15 The Novel Coronavirus and Haemostatic Abnormalities: Pathophysiology, Clinical Manifestations, and Treatment Recommendations

S. Louw, B. F. Jacobson, E. S. Mayne, and T. M. Wiggill

Abstract

The COVID-19 pandemic, caused by the SARS-C0V-2 virus, was initially considered and managed in a similar manner to the previous SARS epidemic as they are both caused by coronaviruses. What has now become apparent is that a major cause of morbidity and mortality in COVID-19 is abnormal thrombosis. This thrombosis occurs on a macro- and microvascular level and is unique to this disease. The virus has been demonstrated in the endothelium of the pulmonary alveoli and as such is thought to contribute to the devastating respiratory complications encountered. D-dimer concentrations are frequently raised in COVID to levels not frequently seen previously. The optimal anticoagulation treatment in COVID remains to be determined, and the myriad of pathophysiologic effects caused by this virus in the human host have also yet to be fully elucidated.

Keywords

COVID-19 · SARS-CoV-2 · Coagulopathy · Thrombosis · Biomarkers · Treatment

15.1 Background

In December 2019, a disease (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus (SARS-C0V-2), was documented in the city of Wuhan in the Hubei province in China, which rapidly spread to the rest of the world. To date, according to the World Health Organisation (WHO), there have been more than 17 million COVID-19 infections and 677 thousand deaths in 216 countries, with an estimated mortality rate of approximately 3.9% (as of July 31, 2020). As the world struggles with the health, social, and economic impact of this pandemic, the medical fraternity is assessing various aspects of this viral disease with scientific publications

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detailing the involvement of multiple organ systems in the human host [1, 2].

15.2 Coagulation System

The coagulation system is integral to the innate immune response to severe infection and patients with severe COVID-19 disease commonly present with systemic coagulation abnormalities such as disseminated intravascular coagulation (DIC) and other thrombotic microangiopathies [3]. As such, the International Society on Thrombosis and Haemostasis (ISTH) recommends measuring D-dimers, prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count in all hospitalised patients with COVID-19 [4]. Patients with the disease are also predisposed to both venous and arterial thromboembolism, related to a hypercoagulable state [5–7].

15.3 COVID-19 Coagulopathy

The SARS-C0V-2 virus gains access to human cells by binding to the angiotensin-converting enzyme (ACE) 2 proteins on cell membranes of various human tissues including the heart, lungs, and brain with an estimated 20-fold increased affinity compared to SARS-COV [8, 9]. Viral DNA has consequently been detected in multiple organs including alveolar type II epithelial cells and monocytes [9]. Cell invasion by SARS-C0V-2 also depends on the availability of the protease transmembrane protease serine 2 (TMPRSS-2) [10]. SARS-C0V-2 viral infection consequently results in significant inflammation because of wide tissue distribution and release of pro-inflammatory cytokines culminating in a systemic inflammatory response syndrome (SIRS) with multiorgan dysfunction (MODS) related to accelerated cell death in many organs [11, 12]. SIRS results in endothelial cell (EC) damage secondary to complement activation, direct viral infection of ECs, and the cytolytic action of cytotoxic T cells. Damage to ECs with activation of the coagulation system manifests as an immunothrombotic syndrome with generalised small vessel vasculitis and microthrombosis resulting in a consumptive coagulopathy [11–13].

Approximately 71% of patients (in some studies) who died from COVID-19 met the ISTH scoring criteria for DIC (Table 15.1), and it is therefore recommended that laboratory tests in patients admitted with COVID-19 should include the markers of haemostasis included in this scoring system [14, 15].

Repeated measurements of these markers may be indicated to identify a worsening coagulopathy which may warrant an increase in the level of care, blood product support, and possibly therapies including anticoagulation and immunosuppression therapy [3, 13].

D-dimer levels on admission serves as a prognostic marker of the severity of COVID-19 disease with levels greater than 2.0 μg/mL (i.e., a fourfold increase) predicting in-hospital mortality [17–19]. The PT in COVID-19 non-survivors at admission was also mildly prolonged at a mean

Table 15.1 International Society on Thrombosis and Haemostasis (ISTH) scoring criteria for disseminated intravascular coagulation (DIC) [3, 16]

Criteria:	Assigned score:	Relevance in COVID-19
Platelet count (x 10^9/L)	≥100 = 0	Thrombocytopaenia may be prognostic, but this is inconsistent [17]
	50–99 = 1	
	<50 = 2	
Fibrinogen (mg/dL)	≥100 = 0	Decreased in patients progressing to overt DIC [3]
	<100 = 1	
Prothrombin time (PT) prolongation above upper limit of normal (ULN) (seconds)	<3 = 0	May be subtly prolonged (15.5 s for survivors vs 13.6 s for non-survivors) [3]
	3–6 = 1	
	>6 = 2	
D-dimer increase above upper limit of normal (ULN) (ng/mL)	<2 = 0	Levels >2.0 ug/mL predict mortality [17–19]
	2–4 = 2	
	>4 = 3	
Total score	<5 = No overt DIC	
	≥5 = Overt DIC	

level of 15.5 s versus 13.6 s in survivors. This subtle prolongation in PT may not be appreciated if the PT is converted to an international normalised ratio (INR) [3]. Low platelet count (thrombocytopenia) is an indicator of sepsis-related mortality in critically ill patients [20], but this is not consistently the case in COVID-19 patients. Studies have documented platelet counts of less than 100×10^9/L in as few as 5% of hospitalised COVID-19 patients on admission [21], but lower platelet counts correlate with mortality [22]. Thrombocytopenia at the time of admission may therefore be a prognostic marker but is inconsistent [17]. Measuring fibrinogen and antithrombin levels may also be of value as decreased levels are indicative of progression to an overt DIC [3].

15.4 Thrombotic Manifestations

There is an increased prevalence of venous thromboembolic disease (VTED) in patients with COVID-19 [23], and this is associated with poor prognosis. It is unclear whether the risk of VTED is greater for COVID-19-related sepsis than for other septic processes [24]. Hypercoagulability relates to cytokine release [including interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-α)], hypoxia, immobilisation, and dehydration. Interestingly, DIC also appears to contribute to the increased risk of VTED [5, 25–29]. Increasing age and presence of a coagulopathy denoted by prolongation of the PT and aPTT, although counterintuitive, were independent predictors of thrombotic complications in a study on 184 Dutch patients admitted to the intensive care unit (ICU) with COVID-19 pneumonia [25]. Deep vein thromboses (DVTs) and pulmonary emboli (PE) have been documented in up to 27% of patients with COVID-19 admitted to ICU with PE constituting 80% of events [25]. VTED can occur despite prophylactic anticoagulation therapy [5, 25, 30]. Pulmonary thrombi in COVID-19 may not be embolic but rather related to in situ pulmonary thrombosis secondary to endotheliitis [24]. Thromboses also develop in extracorporeal circuits for continuous veno-venous hemofiltration (CVVH) and central venous catheters and can also manifest as extensive thrombophlebitis [5].

The clinical diagnosis of VTED can be challenging in ICU patients with COVID-19 because of the clinical overlap with the COVID-19 pneumonia and difficulties with clinical examination [5, 31]. Radiologic confirmation of VTED may be required consisting of Duplex Doppler investigation for DVT and CT pulmonary angiography (CTPA) for PE, which is preferred over ventilation perfusion scan (VQ scan) because of the COVID-19-related lung changes and the risk of aerosolised spread of the virus [24, 32].

Laboratory evidence of the hypercoagulable state in patients admitted with COVID-19 includes elevated fibrinogen and D-dimer levels as well as short clot formation time (CFT) and higher maximum clot firmness (MCF) on thromboelastometry [30]. Both D-dimer and fibrinogen levels are elevated, and D-dimer levels three–fourfold higher than the upper limit of normal are an indication for admission irrespective of the clinical presentation. Serial monitoring of D-dimers may be useful as a sudden elevation may denote the development of VTED (although a background raised D-dimer may be seen in most patients reducing the predictive value) [29]. Decreases in the natural anticoagulants, protein C, and antithrombin, and increases of plasminogen activator inhibitor-1 (PAI-1) levels as well as presence of antiphospholipid antibodies have also been documented in COVID-19 patients and contribute to the hypercoagulability [26].

15.5 Arterial Thromboses

15.5.1 Cardiac Events

Elevation of cardiac biomarkers, such as high-sensitivity cardiac troponin (hs-troponin) and creatinine kinase-MB (CKMB), is common in patients with COVID-19 with an overall prevalence of acute myocardial injury of up to 38% and acute myocardial infarction of 20% [7]. There is an apparent linear relationship between the magnitude of elevation of cardiac troponin

and COVID-19 severity and overall prognosis [31, 33, 34]. Additional cardiac manifestations of COVID-19 include arrhythmias, worsening of existing or new onset of heart failure which can be exacerbated by electrolyte disturbances, hypoxia, and myocardial ischaemia [31, 35].

Although the pathogenesis of myocardial injury in COVID-19 is not completely understood, the following mechanisms are postulated: (1) respiratory failure with hypoxic damage to cardiac muscle [36]; (2) inflammatory cytokine storm resultant myocarditis [37]; (3) direct endothelial injury by SARS-CoV-2 viral infection and/or host inflammatory response [38]; (4) downregulation ofACE-2 receptor expression with loss of subsequent protective anti-inflammatory, antioxidative, and vasodilatory signalling pathways in cardiac myocytes [37, 39]; (5) general hypercoagulability with coronary microvascular thrombosis [40]; and (6) inflammation and cardiac strain with coronary plaque rupture and myocardial ischemia/infarction (MI) [7]. COVID-19 viral RNA has been detected in autopsied human heart specimens of patients who died from this viral infection [41].

Since acute myocardial injury in COVID-19 can be asymptomatic and indicated only by underlying elevation of cardiac troponins, various guidelines have been issued with respect to laboratory testing in patients with COVID-19. The Chinese Clinical Guidance for COVID-19 Pneumonia, the WHO document on the management of severe COVID-19, the Asian Critical Care Clinical Trials Group, and the British Medical Journal Best Practice guidelines all advocate for testing of troponins on admission with repeat testing when clinically indicated, but the American College of Cardiology supports testing only if clinically indicated [7]. Evaluation of pro-brain natriuretic peptide (BNP) should be considered if clinical evidence of cardiomyopathy is present [42]. Special investigations that may be indicated include echocardiography, right and left cardiac catheterization with placement of a pulmonary artery catheter for continuous hemodynamic monitoring, and cardiac magnetic resonance imaging (MRI) [7].

15.5.2 Cerebrovascular Accidents

The precise incidence of cerebrovascular accidents (CVAs), i.e., strokes, in patients with COVID-19 is not known, but it is apparent that this is an important complication and has been reported in up to 5.7% of patients with severe disease [43]. COVID-19-related CVAs are predominantly ischaemic, involving large cerebral vessels although haemorrhagic strokes have also been described [43]. These events seem to correlate with underlying severity of systemic disease, the presence of comorbidities such diabetes and hypertension and inflammation in older patients, and the degree of hypercoagulability in younger patients [44].

Human brain endothelial cells display ACE II receptors, and it is postulated that viral interaction with these receptors and the downstream effects are pathophysiological in COVID-related ischaemic CVAs [37]. Antiphospholipid antibodies have also been demonstrated in patients with COVID-19, and together with endothelial dysfunction and a general hypercoagulable state could be contributory [6]. The possibility also exists that strokes in patients with COVID may relate to thromboses in the pulmonary veins which migrate to the left atrium or paradoxical emboli via a patent foramen ovale created by the high pulmonary pressures.

15.6 Microvascular Thrombosis and Endothelitis

Thromboses in the microvascular compartment of the circulation play an important role in the pathogenesis of organ dysfunction in COVID-19. The microvascular thrombosis in COVID-19 and in related disorders is referred to as thromboinflammation since inflammation, together with hypercoagulability and loss of physiological inhibitory control of the coagulation and the innate immune system are pivotal in its development [45, 46]. Healthy microvascular endothelium has powerful antithrombotic properties including a heparin sulphate-containing endothelial glycocalyx [45]. It is not possible to detect

thromboses in the microvasculature with common imaging techniques, and the diagnosis of thrombotic microvascular disease usually relies on clinical, laboratory, and histological observations [47].

Histopathological studies have highlighted the crucial role of ECs in the vascular dysfunction, inflammation, and immunothrombosis in COVID-19. Direct viral infection of endothelial cells and diffuse, inflammation-related endotheliitis with mononuclear cell infiltrate have been demonstrated as well as the presence of microvascular thrombosis in the various organs including the kidney, heart, lung, and liver [15, 38, 45]. ACE 2 and TMPRSS-2, present on the surface of arterial and venous ECs, mediate direct viral entry and damage. Pro-inflammatory cytokines in COVID-19 suppress natural antithrombotic and anti-inflammatory functions of ECs with coagulation system, complement and platelet activation, and leukocyte influx into the microvasculature [48]. Complement deposition with associated microvascular injury and thrombosis has been described in the lungs of COVID-19 patients [49]. Surrogate markers of EC dysfunction, von Willebrand factor and PAI-1 levels, are also increased [15]. However, the COVID-19 microangiopathic thrombosis does not present with the laboratory features of thrombotic thrombocytopenic purpura (TTP). The platelet counts in severe COVID-19 are usually relatively preserved, and red cell fragments (schistocytes) are not a prominent feature. There are only limited case studies in the literature describing patients with COVID-19 and features of TTP [50–52].

15.7 Treatment Recommendations for COVID-19-Related Coagulation Abnormalities

Complete guidance on the treatment recommendations of COVID-19-related haemostatic abnormalities is outside the scope of this review, but prophylactic treatment anticoagulation is recommended particularly in admitted patients.

Prophylactic dose low molecular weight heparin (LMWH) should be considered in patients with COVID-19 coagulopathy as inhibiting thrombin generation may improve outcomes in critically ill coagulopathic patients [53]. LMWH has anti-inflammatory properties and also protects against VTED. The contraindications for LMWH in COVID-19 patients with a coagulopathy include active bleeding and platelet counts $<25 \times 10^9$/L but not prolonged time-to-clot assays, such as PT and aPTT. LMWH activity monitoring with an anti-Factor Xa (a-FXa) assay is advised in all patients as the standard dose of anticoagulation may not protect against VTED in these patients and higher doses (enoxaparin at 0.5mg/kg twice daily) may be required. Bleeding is rare in patients with COVID-19, but the ISTH guidelines with respect to management can be followed if it does occur [54].

VTED prophylaxis is indicated in all patients with severe COVID-19 and for at least 7–14 days after discharge. Evidence is however emerging for all hospitalised patients with mild to moderate disease to also receive VTED prophylaxis in the absence of contraindications. Mechanical intermittent pneumatic compression is advocated in individuals with a contraindication to anticoagulation therapy [24].

Therapeutic dose anticoagulation is indicated in patients with confirmed VTED and in patients with a clinical suspicion of VTED and the presence of high-risk parameters if radiologic imaging is not feasible. Anti-FXa LMWH activity monitoring is indicated to ensure adequate anticoagulation [29]. Although possibly a reasonable approach, given the hypercoagulable state, the use of therapeutic doses of heparin in all hospitalised patients with severe COVID-19 is currently not supported by scientific evidence outside of treatment of VTED or as bridging therapy in patients on vitamin K antagonists (VKA) and cannot be recommended. Trials in this regard are ongoing [5, 24, 55]. Fibrinolytic therapy in patients with ST-elevation MI (STEMI) should be considered in addition to cardiac interventional therapies. Elevated troponins in patients with COVID-19 and a low pre-test probability of an acute coronary event could be a marker of sys-

temic critical illness and should be reviewed in conjunction with other markers of inflammation [56]. The use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with COVID-19 infection is currently an area of active research [44]. For patients with acute COVID-19-related stroke, treatment with fibrinolytic therapy such as tissue plasminogen activator (tPA) may be considered, but it is currently not clear if other anticoagulants such as LMWH or full dose heparin have therapeutic benefit [6]. Novel therapies that impact endothelial dysfunction in COVID-19 patients, including complement inhibitors, are under evaluation [48].

15.8 Future Areas of Research

As our knowledge of the COVID-19 haematologic abnormalities and coagulopathy expand, it is apparent that additional scientific evidence and ongoing studies are required. The optimal dose and duration of heparin treatment as well as the subpopulation of COVID-19 patients with the best benefit-harm ratio must be clearly defined. The role of nonstandard anticoagulants such as thrombomodulin must be established. The effect of SARS-CoV-2 on platelet activation and the antiviral role of platelets need to be further investigated. The utility of non-routine coagulation assays such as thromboelastography and point-of-care haematology and coagulation assays must be clearly established and treatment and investigation algorithms compiled. The pathophysiological role of endotheliitis and complement activation in COVID-19 also warrants further research. There are currently over 450 registered clinical trials worldwide which will expand our knowledge of COVID-19 with the aim of improved patient outcomes [57].

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