Exploring the pathways of inflammation and coagulopathy in COVID-19: A narrative tour into a viral rabbit hole

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ABSTRACT
Worldwide COVID-19 pandemic has taken a huge toll of morbidity and mortality. In selected patients, classified as severe, the overwhelming inflammatory state imposed by this infection is accompanied by a hypercoagulable state, hallmarked by a unique pattern; a marked increase in D-dimer, out of proportion to other markers of coagulopathy. In this review, we turn a spotlight to this phenomenon, offering a unified conceptual model depicting the leading hypotheses of coagulopathy in COVID-19. The key players of the coagulation cascades accompanying the COVID-19 inflammation malfunction on virtually every level; tissue factor expression is amplified, physiological anti-coagulant pathways (anti-thrombin, protein C and S, and the inhibitor of the tissue factor pathway) are impaired and fibrinolysis is inhibited. Components of autoimmunity, the complement system amongst others, further contribute to the pathology. As data continue to gather, our model offers a pathophysiological overview of COVID-19 coagulopathy, defined by the resultant histopathology: either intra-vascular or extra-vascular. We hope this review will facilitate understanding and serve as a lead point to future therapeutic directives.

Introduction
COVID-19 is caused by Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-Cov2) infection, ranging clinically from mild, flu-like illness to a devastating pneumonia [1]. In selected patients, the initial viral stage is followed by overproduction of pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-6, and IL-1) in what has been described as a “cytokine storm,” leading to vascular hyper-permeability, multi-organ failure, and death [2]. The inflammation is known to be accompanied by a hypercoagulable state, manifesting as increased risk for venous thromboembolic events, atrial events and microvascular target-organ damage [3]. This coagulopathy has a unique pattern; a marked increase in D-dimer, out of proportion to other markers of coagulation [3]. The association of marked inflammation and malignant coagulation play a crucial role in determining the fate of severe COVID-19 disease patients. It seems that inter-relations of thrombosis and inflammation cause a bilateral augmentation [4]. Therefore, in the current review, we describe the effect of the COVID-19 inflammation on coagulation, and form a conceptual module for the leading hypothesis based on the identified resultant histopathology of the disease.

COVID-19 associated coagulopathy
Venous-thrombo-embolic events (VTEs) including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), are frequent manifestations in severe COVID-19, seen in up to one-third of patients in the intensive care unit (ICU), even when prophylactic anticoagulation is used [5]. The rate of VTE in non-ICU inpatients is increased to a lesser extent, up to 10% for PE, and up to 22.5% for DVT [6, 7]. There are also arterial events, frequently seen in severe COVID-19. A study in 3334 hospitalized individuals (2505 non-ICU) reported incident of stroke in 1.6% and myocardial infarction in 8.9% [8–10]. Bleeding is less common than clotting in these patients, but it
may occur, especially in the setting of anticoagulation [11]. Aside from the aforementioned overt manifestations of coagulopathy, covert features might play a significant role in COVID-19 associated morbidity and mortality. One such feature is microvascular thrombi demonstrated in autopsies in lungs of the deceased [12].

Typical laboratory derangements of humoral coagulation in COVID-19 (table 1) include prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT). The fibrinogen is usually increased and D-dimer markedly raised.

The D-dimer antigen is a unique marker of fibrin degradation that is formed during fibrinolysis by the sequential action of three enzymes: thrombin, factor XIIIa, and plasmin. First, thrombin cleaves fibrinogen, producing fibrin monomers, which polymerize and serve as a template for factor XIIIa and plasmin formation. Second, thrombin activates factor XIII that is bound to fibrin polymers, to produce the active transglutaminase, factor XIIIa. Factor XIIIa catalyzes the formation of covalent bonds between D-domains of polymerized fibrin. Finally, plasmin degrades the crosslinked fibrin to release fibrin degradation products and expose the D-dimer antigen [13]. A myriad of pathologic (e.g. VTE, arterial thrombosis, disseminated intravascular coagulation (DIC)) and normal conditions (e.g. pregnancy) increase plasma D-dimer levels [14].

It is established that increased D-dimer levels upon hospital admission of COVID-19 patients are associated with worse prognosis [15] (Figure 1). A large meta-analysis concluded that levels over 500 ng/ml were associated with a twofold higher risk for deterioration and fourfold higher risk for death. Higher cut-off values (>2000 ng/ml) are even more accurate in predicting in-hospital mortality with a sensitivity of 92.3% and specificity of 83.3% after adjusting for age, gender, and comorbidities [16]. In other studies for that cutoff value, a tenfold increase in the risk for mortality was observed [17, 18]. A large multicenter study reported a 6% increase in all-cause mortality for every 1000 ng/mL increase in admission D-dimer. That same study identified two distinct groups of patients: those with stable D-dimer levels and with increasing D-dimer trajectory. A total of 14.9% patients in the “stable” group died during follow-up compared with 48.4% patients in the “increasing trajectory” group [19]. Furthermore, most studies show a strong association between D-dimer levels and incidence of all types of VTE in COVID-19 patients [20].

Other coagulation cascade anomalies include increased concentrations of tissue factor (TF), factor VIII, factor V, Plasminogen-activator inhibitor type 1 (PAI-1), plasmin-anti-plasmin (PAP) and a marked increase in Von Willebrand factor (VWF). Changes are also reported in natural anticoagulants: thrombin-anti-thrombin (TAT), protein S and protein C [3, 21–23]. Few studies further evaluated nonconventional hemostasis assays and reported that tissue plasminogen activator (tPA), tissue factor pathway inhibitor (TFPI) and vascular endothelial growth factor (VEGF) were also significantly increased in the critical versus noncritical COVID-19 patients [24, 25]. One study reported ADAMTS-13 levels to be greatly reduced [26]. Various autoimmune antibodies that are linked to hypercoagulable states are reported: anti-phospholipid antibodies (aPL) [27, 28], as well as autoimmune antibodies to Annexin A2 [29]. Furthermore, sustained pro-thrombotic changes in COVID-19 patients were reported even 4 months after

**Figure 1.** Di-dimer surge during the late stage of immune response precedes symptomatic stage of cytokine storm during COVID-19 severe illness.
hospital discharge; The PT, factor V, VWF, fibrinogen, D-dimer, and TAT levels were elevated on admission but normalized on checkup, whereas plasma levels of factor VIII and PAI-1 were elevated both on admission and at follow-up [22].

The interplay of inflammation and coagulopathy

As in other systemic inflammatory entities, inflammation induces coagulation, characterized by widespread intravascular fibrin deposition, a result of both enhanced fibrin formation and impaired fibrin degradation [4]. The following biochemical “players” are involved (Figure 2).

Tissue factor (TF)

Normally, TF is segregated from the bloodstream (generated mainly by extra-vascular monocytes [30]). Whenever it comes in contact with blood (e.g. endothelial damage) it initiates the coagulation cascade [31]. Pro-inflammatory cytokines activate monocytes, the endothelium and platelets to express TF, leading to systemic activation of coagulation [30, 31]. During severe COVID-19, hypoxia causes upregulation of endothelial P-selectin, through which monocytes bind to activated endothelial cells, further expressing pro-thrombotic factors such as TF [32, 33]. In severe COVID-19, TF expression and activity are significantly elevated and associated with increased disease severity and risk of mortality [23].

Physiological anti-coagulant pathways: antithrombin (AT), protein C and tissue factor pathway inhibitor

AT, synthesized by the liver, is the most potent endogenous coagulation inhibitor of thrombin and factor Xa [34]. During severe inflammation, AT levels are reduced due to impaired synthesis and increased clearance [31, 35]. AT function is impaired due to the reduced availability of glycosaminoglycans, acting as physiological, heparin-like cofactor of AT. Under the influence of pro-inflammatory cytokines the synthesis of glycosaminoglycans by endothelial cells is reduced, thus impairing the inhibitory potential of AT [31]. Investigations of AT in COVID-19 to date are limited, but should be of great importance as heparinoids, one of the cornerstones for treatment,
might render ineffective in face of AT depletion [36]. Indeed, AT reduction was related to increased mortality in hospitalized COVID-19 patients [37]. One study reported AT levels below the lower limit of the normal range, in one third of hospitalized COVID-19 patients; among them, two thirds died. Among survivors with low AT levels, 80% required mechanical ventilation. Interestingly, obesity, a risk factor for worse prognosis in COVID-19, is also associated with reduction in AT levels in COVID-19 [38]. Providing AT supplementation for critically ill COVID-19 patients using FFP may therefore improve prognosis but such reports are currently sporadic [39].

Potentially, AT supplementation may contribute to the positive effect of convalescent plasma.

Circulating protein C is activated by endothelial cell bound thrombomodulin, once this is activated by thrombin. Activated protein C (APC) acts with its cofactor protein S to degrade the essential coagulation cofactors Va and VIIIa. The endothelial protein C receptor (EPCR) not only accelerates the activation of protein C several-fold but also serves as a receptor for APC, and binding of APC to this receptor may amplify its anticoagulant and anti-inflammatory effects. In patients with severe inflammation, the protein C system is malfunctioning at virtually all levels (plasma levels of factors C and S are low and thrombomodulin is down regulated with resultant diminished protein C activation). Also, in sepsis the EPCR is down-regulated, negatively affecting the function of the protein C system [31]. Protein S also serves as a ligand for the immunosuppressive receptor tyrosine kinase (TK) MER, expressed by macrophages and other immune sentinels. Protein S depletion may silence MER signaling and activate sentinel cells to express and secrete pro-inflammatory cytokines [40].

In COVID-19, decreased factor C, S with concurrent rise in factors V, Va and VIII are documented [21–23]. It is suggested that a combined effect of both IL6 and hypoxia can further depress key anticoagulants such as protein S. Suggestions for treatments directed at augmenting such natural anticoagulants have not yet been tested [40, 41].

**Tissue factor pathway inhibitor**

Tissue factor pathway inhibitor is another important endogenous regulator of Tissue factor pathway activity and thrombin generation, thereby impairing the triggering mechanism of the extrinsic pathway. It is expressed by endothelial cells and platelets, and inhibits factor Xa via direct inhibition and also, subsequent activation of TF/FVIIa complex [24, 42]. TFPI is overly expressed by the body in an attempt to reduce tissue factor activity, and was found Increased in COVID-19 patients, similarly to patients with sepsis [24].

Of note is that plasma concentration of TFPI are greatly increased following intravenous heparin administration; this release of endothelial TFPI may contribute to heparins’ anti-thrombotic efficacy, theoretically may assist preventing development of capillary micro thrombi [43]. Recombinant TFPI is being evaluated as a potential anticoagulant, with its potential beneficial effect for sepsis currently being studied, but was not yet tested in COVID-19 patients [42].

**Effects of inflammation on fibrinolysis**

The alveolar space is a pro-fibrinolytic environment and deranged fibrinolysis play a role in several lung
The stable fibrin clot is degraded by plasmin, releasing D-dimer among other degradation products. During inflammation, cytokines such as TNF-α and IL-1β in the circulation lead to the release of plasminogen activators, particularly tissue-type plasminogen activator and urokinase-type plasminogen activator from vascular endothelial cells. However, this increase in plasminogen activation and subsequent plasmin generation is counteracted by a delayed but sustained increase in plasminogen-activator inhibitor-1 (PAI-1). The net result is inhibited fibrinolysis and consequent microvascular thrombosis [45]. COVID-19 patients show elevated fibrinogen levels, with higher values linked to severe disease, and in the late stages, thrombolysis decreases fibrinogen levels and increase fibrin-degradation products [20]. Patients showed an elevated tPA, and critically ill showed a further rise compared to non-severe patients. In one study, tPA was the best predictor of death, with levels of PAI-1 and D-dimer tracked most closely with impaired oxygenation efficiency [44, 46]. The elevated tPA may explain part of the increased D-dimer seen in patients, due to dysfunctional fibrinolysis [46]. To date, tPA was given only as salvage treatment to few COVID-19 patients with respiratory failure, but related improvement was noted in their respiratory status [47]. Attempts to treat non COVID-related ARDS showed a promising lead in animal models, and one phase 1 human clinical trial [47].

The complement system and microangiopathic phenomenon

The complement system, initiated by three pathways; classical, alternative, and lectin, play a critical and complex role in the pathogenesis of COVID-19. Complement dysregulation also plays a role in cases of thrombotic, micro-angiopathy anemia (TMA) [48]. ADAMTS13 protein main function is to cleave von Willebrand factor (VWF) anchored to the endothelial surface at the sites of vascular injury. ADAMTS13 deficiency may result in thrombotic thrombocytopenic purpura (TTP). Its levels are significantly reduced in COVID-19 patients when compared to healthy controls, with levels <30% significantly associated with a higher mortality [26].

NETosis

Neutrophils clear viruses not only through phagocytosis of viral particles, but also by releasing neutrophil extracellular traps (NETs), made up of DNA, histones and proteins derived from intracellular granules. Alongside its role in controlling pathogens, it also induces coagulation through tissue factor presentation, factor XII activation, and direct platelet binding. It is established that NETosis contributes to pathologic occlusion of arteries, veins, and microvasculature. There are evidence that SARS-CoV-2 virus activates NETosis in human neutrophils [23, 49]. Interventions directed at NET formation reduction are used to loosen sputum and relieve symptoms of Cystic fibrosis patients [49]. Attempt to treat ARDS with NET inhibitors were so far inefficient [50].

Resultant COVID-19 histopathology

Above-mentioned attributes of COVID-19 associated hypercoagulability lead, in selected patients, to a catastrophic combination of intravascular and extravascular fibrin deposition and thrombosis. This bivalent catastrophe stands at the epicenter of COVID-19 pathophysiology. The following paragraphs will attempt to present a unified theory combining all previously aforementioned pathophysiologic phenomenon.

Intravascular coagulopathy in COVID-19

Intravascular hypercoagulability, stemming from all components of Virchow’s triad (endothelial injury, stasis and hypercoagulable state), is a hallmark of severe COVID-19. Microvascular thrombosis in the lungs of COVID-19 patients was reported early in the pandemic [51]. In a recent systematic review of lung histopathology features, micro-thrombi were found in 57% of COVID-19 and 58% of SARS patients, as compared with only 24% of H1N1 influenza patients [52]. These findings coexist simultaneously with endothelial dysfunction, and significant pulmonary vascular dilatation in other, less damaged lung regions. Taken together, these explain the combined dead-space and shunt physiology, as well as the preserved pulmonary hemodynamics and normal right ventricular function in COVID-19 patients [53]. Therefore, improvement in oxygenation noted with increased PEEP in hypoxemic COVID-19 patients may be attributable to decreased cardiac output, leading to decreased shunt fraction rather than to alveolar recruitment [54]. Micro thrombi are also effecting other organs, e.g. COVID-19 patients frequently have non-occlusive cardiac fibrin micro-thrombi, without universal acute ischemic injury [55].

Early reports attributed the rise in D-dimer to DIC or sepsis-induced coagulopathy (SIC) [37, 56]. While this pattern shares some features with both it is
definitely a distinct entity; the major clinical finding in acute decompensated DIC is bleeding, whereas in COVID-19 thrombosis prevail. Other coagulation parameters in COVID-19 are distinct from DIC: The absence of thrombocytopenia, high fibrinogen and high factor VIII activity, suggesting that major consumption of coagulation factors does not occur in COVID-19 [11]. While DIC and SIC can occur as disease progress, they are less common when validated diagnostic criteria are applied [32].

The involvement of the complement system, along with low levels of ADAMTS13 raised the question whether the micro-thrombi formed are a part of a unique TMA. The complement system has been implicated in the etiology of syndromes presenting with a clinical triad: microangiopathic hemolytic anemia, thrombocytopenia, and organ damage. Despite the absence of anemia and thrombocytopenia COVID-19 shares key features with other complement mediated TMA syndromes [57]. As previously described, reduced ADAMTS13 levels were observed in COVID-19. Few studies have yet attempted use of plasma exchange in life-threatening COVID-19 [58].

Autoimmunity may play a key role in the intra-vascular pathophysiology of COVID-19. The timing of the severe respiratory distress, about 10 days after infection, appears to coincide with the development of an adaptive immune response. In addition, an initial autoimmune injury can cause cellular damage, which in turn, may lead to epitope spreading and autoimmunity to other self-antigens. Various autoimmune diseases were associated with COVID-19 infection, one is emergence of antiphospholipid antibodies [59], explaining prolongation of phospholipid-dependent clotting time assays seen in COVID-19. Sporadic reports even suggested a synergistic pro-coagulant effect of these autoantibodies and covid-19 infection [60]. Lupus anticoagulant, anti-cardiolipin antibodies anti-β2GPI antibodies presence were all reported in COVID-19 patients, thus relationship between COVID-19 coagulopathy and aPL is possible. Nevertheless, further investigations concluded that the sheer presence of antibodies was not associated with major thrombotic events [28]. Of note, antiphospholipid antibodies are common in the general population, especially during infection [61].

Anti-PF4 antibodies may also play a role in the natural pathophysiology of the disease. These antibodies, traditionally associated with heparin-induced thrombocytopenia (HIT) were reported in a high percentage of COVID-19 patients, clinically suspected of having HIT, with high titer anti-PF4/heparin antibodies. However, when functional tests were performed, many of them had a negative result [62]. Entering the new era of the pandemic, vaccines are becoming widely available. Recent reports describe a PF4-dependent syndrome that is unrelated to the use of heparin therapy and can occur after the vaccination. Healthy individuals presented with acute atypical thrombosis, primarily of the cerebral veins, and concurrent thrombocytopenia. All of the patients had d-dimer levels at presentation that were much higher than would be expected in patients with acute venous thromboembolism [63, 64].

**Extravascular coagulopathy in COVID-19**

Notwithstanding to all of the above, COVID-19 patients are partially resistant to anticoagulation. Several mechanisms have been proposed, for example, anti-thrombin deficiency as previously described that can result in heparinoid resistance. This is explained, in part, by concurrent extravascular clotting and fibrin deposition evading endovascular anticoagulants. Indeed, coagulation and fibrinolysis do not always occur merely within the vascular space, especially in the lungs. One prominent feature of airway inflammation is leakage of plasma proteins including fibrinogen and thrombin into the airway lumen. Extravascular thrombin can convert fibrinogen into fibrin. The physiological purpose of this extravascular fibrin is presumably serving as a matrix on which inflammatory cells can attach and function, similarly to the intravascular activity of NETs. Extravascular fibrin breakdown also explain the marked increase in D-dimer noted in patients with malignancies even in the absence of clots within the circulation. Accordingly, extravascular fibrinolysis may be relevant to COVID-19. The intense lung inflammation is associated with elevated fibrinogen levels. Cross-linked fibrin generated from the markedly increased fibrinogen that leak into the extravascular space would be broken down by plasmin or proteolytic enzymes released from activated neutrophils. D-dimer formed in this manner may not signify thrombus formation but could predict the need for mechanical ventilation, arising from lung exudates [65].

**Conclusion**

COVID-19 associated SARS is known to be a bi-modal disease, with a viral stage followed by an inflammatory one. Up-to-date, no effective anti-viral medication has significantly changed the natural history of disease and only steroids are agreed, worldwide, as “game changers” when given at certain timings. The above should not be regarded as true
therapies for this devastating pandemic. Addressing more profound pathophysiology should be the rule of the hour. In the current review, we addressed and analyzed the interplay of inflammation and coagulopathy induced by COVID-19. Resultant fibrin deposition, within and outside blood vessels is only partially reversed by conventional anticoagulation. It is time to reevaluate therapeutic targets and design appropriate therapies.

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