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PERSPECTIVES

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Contribution of the von Willebrand factor/ADAMTS13 imbalance to COVID-19 coagulopathy

Ryan Seth,[1] Thomas A. J. McKinnon,[2] and X. Frank Zhang[1]

[1]*Department of Bioengineering, Lehigh University, Bethlehem, Pennsylvania and* [2]*Department of Immunology and Inflammation, Centre for Haematology, Imperial College London, London, United Kingdom*

Abstract

The 2019 coronavirus disease (COVID-19) is the disease caused by SARS-CoV-2 infection. Although this infection has been shown to affect the respiratory system, a high incidence of thrombotic events has been observed in severe cases of COVID-19 and in a significant portion of COVID-19 nonsurvivors. Although prior literature has reported on both the coagulopathy and hypercoagulability of COVID-19, the specifics of coagulation have not been fully investigated. Observations of microthrombosis in patients with COVID-19 have brought attention to potential inflammatory endothelial injury. Von Willebrand factor (VWF) and its protease, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), play an important homeostatic role in responding to endothelial injury. This report provides an overview of the literature investigating the role the VWF/ADAMTS13 axis may have in COVID-19 thrombotic events and suggests potential therapeutic strategies to prevent the progression of coagulopathy in patients with COVID-19.

coagulopathy; COVID-19; endothelium; thrombosis; von Willebrand factor

INTRODUCTION

The 2019 coronavirus disease (COVID-19) outbreak has had a devastating impact across the world. The outbreak and the virus causing the disease, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were first identified in Wuhan, China, in December 2019. As of November 2021, the number of deaths from COVID-19 has climbed above 5 million worldwide. Instances of coagulopathy and thrombosis have been found to be common in patients with COVID-19 and nonsurvivors. This report will provide our perspective on COVID-19 coagulopathy and its potential connection with viral infection and von Willebrand factor/ADAMTS13 imbalance.

THROMBOTIC EVENTS IN PATIENTS WITH COVID-19

Studies in The Netherlands, France, and Italy, observed rates of venous thromboembolism (VTE) and arterial thrombosis of 15% and 30%, respectively, in critically ill patients with COVID-19, despite their receipt of anticoagulant thromboprophylaxis (1–3). However, this increased incidence remains disputed. In a multicenter retrospective study in Massachusetts, Al-Samkari et al. (4) reported rates of VTE at 7.6%, a figure more in line with rates of disease in noncritically ill patients with COVID-19. In addition, thrombotic complications were observed in 31% of 184 patients in ICU, although pulmonary emboli were observed in 27% (5). Yet, hypercoagulability is not limited to this group; 72% of patients with COVID-19 who had been diagnosed with a pulmonary embolism (PE) after computer tomography (CT) pulmonary angiography did not have severe enough disease to qualify for ICU care (6). PE has been determined as the cause of death in a significant portion of patients with COVID-19, but PE in patients with COVID-19 is often overlooked until autopsy. Autopsies revealed an incidence of deep venous thrombosis in 58% of patients with COVID-19, none of whom had preclinical evidence of PE (7). PE was the direct cause of death in 33% of these patients (7). In a separate autopsy study, alveolar-capillary microthrombi were more abundant in COVID-19-afflicted lungs compared with influenza-afflicted lungs by a factor of 9 (8). The incidence of thrombogenesis is closely correlated with the high mortality observed in severe COVID-19 cases; 50% of nonsurvivors presented a procoagulant state, whereas only 7% of survivors were procoagulant (9). Thus, the presence of coagulopathy in patients with COVID-19 is more common than previously thought and has significant implications for patient mortality.

COVID-19 COAGULOPATHY

The most appropriate description of the COVID-19 coagulopathy is a mild form of sepsis-induced diffuse intravascular coagulopathy (DIC) and localized pulmonary thrombotic

Correspondence: T. A. J. McKinnon (t.mckinnon03@imperial.ac.uk); X. F. Zhang (xiz310@lehigh.edu).
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microangiopathy (TM). Studies examining ICU and non-ICU patients with COVID-19 observed normal in vitro thrombin generation despite adherence to an anticoagulant regimen, suggesting that traditional anticoagulant therapy was insufficient in preventing clotting (10–12). The decreased fibrinolytic potential observed in patients with COVID-19 may be explained by decreased local anticoagulant activity caused by endothelial injury and subsequent decreases in thrombomodulin and endogenous heparinoids (10). Elevated D-dimer levels have been observed in most patients with COVID-19, and the magnitude of D-dimer levels is closely associated with patient mortality (7, 9, 10, 12–16). Modest thrombocytopenia has been observed in 70%–95% of patients with severe COVID-19 in addition to modest increases in prothrombin time (7, 9, 10, 12, 13, 16). Patients with severe COVID-19 have modest elevations in fibrinogen levels that rapidly decline before death (10, 12, 13, 17–21). Strikingly high levels of lactate dehydrogenase and C-reactive protein have been observed in COVID-19 nonsurvivors (7). Exceedingly high D-dimer levels and milder incidences of thrombocytopenia distinguish COVID-19 coagulopathy from sepsis-induced DIC, which features lower D-dimer levels and severe thrombocytopenia (9). The COVID-19 coagulopathy is separate from traditional TM as the observation of schistocytes, hemolysis, and severe thrombocytopenia is rare in patients with COVID-19 (9).

ENDOTHELIAL INJURY IN COVID-19

Endothelial cell injury has been a primary finding in autopsies of COVID-19 nonsurvivors and may contribute significantly to the procoagulant state observed in these patients. Swelling, disruption of junctions, and loss of contact with the basilar membrane have been observed in endothelial cells. Transmission electron microscopy (TEM) also revealed ultrastructural damage to the endothelium (14). A study of 68 patients with COVID-19 further supports that endothelial cell injury plays a major role in the observed coagulopathy; von Willebrand factor (VWF) antigen, soluble P-selectin, and PAI-1, markers of endothelial cell injury, were elevated in ICU patients compared with non-ICU patients (10, 12, 22, 23). In addition, thrombomodulin, a vasculoprotective membrane glycoprotein expressed on the luminal surface of vascular endothelial cells also associated with endothelial cell injury (24), was correlated with increased mortality (22). Patients with elevated soluble thrombomodulin were discharged from the hospital at a significantly lower rate (10, 12, 22).

Endothelial dysfunction is a known contributor to thrombosis, where dysfunction leads to the exposure of subendothelial collagen to blood, prompting the initial adhesion of platelets to collagen (25). Inflammation-induced endothelial cell injury in COVID-19 may also result in a large release of plasminogen activators, providing a potential explanation for high D-dimer levels and fibrin degradation products observed in severe COVID-19 coagulopathy (9). Although it is unclear how many factors contribute to endothelialitis observed in patients with COVID-19, direct SARS-CoV-2 infection has been observed in endothelial cells of nonsurvivors and may account for widespread endothelial cell dysfunction (8, 26). Angiotensin-converting enzyme 2 (ACE2) (18) has been reported as the receptor mediating the entry of SARS-CoV-2 (27, 28), and prior studies suggest the expression of ACE2 on human endothelium (28, 29). However, a recent study indicated that human endothelial cells express little to no ACE2 and may not support productive infection of SARS-CoV-2 (30). Therefore, the endothelial damage observed in patients with COVID-19 may likely stem from indirect mechanisms, including infection of neighboring cells, complement activation, and/or circulating proinflammatory cytokines.

HEMOSTATIC ROLE OF VWF/ADAMTS13 AXIS

A potential explanation for the thrombotic events observed in patients with COVID-19 may be triggered by an imbalance between levels and activity of VWF and its protease, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). VWF and ADAMTS13 play an important role in vascular thrombosis.

VWF is a large multimeric protein formed of up to 200 monomers. After synthesis in platelets and endothelial cells and removal of their signal peptides, pro-VWF subunits associate in the endoplasmic reticulum into COOH-terminal "tail-to-tail" dimers by the formation of disulfide bonds between the CK domains. These dimers further multimerize in the Golgi apparatus by forming "head-to-head" disulfide bonds connecting the amino-terminal D3 before secretion (Fig. 1*A*). Also occurring in the Golgi is the maturation step, where pro-VWF is cleaved by furin and becomes the mature protein (from D′ to CK). Among the 12 domains of matured VWF, the A1-A2-A3 tridomain is central to VWF's function. Upon tissue damage, the A3 domain first anchors the VWF onto subendothelial collagen under blood flow. Subsequently, the A1 domain, via its engagement with the platelet GPIb, captures platelets from the flowing blood (Fig. 1, *A* and *B*) (31). The A2 domain, which can be subjected to mechanoenzymatic cleavage by ADAMTS13, provides a "shear bolt" mechanism to prevent excessive platelet adhesion (31).

The size of VWF (i.e., how many monomers make up the multimer) is critical to its hemostatic functional capacity. Newly secreted ultralarge VWF (ULVWF) that contains hundreds of monomers can generate spontaneous thrombosis and are, therefore, thrombotic to the body (31). These ULVWF must be degraded to shorter forms to decrease their thrombogenic potential. The size of VWF is controlled by the blood enzyme ADAMTS13, which cleaves the scissile bond between residues Y1605 and M1606 within the A2 domain.

ADAMTS13 is secreted as a relatively active enzyme, primarily from hepatic stellate cells (32), endothelial cells (33, 34), and megakaryocytes/platelets (35). ADAMTS13 regulates the activity of VWF by cleaving ULVWF (>10,000 kDa) into hemostatically active circulating VWF of lower weight (<10,000 kDa) (36). A deficiency in ADAMTS13 can lead to the accumulation of these ULVWF multimers, further resulting in consumptive thrombocytopenia and microvascular thrombosis (36). In addition, an imbalance between levels of VWF and ADAMTS13 is implicated in arterial thrombosis (37) and ischemic stroke (38, 39). An abnormal VWF:ADAMTS13

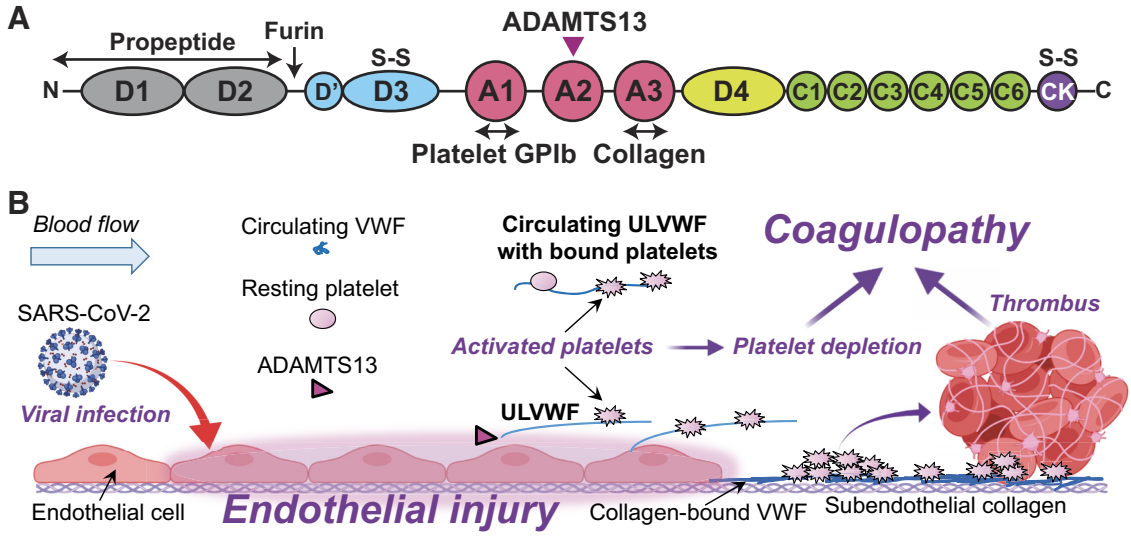

Figure 1. *A*: schematic illustration of VWF's domain arrangement and the key functions of the A domains. *B*: model connecting viral infection, endothelial injury, the VWF/ADAMTS13 axis, and COVID-19 coagulopathy. Created with BioRender.com and published with permission. ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; VWF, von Willebrand factor.

ratio has also been positively correlated with myocardial infarction in young women (40). In a study of acute ischemic brain injury, a VWF:ADAMTS13 ratio of >2.6 has been identified to predict mortality (41).

Biotherapeutics targeting the VWF/ADAMTS13 axis have been under active study during the past 2 decades. Recombinant VWF (rVWF) and recombinant ADAMTS13 (rADAMTS13), for example, have been developed by Baxalta (currently part of Takada). rVWF was approved by the Food and Drug Administration (FDA) in 2015 for treating von Willebrand Disease (VWD) (42), a hereditary bleeding disorder causing a defect or deficiency in VWF. rADAMTS13 is currently under a phase 3 clinical trial for thrombotic thrombocytopenic purpura (TTP) (43), a rare disease caused by ADAMTS13 deficiency. Moreover, caplacizumab, a bivalent nanobody targeting VWF, was approved by the FDA in 2019 for treating acquired TTP (aTTP) (44, 45), a TTP deficiency due to the presence of inhibitory autoantibodies. A recent study indicated that caplacizumab binds the A1 domain (i.e., the platelet-binding domain) of VWF and allosterically inhibits the A1-platelet GPIbα receptor interaction under low and moderate shear, thereby exerting its antithrombotic function (46).

A POSSIBLE CONNECTION BETWEEN COVID-19 COAGULOPATHY AND VWF/ADAMTS13 IMBALANCE

Despite the role of the VWF/ADAMTS13 axis in microvascular hemostasis, its connection to the coagulopathy observed in patients with COVID-19 has not been seriously considered. The few studies investigating this connection have discovered a positive correlation between an imbalance of VWF/ADAMTS13 activity levels and COVID-19 severity and mortality. Several studies have observed elevated levels and activity of VWF and decreased activity of ADAMTS13 in patients with COVID-19 (10–12, 23, 47–52). In addition, a retrospective study examining 3,672 plasma samples identified a correlation between elevated levels of VWF and markers of coagulation (53). One study reported lower ADAMTS13 levels in 88 patients with COVID-19 compared with healthy controls (50). Lower ADAMTS13 levels and higher VWF levels were also observed in COVID-19 nonsurvivors compared with survivors (11, 48, 54). Lower levels of ADAMTS13 were inversely correlated with D-dimer, fibrinogen, and VWF antigen (11). Similarly, several other studies found a decrease in ADAMTS13 activity and an increase in VWF activity in critically ill patients with COVID-19 (34, 51, 55). Furthermore, 50 hospitalized patients with COVID-19 were noted as having a 47% decrease in ADAMTS13 activity (56). A prospective study of patients with COVID-19 found an increase in VWF aggregation by a factor of 5 as well as a significant decrease in ADAMTS13:VWF ratios without any significant decrease in ADAMTS13 levels compared with healthy controls (57). An additional study observed a similar increase in VWF activity with no change in ADAMTS13 levels (53). Although studies suggest COVID-19 pathology includes a reduction in ADAMTS13 activity and an increase in VWF activity, the existing body of literature is limited by an insufficient number of observations and a lack of standardization in the timing of VWF/ADAMTS13 measurements during COVID-19 pathogenesis.

All the coagulation and endothelial injury endpoints discussed in this review and their association with COVID-19 are summarized in Table 1.

A PROPOSED MODEL CONNECTING COVID-19 COAGULOPATHY, ENDOTHELIAL INJURY, AND VWF/ADAMTS13 IMBALANCE

Based on the abovementioned evidence from literature and our studies on VWF, ADAMTS13, and endothelial dysfunction, we propose the following working model: SARS-CoV-2 infection to the surrounding tissues of endothelium or

Table 1. *Coagulation and endothelial injury endpoints associated with COVID-19*

Endpoint Marker	Physiological Function	COVID-19 Association	References
Coagulation			
1. Prothrombin time (PT)	PT is an assay that examines the efficiency of the extrinsic and common clotting pathways. PT is influenced by activities of fibrinogen, prothrombin, and factors V, VII, and X.	Modest increase in PT observed in patients with severe COVID-19.	9, 15, 16, 13, 10, 12
2. Platelet count	Upon endothelial injury, platelets adhere to exposed collagen, secrete granules, and aggregate, forming a platelet plug.	Modest thrombocytopenia observed in a majority of patients with severe COVID-19. Greater magnitude of thrombocytopenia observed in nonsurvivors.	9, 7, 15, 10, 12
3. D-dimer (XDP)	D-dimer-containing compounds are formed by plasmin degradation of factor XIIIa cross-linked fibrin.	Elevated D-dimer levels are observed in most patients with COVID-19. Magnitude of D-dimer elevation is closely associated with mortality.	9, 14, 7, 15, 16, 13, 10, 12, 17, 53, 52
4. Fibrinogen	Fibrinogen is the substrate of thrombin; cleavage of fibrinopeptide A from fibrinogen initiates fibrin polymerization.	Modestly elevated fibrinogen levels observed in patients with severe COVID-19. Elevated fibrinogen levels on admission are associated with poor outcomes. Rapid decrease in fibrinogen levels observed in some patients with COVID-19 before death. Elevated levels associated with need for respiratory support.	18, 20, 21, 13, 19, 10, 12, 17, 11
5. Activated partial thromboplastin time (aPTT)	aPTT is an assay examining the efficiency of the intrinsic and common clotting pathways. aPTT can detect deficiencies in factors VIII, IX, and XI as well as reduced activity of fibrinogen, prothrombin, and factors V and X.	Prolonged aPTT observed in patients and positively associated with mortality.	16, 13
6. Lactate dehydrogenase (LDH)	Enzyme involved in anaerobic metabolism; LDH is released during clotting.	Exceedingly elevated levels observed in COVID-19 nonsurvivors	7
7. Prothrombin	Precursor to thrombin, a serine protease-converting fibrinogen to fibrin	Decreased levels observed in patients with COVID-19 and nonsurvivors	10, 12
8. Thrombin-antithrombin complex (TAT)	Complex of thrombin and antithrombin indicative of elevated thrombin levels and a hypercoagulable state	Strongly elevated in patients with COVID-19	10, 12
9. Plasmin-antiplasmin complex (PAP)	PAP is responsible for dissolution of fibrin polymers into soluble fragments.	Elevated in patients with COVID-19	10, 12
10. Antithrombin	Plasma protease inhibitor that inactivates thrombin and coagulation factors in the intrinsic and common pathways	Elevated levels observed in nonsurvivors	10, 12
11. Factor VII	Serine protease that activates factor IX to factor X once bound to tissue factor	Decreased levels of activated factor VII observed in patients	10
12. Factor VIII	Factor VIII accelerates factor IXa-mediated activation of factor X.	Elevated in patients with COVID-19 and associated with required respiratory support	12, 17
Endothelial injury			
1. Ultrastructural damage and necrosis		Ultrastructural damage to and necrosis of endothelial cells observed with microscopy	8, 14
2. von Willebrand factor	Binds subendothelial collagen under blood flow and captures platelets from flowing blood.	Elevated levels and activity of VWF observed in patients with COVID-19. Elevated levels of VWF antigen observed in ICU compared with non-ICU patients with COVID-19 Elevated levels associated with need for respiratory support	47, 48, 49, 22, 50, 51, 54, 10, 12, 17, 53, 11, 52, 23
3. Soluble P-selectin	Marker for platelet and endothelial cell activation	Elevated in ICU and non-ICU patients with significantly higher levels observed in ICU patients	22, 23
4. sCD40L	Marker for platelet and T cell activation	Significantly elevated in ICU patients	22
5. Plasminogen activator inhibitor-1 (PAI-1)	Principal inhibitor of tissue plasminogen activator and urokinase; marker for risk of thrombosis	Significantly elevated in ICU and non-ICU patients	22, 10, 12, 23
6. Soluble thrombomodulin	Marker for endothelial cell activation	Significantly correlated with mortality in ICU patients and all patients with COVID-19	22, 10, 12
7. C-reactive protein	Marker of inflammation and complement activation	Exceedingly elevated levels observed in COVID-19 nonsurvivors	7
8. SARS-CoV-2 infection of endothelial cells		Direct infection of endothelial cells has been observed in patients with COVID-19.	8, 26

circulating proinflammatory cytokines induces endothelial secretion of ULVWF into the bloodstream, causing an imbalance in VWF/ADAMTS13. The insufficiency of ADAMTS13 cleavage of ULVWF may result in hypercoagulability, including spontaneous thrombus formation in blood vessels and VWF adhesion on the exposed subendothelial collagen due to endothelial injury. Platelet adhesion to VWF may also trigger a recently identified mechanotransduction pathway that leads to platelet activation and depletion (58, 59), potentially causing mild thrombocytopenia (Fig. 1*B*).

Although the model can explain the clinical observations of COVID-19 coagulopathy and the connection among hypercoagulability, coagulopathy, endothelial injury, and VWF/ADAMTS13 imbalance, vigorous experimental, and clinical studies are required to test the model fully. Nonetheless, based on the model, several therapeutic interventions could be suggested to treat COVID-19-induced coagulopathy.

First, the imbalance of the VWF:ADAMTS13 ratio could be adjusted by infusion of rADAMTS13 (43). Indeed, a recent study from a cohort of 36 patients with severe COVID-19 indicated that incubation of plasma samples from these patients with rADAMTS13 reduced the abnormal ULVWF in a time- and concentration-dependent manner, suggesting a therapeutic potential of rADAMTS13 in restoring the VWF/ADAMTS13 imbalance (60). VWF-induced thrombosis may also be reduced by caplacizumab (61). In addition, *N*-acetylcysteine has been reported to reduce intrachain disulfide bonds in ULVWF, thereby exerting a thrombolytic effect (62), and has been in clinical trials as a potential therapy to improve COVID-19 outcomes by reducing the risk of thrombosis (63).

SUMMARY

In conclusion, there is strong evidence from the literature that the SARS-CoV-2 infection causes endothelial cell injury, likely due to an indirect mechanism. The ULVWF released from injured endothelium likely causes an imbalance of the VWF:ADAMTS13 ratio, leading to thrombosis and platelet activation. Therefore, endothelial injury and dysfunction account, at least partially, for the coagulopathy and hypercoagulability observed in patients with COVID-19. Targeting the VWF/ADAMTS13 axis may provide a new strategy to reduce COVID-19 systemic complications.

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Present address of R. Seth: Case Western Reserve University School of Medicine, 9501 Euclid Ave, Cleveland, Ohio.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.S., T.A.J.M., and X.F.Z. conceived and designed research; R.S. and X.F.Z. performed experiments; R.S. and X.F.Z. analyzed data; R.S. and X.F.Z. interpreted results of experiments; X.F.Z. prepared figures; R.S. and X.F.Z. drafted manuscript; R.S., T.A.J.M., and X.F.Z. edited and revised manuscript; R.S., T.AJ..M., and X.F.Z. approved final version of manuscript.

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