence of antiphospholipid antibodies (aPLs), and accompanied by clinical sequelae of arterial and venous thrombosis and/or recurrent foetal loss. An increasing incidence of aPLs in association with thrombotic sequelae has been found in COVID-19, particularly as a risk factor for cerebral infarction. In one report, three patients suffered multiple cerebral infarctions associated with the detection of IgA anticardiolipin aPLs, and IgA and IgG beta 2 glycoprotein I antibodies.⁴³ Another recent cohort study identified aPLs in 47.0% (31 of 66) of patients using a cutoff of >20 chemoilluminiscent units and in 31.8% (21 of 66) of patients when using a higher cutoff of >40 units.²¹ All patients found to have aPLs were noted to be critically ill (admitted to ICU). In another study, aPLs were found in the majority of patients admitted to the ICU (87.7% of 150 patients).⁴⁴ Interestingly, IgA isotype (most commonly associated with mucosal infection) aPLs were the most common in COVID-19 patients and are also significantly and independently associated with acute MI and acute cerebral ischaemia.

Obesity and adipose tissue signalling (E in Figure 1)

Obesity has been increasingly recognized as a determinant of severe disease and worse outcomes in patients infected with COVID-19.⁴⁵ Adipose cells have also been characterized to express ACE-2 (the primary extracellular entry mode for COVID-19 virions), and obesity has been shown to increase its expression. Furthermore, adipose tissue

Table 3: Interim treatment guidelines for COVID coagulopathy

Guidelines	VTE prophylaxis*			Standard treatments*VTE treatment
	Inpatients	ICU	Post-hospital discharge	
International Society on Thrombosis and Haemostasis (ISTH) ⁵⁰	PD-LMWH or PD-UFH, MTP when Rx contraindicated ID-LMWH in high risk [†]	PD-LMWH or PD-UFH +/- MTP ID-LMWH in high risk [†]	PD-LMWH or DOAC for 2–6 weeks	Standard treatment [‡] TD-LMWH preferred for inpatients over oral agents
American Society of Hematology (ASH) ⁴⁸	PD-LMWH preferred over PD-UFH PD-AC preferred over ID-AC	PD-LMWH or PD-UFH preferred over ID-AC	Recommends against routine discharge AC	Standard treatment [‡] TD-LMWH or TD-UFH preferred for inpatients
American College of Cardiology (ACC) ⁵¹	PD-AC, ID-AC and TD AC in clinical trials only	PD-AC, ID-AC and TD AC in clinical trials only	Recommends for discharge AC (DOAC preferred) based on risk score [†]	Standard treatment [‡]
American College of Chest Physicians (ACCP) ⁵²	PD-LMWH or fondaparinux preferred over PD-UFH Cautions against use of DOACs ID-AC and TD-AC not recommended	PD-LMWH over PD-UFH Cautions against fondaparinux/DOACs and anti-platelet agents ID-AC and TD-AC not recommended Against addition of MTP to Rx therapy Suggest use of MTP when Rx contraindicated	Recommends against routine discharge AC	Standard treatment [‡] TD-LMWH preferred over TD-UFH and both preferred over oral agents Suggest dose increase of LMWH by 25–30% for recurrent VTE despite TD-LMWH TD-LMWH suggested for recurrence on oral agent
National Institutes of Health (NIH) ⁴⁹	PD-LMWH or PD-UFH recommended ID-AC and TD-AC not recommended	PD-LMWH or PD-UFH recommended ID-AC and TD-AC not recommended	Recommends against routine discharge AC	Standard treatment [‡]

*Example treatments: PD-LMWH – e.g. enoxaparin 40 mg SC daily; ID-LMWH – e.g. enoxaparin 40 mg SC BID; TD-LMWH – e.g. enoxaparin 1 mg/kg SC q12h or 1.5 mg/kg SC daily; PD-UFH – heparin 5000–7500 mg SC BID/TID; ID-UFH – IV heparin drip with Factor Xa goal 0.1–0.3 IU/mL; TD-UFH – IV heparin drip with Factor Xa goal 0.3–0.7 IU/mL; DOAC – e.g. include apixaban, betrixaban, rivaroxaban, dabigatran (see manufacturer label for dosing); MTP – intermittent pneumatic compression devices and elastic compression stockings.

[†]High risk defined by Padua score or VTE IMPROVE score.⁵³

[‡]Standard treatment as defined by ASH 2018 guidelines for management of venous thromboembolism.⁵⁴

AC = anticoagulant; BID = twice daily; DOAC = direct acting oral anticoagulant; ICU = intensive care unit; ID = intermediate dose; IV = intravenous administration; LMWH = low molecular weight heparin; PD = prophylactic dose; q12h = every 12 hours; Rx = treatment; SC = subcutaneous administration; TD = therapeutic dose; TID = three times daily; UFH = unfractionated heparin; VTE = venous thromboembolism.

has previously been shown to have a role in regulation of inflammation through elaboration of cytokines IL-6, tumour necrosis factor- α (TNF- α), macrophage chemoattractant protein-1, and its reservoir of both paracrine/endocrine hormone mediators.⁴⁶ Local release of such factors may explain sites of 'abnormal' thrombosis such as cerebrovascular accident (CVA), MI in young patients, or why this subset of patients experiences worse end-organ damage and ultimately mortality. Systemic release of such adipokines may mediate vascular thrombosis through promotion of Virchow's triad in the form of increased venous stasis, endotheliopathy and release of hypercoagulable proteins (soluble urokinase plasminogen activator receptor and/or PAI-1).⁴⁷ Ultimately further studies are necessary to completely characterize the complex interplay between obesity and COVID-19.

Management

Laboratory biomarkers in disease prediction and prognostication

As shown in Table 1, several haematological parameters have been found to be abnormal with COVID-19 infection and may correlate with disease severity or as predictors for clinical outcomes, such as need for mechanical ventilation, ICU admission or mortality. At this time, prospective trial-based evidence is lacking and the utility of such parameters in clinical decision making remains uncertain. Based on societies including the American Society of Hematology (ASH) and the National Institutes of Health (NIH), current recommendations advocate

for measurement of platelet counts, PT, aPTT, fibrinogen and D-dimer in inpatients as proposed prognosticators, but do not recommend sole use of laboratory tests to guide clinical imaging or treatment for VTE.^{48,49} Similarly, laboratory testing is not recommended in asymptomatic outpatients and should not be used to decide level of care (admission to inpatient or transfer from inpatient to ICU).⁴⁹

Current recommendations for management/ treatment interventions

Several organizations have published guidelines and interim recommendations for the management of thromboprophylaxis and VTE treatment in the inpatient setting, critical care setting and upon discharge.^{...} To date, there are no clear indications for prophylactic anticoagulation in non-hospitalized cohorts. Current practice guidelines for hospitalized patients, including inpatients, critically ill ICU patients and post-hospital discharge, are summarized in Table 3.⁴⁸⁻⁵²

Inpatient setting

Unless there are contraindications, recommendations include the use of prophylactic dose anticoagulation for the prevention of VTE in hospitalized patients. Heparin-based anticoagulation using either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over direct acting oral anticoagulants (DOACs) or vitamin K antagonists due to risks of impaired metabolism or excretion in the setting of end-organ dysfunction (hepatic, renal), which often accompanies severe COVID-19

Table 4: Summary of key selected clinical trials for antithrombotic therapy in COVID-19

Ongoing trials	Official trial name	Sites/Country	Enrolment (n)	Arms	Primary outcome	Prelim. results	Interim conclusion
Inpatient trials	ATTACC ⁵⁵	58 sites, USA/Canada, Brazil, Mexico	3000	Therapeutic AC for 14 days or until hospital discharge with LMWH or UFH versus standard-of-care prophylactic dose AC with LMWH or UFH	Composite improved mortality or reduced need for organ support in 21 days	Superiority (OR 1.27, CI 1.03–1.58) in hospitalized group Futility (predefined as OR <1.2) in critically ill group OR 0.83, CI 0.67–1.03	Therapeutic dose AC superior to usual care thromboprophylaxis in hospitalized (non-severe) group Therapeutic dose AC futile compared with prophylactic dose AC in critically ill group
	REMAP-CAP ⁵⁶	290 sites, USA/Canada, UK, Ireland, EU, Saudi Arabia, Australia, New Zealand, Nepal, India Pakistan	7100				
	ACTIV-4a ⁵⁵	60 sites, USA, Spain	2000				
	INSPIRATION ⁵⁶	10 academic centres, Iran	600	Therapeutic AC with LMWH twice daily versus prophylactic dose LMWH	Composite of venous or arterial thrombosis, treatment with ECMO, or mortality within 30 days	No difference in primary outcome (45.7% in intermediate dose versus 44.1% in prophylactic dose) OR 1.06, 95% CI 0.76–1.48; p=0.70	Prophylactic dose LMWH non-inferior to therapeutic dose AC
	RAPID ⁵⁷	28 sites, Canada	465	Therapeutic versus prophylactic UFH	Composite of ICU admission, non-invasive or invasive mechanical ventilation or mortality within 28 days	No difference in primary outcome (16.2% in therapeutic dose versus 21.9% in prophylactic dose) OR 0.69, 95% CI 0.43–1.10; p=0.12	Prophylactic dose LMWH non-inferior to therapeutic dose AC
	ACTION ⁵⁸	31 sites, Brazil	3331	Therapeutic AC with rivaroxaban (20 mg or 15 mg daily) or enoxaparin 1 mg/kg BID or UFH followed by rivaroxaban to day 30 versus prophylactic LMWH or UFH	Hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen to day 30, analysed with the win ratio method	No difference in primary outcome (34.8% wins in the therapeutic group versus 41.3% in the prophylactic group) Win ratio 0.86, 95% CI 0.59–1.22; p=0.40	Prophylactic dose AC (LMWH or UFH) non-inferior to therapeutic dose AC (rivaroxaban, LMWH or UFH)
	FREEDOM COVID ⁵⁹	21 sites, USA, Mexico, Brazil, Columbia, India	3600	Prophylactic LMWH versus therapeutic LMWH versus therapeutic apixaban (5 mg PO q12h)	Time to event for composite of all-cause mortality, intubation requiring mechanical ventilation, systemic thromboembolism in 30 days	No results posted	
	COVID-PACT ⁶⁰	Brigham and Women's Hospital, USA	750	Therapeutic AC (LMWH or UFH) + anti-platelet (clopidogrel) versus therapeutic AC no anti-platelet versus prophylactic AC (LMWH or UFH) + anti-platelet versus prophylactic AC no anti-platelet	Hierarchical composite: death due to venous or arterial thrombosis, pulmonary embolism, clinically evident DVT, type 1 MI, ischaemic stroke, systemic embolism or acute limb ischaemia, or clinically silent DVT in 28 days or until hospital discharge	No results posted	

Table 4: Continued

Ongoing trials	Official trial name	Sites/Country	Enrolment (n)	Arms	Primary outcome	Prelim. results	Interim conclusion
Post-discharge trials							
ACTIV-4c ⁵¹	COVID-19 thrombosis prevention trials: post-hospital thromboprophylaxis: a multicentre, adaptive, prospective, randomized trial evaluating the efficacy and safety of antithrombotic strategies in patients with COVID-19 following hospital discharge	107 sites, USA	5320	Post-discharge prophylaxis	Composite outcome of symptomatic DVT, PE, other VTE, ischaemic stroke, MI, other arterial thromboembolism, and all-cause mortality in 30 days	No results posted	
Outpatient trials							
ACTIV-4b ⁵²	COVID-19 outpatient thrombosis prevention trial: a multicentre adaptive randomized placebo-controlled platform trial evaluating the efficacy and safety of antithrombotic strategies in COVID-19 adults not requiring hospitalization at time of diagnosis	71 sites, USA	657	Prophylactic dose apixaban (2.5 mg BID) versus therapeutic dose apixaban (5 mg BID) versus aspirin (81 mg daily) versus placebo	Composite endpoint of need for hospitalization for cardiovascular/ pulmonary events, symptomatic DVT, PE, arterial thromboembolism, MI, ischaemic stroke, and all-cause mortality for up to 45 days after initiation of assigned treatment	No results posted	
PREVENT-HD ⁵³	A multicentre, randomized, placebo-controlled, pragmatic phase III study investigating the efficacy and safety of rivaroxaban to reduce the risk of major venous and arterial thrombotic events, hospitalization and death in medically ill outpatients with acute, symptomatic COVID-19 Infection	18 sites, USA	4000	Prophylactic dose rivaroxaban (10 mg once daily) versus placebo for 35 days	Time to first occurrence of a composite endpoint of symptomatic VTE, MI, ischaemic stroke, acute limb ischaemia, non-central nervous system systemic embolization, all-cause hospitalization, and all-cause mortality in 35 days	No results posted	

AC = anticoagulation; BID = twice daily; CI = confidence interval; DVT = deep venous thrombosis; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; LMWH = low molecular weight heparin; MI = myocardial infarction; OR = odds ratio; PE = pulmonary embolism; PO = oral administration; q12h = every 12 hours; UFH = unfractionated heparin; VTE = venous thromboembolism.

infection. The International Society of Thrombosis and Haemostasis (ISTH) recommends the use of higher doses of anticoagulation (termed 'intermediate dose') for high-risk patients as defined by VTE risk prediction models such as Padua or IMPROVE.⁵³ This diverges from the remaining agencies, which recommend against the use of higher doses of anticoagulation outside of randomized controlled clinical trials and in the absence of high-quality evidence (see *Table 4* and Ongoing clinical trials, below). Additionally, all organizations recommend mechanical thromboprophylaxis be used when pharmacological anticoagulation is contraindicated due to high risk for bleeding. Of note, guidelines have not been updated to reflect interim results of ongoing clinical trials (discussed in more detail below), which suggest possible improved outcomes with the use of therapeutic dose anticoagulation for thromboprophylaxis in moderately ill hospitalized inpatients.⁵⁵

Intensive care unit setting

Uniformly similar guidelines exist regarding thromboprophylaxis strategies in the critical care setting. Prophylactic dose anticoagulation is recommended in all critically ill patients (unless contraindicated) using LMWH or UFH over DOACs. Intermediate and therapeutic dose anticoagulation are generally not recommended because of concerns over excess bleeding and are reserved for clinical trials at this time. Comparable to current recommendations in moderately ill hospitalized patients, the ISTH recommends intermediate dose anticoagulation in high-risk patients based on VTE risk predictions models (Padua/IMPROVE).^{49,52} Importantly, preliminary data from recent ongoing clinical trials have supported the lack of benefit and possible harm with the use of therapeutic anticoagulation in this setting.⁵⁴

Outpatient post-hospital management

Post-discharge anticoagulation remains controversial at this time and is an active area of clinical studies. ISTH and the American College of Cardiology recommend possible discharge anticoagulation, whereas ASH, the American College of Chest Physicians and the NIH recommend against its use.⁴⁷⁻⁵¹

Treatment of suspected or proven venous thromboembolism

Recommendations for treatment of documented or high-suspicion venous or arterial thrombosis remain clearer, and all organizations recommend the use of established 'standard' treatment (non-COVID) guidelines for all hospitalized patients.^{47-51, 53}

Ongoing clinical trials

Ongoing randomized clinical trials continue to investigate the safety and efficacy of various thromboprophylaxis strategies in the inpatient and outpatient setting (summarized in *Table 4*).⁵⁵⁻⁶³

At the time of writing, interim data are available from several studies including a collaborative international multiplatform randomized control trial (mprRCT) incorporating data from three studies: Antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC), Accelerating COVID-19 therapeutic interventions and vaccines-4 (ACTIV-4a), and Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP).⁵⁵ This mprRCT seeks to compare the efficacy of therapeutic dose anticoagulation versus prophylactic dose anticoagulation in improving mortality or need for organ support in hospitalized COVID-19 patients classified as moderately or critically ill. As of December 2020, all three trials ceased enrolment of critically ill patients due to safety concerns (pre-defined futility), and also stopped enrolment of moderately ill patients after meeting the pre-specified criteria for superiority in this group.⁵⁵ Interim conclusions based on pooled data analysis demonstrated superiority in the therapeutic dose anticoagulation arm compared with the prophylaxis arm in moderately ill COVID-19 patients (OR 1.27, 95% CI 1.03–1.58) but also met the pre-defined criteria for futility (OR <1.2) in the critically ill group (OR 0.83, 95% CI 0.67–1.03).⁵⁵ The majority of these studies are actively recruiting, and firm conclusions await their completion.

Conclusions

In summary, SARS-CoV-2 infection often presents with a distinct form of coagulopathy responsible for significant morbidity and mortality in afflicted patients. Laboratory elevations in coagulation parameters such as D-dimer, fibrinogen, vWF antigen/activity have shown to serve a predictive role in forecasting disease severity or increased rates of thrombosis, and a prognostic role in association with increased mortality. Unique pathophysiological mechanisms have been identified as contributing to the development of COVID coagulopathy. SARS-CoV-2 entry via ACE-2 receptors precipitates a potent host immune response, endothelial damage, and activation of tissue macrophages and neutrophils leading to a prothrombotic state.

Observed rates of thromboembolic complications such as DVT, PE, MI and CVA have varied significantly during the pandemic, with notable improvement after the implementation of increased use of thromboprophylaxis during inpatient care. While several interim guidelines have been proposed by major organizations, the optimal anticoagulant dose for thromboprophylaxis in the inpatient (non-ICU) and critical care settings is currently not well established pending the results of several key randomized clinical trials, which are actively recruiting patients. □

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Appendix 1

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for study selection

