HHS Public Access

Author manuscript

Curr Drug Targets. Author manuscript; available in PMC 2023 July 03.

Published in final edited form as:

Curr Drug Targets. 2022 ; 23(17): 1593–1602. doi:10.2174/1389450123666220826162900.

Fibrinogen, Fibrin, and Fibrin Degradation Products in COVID-19

Kadri Kangro[1], **Alisa S. Wolberg**[1], **Matthew J. Flick**[1,*]

[1]Department of Pathology and Laboratory Medicine, UNC Blood Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the highly pathogenic and highly transmissible human coronavirus that is the causative agent for the worldwide COVID-19 pandemic. COVID-19 manifests predominantly as a respiratory illness with symptoms consistent with viral pneumonia, but other organ systems (*e.g.*, kidney, heart, brain) can also become perturbed in COVID-19 patients. Accumulating data suggest that significant activation of the hemostatic system is a common pathological manifestation of SARS-CoV-2 infection. The clotting protein fibrinogen is one of the most abundant plasma proteins. Following activation of coagulation, the central coagulation protease thrombin converts fibrinogen to fibrin monomers, which self-assemble to form a matrix, the primary structural component of the blood clot. Severe COVID-19 is associated with a profound perturbation of circulating fibrinogen, intra- and extravascular fibrin deposition and persistence, and fibrin degradation. Current findings suggest high levels of fibrinogen and the fibrin degradation product D-dimer are biomarkers of poor prognosis in COVID-19. Moreover, emerging studies with *in vitro* and animal models indicate fibrin(ogen) as an active player in COVID-19 pathogenesis. Here, we review the current literature regarding fibrin(ogen) and COVID-19, including possible pathogenic mechanisms and treatment strategies centered on clotting and fibrin(ogen) function.

Keywords

Fibrinogen; fibrin; D-dimer; coagulation; fibrinolysis; COVID-19

1. INTRODUCTION

Coronavirus disease that initiated a worldwide pandemic towards the end of the year 2019 (*i.e.*, COVID-19) is caused by the severe acute respiratory syndrome coronavirus

*Address correspondence to this author at the Department of Pathology and Laboratory Medicine and the UNC Blood Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; matthew_flick@med.unc.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

CONSENT FOR PUBLICATION

Not applicable.

2 (SARS-CoV-2) [1]. SARS-CoV-2 first emerged in Wuhan, China, in 2019, and still poses a global threat due to the development of new viral variants that might escape the vaccine-induced immunity [2]. A significant challenge for managing the spread of the virus is that approximately one-third of patients with COVID-19 are asymptomatic [3]. Further, for those that develop COVID-19, clinical symptoms may range from mild to severe, and critically ill hospitalized patients with respiratory failure may require mechanical ventilation [4]. Although considered primarily a disease of the respiratory system, clinical observations in the early stages of the pandemic recognized that COVID-19 provokes severe coagulation abnormalities in some patients (termed “COVID-19-associated coagulopathy” or CAC) that include abnormalities in clotting parameters and heightened risk of both venous and arterial thrombosis and an acquired consumptive coagulopathy [5–7]. The reported incidence of thrombotic complications in COVID-19 ranges from 7 to 60% [8, 9]. Deep vein thrombosis and pulmonary embolism are the most commonly reported thrombotic events in SARS-CoV-2 infection [10, 11], but some studies have suggested that ~58% of COVID-19 fatalities are related to arterial thrombosis (*e.g.*, coronary artery, aortic, cerebral artery) [12, 13]. Microvascular thrombosis, particularly in the lungs, has been reported in 57% of patients with COVID-19, which is considerably higher than the ~24% rate reported for influenza A patients [14]. Perhaps as expected, the highest estimates of thrombotic complications are found in those individuals with severe disease and requiring an ICU admission [8, 9].

A substantial number of reports have attempted to characterize and define CAC and its pathophysiology based on standard and non-standard laboratory tests, imaging studies, and patient autopsy findings. These studies suggest SARS-CoV-2 induces changes in both coagulation and fibrinolytic system function and activity. It is currently unknown whether CAC is a single entity with a common point of initiation or whether CAC is a heterogenous condition with specific triggers and pathogenic mechanisms driving the coagulation disorder in individual patients or patient populations. What has become clear from the nearly two thousand publications as of March 2020 is that CAC appears to be distinct from classical settings of systemic coagulopathy (*e.g.*, disseminated intravascular coagulation [DIC]), suggesting a unique etiology that requires a new understanding of the operant mechanisms. A number of candidate biomarkers and causative mechanisms have emerged, including quantitative changes to soluble clotting and fibrinolytic factors, endothelial cell dysfunction, platelet hyperactivation, and immune cell-mediated coagulation. Regardless of the underlying initiator and pathways, a downstream functional and mechanistic point of commonality for each of these potential mechanisms in CAC is a profound perturbation of fibrinogen and/or fibrin (collectively fibrin[ogen]).

Fibrinogen plays a seminal role in hemostasis and thrombosis as the primary structural/matrix component of the blood clot. Fibrin(ogen) is essential for clot formation, growth, and stabilization. Insufficient fibrinogen is a major risk factor for bleeding [15, 16], and elevated fibrinogen is a risk factor for thrombosis [17, 18]. Elimination of fibrinogen or fibrin polymerization is protective in mouse models of both venous and arterial thrombosis [19, 20]. Substantial progress has been made in understanding the mechanisms linking fibrinogen to both hemorrhagic and thromboembolic diseases.

In the context of COVID-19, both quantitative and qualitative changes have been documented in circulating fibrinogen, as well as in each of its end products (*i.e.*, fibrin monomers, fibrin polymers [matrix], and fibrin degradation products). Intriguingly, similar changes in fibrin(ogen) species have been detected in other thromboinflammatory diseases, such as diabetes, hypertension, and obesity, and these disease states are the most frequent underlying comorbidities linked to COVID-19 [21]. Exposure to environmental factors, such as air pollutants and smoking, is also associated with perturbation of fibrin(ogen) and exacerbation of COVID-19 severity [22, 23]. Collectively, these associations suggest a hyperactivated coagulation system and reactive changes to fibrin(ogen) in SARS-CoV-2 infection are primary or secondary drivers of poor patient outcomes [7, 24].

Here, we review current literature linking COVID-19 pathophysiology with abnormalities in fibrin(ogen), including data underpinning changes in circulating fibrinogen and fibrin degradation products with COVID-19 disease progression and severity. Further, we review the substantial evidence supporting intravascular and extravascular fibrin formation following infection with SARS-CoV-2. We describe putative mechanisms by which persistent fibrin deposits may drive COVID-19 disease progression, morbidity, and mortality. Finally, we highlight current treatment strategies aimed full or in part at mitigating the contribution of fibrin(ogen) to COVID-19 disease progression.

2. FIBRINOGEN, FIBRIN, AND FIBRIN DEGRADATION PRODUCTS

In healthy individuals, fibrinogen circulates at relatively high concentrations in plasma (2–5 mg/mL), and is one of the most prevalent coagulation proteins. Fibrinogen is primarily synthesized in hepatocytes. The fully assembled fibrinogen molecule is a hexamer consisting of three dimers of Aα, Bβ, and γ polypeptide chains $(A\alpha B\beta\gamma)_2$, which are crosslinked by 29 disulfide bridges, forming a soluble 340 kDa glycoprotein [25, 26]. The assembled fibrinogen protein is divided into a central E nodule that comprises the N-termini of all six chains and two distal D nodules that contain the C-termini of the Bβ and γ chains [25, 27]. The C-termini of the Aα chains loop back and are positioned near the E nodule [25].

Activation of coagulation leads to the production of the enzyme thrombin. Proteolytic cleavage of short N-terminal fibrinopeptides A and B from the Aα- and Bβ- chains of fibrinogen by thrombin results in the formation of fibrin monomer [28, 29]. Fibrin monomers polymerize into fibrin fibrils that organize through lateral aggregation and branching to form an insoluble elastic and viscous network [29, 30]. Thrombin also activates the transglutaminase factor XIII that crosslinks fibrin fibers and incorporates inhibitors of fibrinolysis (*i.e.,* α2-antiplasmin) into the meshwork (Fig. 1). Notably, crosslinked fibrin matrices can be formed either within the vasculature, comprising the structural component of a thrombus, or within the extravascular space and tissue parenchyma.

Fibrin is intended to serve only as a provisional matrix. Ultimately, fibrin is targeted for proteolytic degradation [31]. During this fibrinolytic phase, plasminogen is converted into plasmin by one of two main activators: urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) [32]. Both uPA and tPA are inhibited by the plasminogen activator inhibitor-1 (PAI-1) [33, 34]. Plasminogen activation is also downregulated

by thrombin/thrombomodulin-mediated activation of the thrombin-activated fibrinolysis inhibitor (TAFI) [35]. Plasmin-mediated cleavage of fibrin generates fibrin degradation products (FDPs) that include E fragment, and two D fragments that remain crosslinked: the D-dimer [36]. D-dimer is used as a clinical readout for fibrin formation and subsequent fibrin breakdown, and is a biomarker of thrombosis. FDPs are eliminated through multiple pathways; FDPs released into circulation are eliminated through the liver, whereas FDPs formed within tissues are likely cleared by CCR2+ macrophages and perhaps other scavenger cells [37].

2.1. Fibrinogen in COVID-19

In inflammatory settings that trigger an acute phase response (APR), fibrinogen expression and synthesis are increased by 2–3-fold, and levels can exceed 8 mg/mL [38]. Viral infection in general, and SARS-CoV-2 infection in particular, provoke an APR. Clinical studies report evidence of a cytokine storm and increased serum levels of proinflammatory cytokines, including interleukin-2, -6, -7, -8, -10, G-CSF, interferon γ, MCP-1, MIP1α, and TNFα in patients with COVID-19 [39]. Although these cytokines have pleiotropic effects that can enhance the hypercoagulable state through multiple mechanisms, it is notable that several of these soluble inflammatory mediators have specifically been linked to increased circulating fibrinogen. In particular, high circulating IL-6 levels have been identified in patients with COVID-19 and associated with more severe outcomes, including ICU admission and death. IL-6 signaling increases fibrinogen synthesis, and consequently enhances plasma fibrinogen levels [40]. Multiple studies have documented higher circulating fibrinogen levels in COVID-19 patients [41–44]. A meta-analysis of 35 studies examining fibrinogen levels revealed significantly increased circulating fibrinogen in severe COVID-19 compared to non-severe COVID-19 patients [45]. Moreover, studies have detected a statistically significant, positive association between circulating fibrinogen level and the overall incidence of thrombotic complications resulting from COVID-19. An example of this association is patients with COVID-19 lung disease requiring extracorporeal membrane oxygenation (ECMO). These patients develop venous thromboembolic events at a substantially higher rate than non-COVID-19 patients on ECMO [43, 46–48].

In patients with COVID-19, elevated circulating fibrinogen is likely not just a biomarker of thrombosis risk but also a contributor to thromboembolic events. Functional studies of hyperfibrinogenemia in the absence of changes in other clotting factors in mouse models and *in vitro* systems illustrated that high plasma fibrinogen shortens the time to vessel occlusion following both arterial and venous challenges [49]. Faster occlusion was secondary to changes in fibrin formation, structure, and stability that appear to mediate, at least in part, the relationship between fibrinogen and thrombosis. Specifically, high plasma fibrinogen increased thrombus fibrin content, promoted faster fibrin formation, and increased fibrin network density, strength, and stability [49]. Hyperfibrinogenemia also led to the production of a fibrin meshwork resistant to fibrinolysis [49]. Analyses of whole blood and plasma from COVID-19 patients suggest elevated fibrinogen and abnormalities in fibrin formation, structure, and stability as features of SARS-CoV-2 infection.

2.2. Fibrin Formation in COVID-19

In vitro studies of plasma clotting detected enhanced fibrin formation in plasma from patients with COVID-19 (both in and out of the ICU) that resembled results found in patients with sepsis [41, 50]. Increased fibrin appeared to be secondary to both enhanced procoagulant activity (thrombin generation) as well as increased levels of fibrinogen, suggesting heightened propensity for producing fibrin to be a fundamental feature of both moderate and severe COVID-19 (Fig. 2). Whereas these findings are consistent with increased thrombosis and fibrin deposits in the lungs of severe COVID-19 patients, they must also be reconciled with the paradoxical finding that significantly elevated D-dimer is a biomarker of morbidity and mortality in COVID-19.

2.3. Fibrin in COVID-19: Intravascular Deposits (Thrombosis)

Postmortem studies of tissues collected from patients who have died from COVID-19 have consistently revealed fibrin-rich thrombi, particularly in vessels of the lung but also of the kidney, heart, and brain [51–53]. Khismatullin *et al.* documented heterogeneity of fibrin structural types within tissues by both histological and ultrastructural analysis. Intravascular fibrin was generally in the form of dense matrices separated from areas of packed and deformed red blood cells (polyhedrocytes) [54]. In this same study, analyses of two COVID-19 patients attributed the cause of death to massive pulmonary embolism, revealing large pulmonary clots with polyhedrocytes as the major structural feature. Fibrin was the second most abundant structural element with three predominant morphological types: individual fibers, bundle fibers, and fibrin fragments with truncated, free ends believed to be derived from proteolytic cleavage. Fibrin was present throughout the clots, and truncated fibers were found at the clot periphery. In a recent multicenter autopsy study from the US and Italy, fibrin-rich thrombi were observed in large vessels of the lung in roughly half of the patients and in small vessels in >80% of subjects [55]. Notably, studies in mice and blood samples from humans have shown that fibrin formation and crosslinking by activated factor XIII promote red blood cell retention in venous thrombi, and thus, mediate clot mass and size [28, 30, 56]. Abnormalities in fibrin formation and/or structure or a failure of fibrin crosslinking by factor XIII can enhance clot embolization and occlusion of downstream vessels [57, 58]. These observations are consistent with additional studies of plasma from COVID-19 patients illustrating an altered fibrin clot structure characterized by thin fibers organized into a highly dense matrix [50, 59]. Thus, fibrin detected in thrombi from COVID-19 patients may be an end-stage effector and structural determinant of vaso-occlusive and thromboembolic events.

2.4. Fibrin in COVID-19: Extravascular Deposits

Postmortem studies have consistently observed extravascular fibrin deposits predominantly in the lung alveolar space, as well as other organ systems. Fibrin deposition in conjunction with dead cells and surfactant attached to the alveolar septa were observed using histological techniques and scanning electron microscopy from COVID-19 patients who died of respiratory failure [54]. An autopsy study from Houston, Texas, observed distinctive interstitial lymphocytic pneumonitis with intra-alveolar fibrin deposits [60]. Similarly, a study in Budapest, Hungary involving 100 autopsy cases, observed lung abnormalities,

including alveolar damage, macrophage infiltration, and vascular and alveolar fibrin aggregates in the lung, with macro- and microvascular thrombi and thrombo-emboli in lung, kidney, and liver [61]. A study focusing on COVID-19-driven reactive changes in the liver found pathological heterogeneity. Across the 4 patients analyzed, thrombotic sinusoiditis with rich fibrin deposits/aggregates was a consistent feature that also included a mixture of red blood cells, leukocytes, and 'ground glass' hepatocytes [52]. Fibrin-rich deposits have also been reported in cardiac tissue both coincident with and independent from evidence of myocarditis [60, 61].

The potential pathological consequences of extravascular fibrin deposits in COVID-19 disease progression and severity remain largely speculative. One potential mechanism is that the accumulation of fibrin in complex with other protein and non-protein component secretions (*e.g.*, mucous) in the airspace could both impair gas exchange within alveoli and mediate lung epithelial cell injury. Fibrin has been shown to bind to and impair surfactant protein function in acute lung injury models [62]. Fibrin has been observed in complex with surfactant, mucous, and cellular infiltrates in multiple forms of lung injury, including in patients who developed pneumonia secondary to COVID-19 infection and died [63].

A second possible mechanism by which fibrin accumulation in the airspace may influence lung function and patient outcome in COVID-19 is by serving as a local driver of inflammatory cell function and subsequent tissue injury following SARS-CoV-2 infection. In a number of inflammatory disease models, local extravascular fibrin deposits have been shown to be a spatially defined cue signaling inflammatory cell activation that promotes tissue injury. A primary mechanism of action is fibrin engagement of innate immune cells *via* the leukocyte integrin receptor $\alpha_M\beta_2$. Indeed, Fib$\gamma^{390–396A}$ mice expressing a mutant form of fibrinogen, which has normal clotting function but lacks the $\alpha_M\beta_2$-binding motif, have been found to be protected in models of inflammatory arthritis, neuromuscular disease, colitis, and others [56, 64–66]. Intriguingly, these same Fib$\gamma^{390–396A}$ mice incurred more severe disease in a model of *S. aureus* peritonitis bacterial infection [67]. Here, Fib$\gamma^{390–396A}$ mice displayed compromised host defense characterized by diminished ability to eliminate the microbes within the peritoneal cavity, leading to enhanced bacterial dissemination [68]. These findings are consistent with fibrin driving innate immune cell function, as macrophages were shown to be a primary effector cell mediating the bacteria-killing mechanism [68]. The ultimate contribution of fibrin-immune cell interactions remains to be determined. Primarily, adaptive immune cells (*e.g.*, CD4+, CD8+ T cells and B cells) mediate viral clearance [69]. However, unchecked innate immune cell function appears to mediate lung tissue injury following SARS-CoV-2 infection. Given the capacity of the fibrin matrix to engage innate immune cells and drive their effector function, we postulate that fibrin deposits in the airspace of COVID-19 patients exacerbate neutrophil and macrophage inflammatory function to drive lung injury (Fig. 3). However, definitive experimental evidence is currently lacking.

Another possible context to consider extravascular fibrin deposits is in the condition termed 'long COVID' [70, 71]. A number of post-acute sequelae of SARS-CoV-2 infection have come to define long COVID, including neurocognitive defects [72, 73]. Extravascular fibrin deposits drive neuroinflammatory diseases of the central nervous system, including cerebral

amyloid angiopathy and Alzheimer's Disease [74–77]. Fibrin-driven pathogenesis in these disease states was linked to the formation of lysis-resistant fibrin-amyloid complexes [77, 78]. Fibrin within the brain parenchyma can drive activation of microglial cells and invading monocyte/macrophages, leading to brain tissue damage [79]. Whether these same mechanisms contribute to long COVID remains to be established.

2.5. Fibrin Degradation in COVID-19

The identification of high levels of the FDP D-dimer was one of the first prognostic markers of poor outcomes in COVID-19 patients [42]. The initial observation has been confirmed through multiple follow-up reports. Studies have documented dramatic increases in D-dimer levels, especially in critically ill patients [43] and in non-survivors [42], whereas levels of D-dimer in non-critically ill patients [43] and in survivors [42] remain relatively stable. Notably, high D-dimer levels are not unique to severe COVID-19, but have been associated with the severity of other inflammatory and infectious diseases, including sepsis [80, 81]. In a direct comparison of patients with COVID-19 or sepsis, D-dimer levels were actually higher in sepsis patients in the ICU than in patients with either moderate or severe COVID-19 [41]. The precise pathophysiological meaning and consequences of elevated D-dimer in COVID-19 remain largely undefined. As elevated D-dimer is indicative of both fibrin deposition and breakdown (fibrinolysis), understanding the balance of fibrin formation (*i.e.,* coagulation activity) *vs.* breakdown is critical for interpreting D-dimer as a biomarker in COVID-19. The association of COVID-19 with thrombosis and the presence of persistent fibrin deposits in multiple tissues of severe COVID-19 patients suggest that fibrin formation outpaces fibrin clearance in severe COVID-19 (Fig. 2). Therefore, it might be important to monitor both fibrinogen and D-dimer levels in tandem [82] with the hypothesis that 1) an increase in fibrinogen without an increase in D-dimer may signal a transition to a state of fibrin persistence, as has been seen in severe COVID-19, whereas 2) an increase in D-dimer accompanied by steady state or decreased fibrinogen levels signals a homeostatic balance of fibrin formation and clearance in mild or recoverable disease (Fig. 3).

Persistent fibrin deposits, despite elevated D-dimer, suggest a plasmin(ogen) activation insufficiency in severe COVID-19, but what is the molecular basis? Direct analysis of plasmin generation in plasma from COVID-19 patients revealed preserved and even increased plasmin generation potential as marked by an accelerated time to peak, peak level, and endogenous plasmin potential [41]. Thus, it appears that circulating plasminogen itself is not consumed in COVID-19. High PAI-1 levels, which have been documented in COVID-19 patient plasma, may inhibit fibrinolysis and enhance fibrin persistence, enabling micro- or macrovascular thrombosis and/or the accumulation of extravascular fibrin deposits [34, 83, 84]. The endotheliopathy that accompanies COVID-19 may enhance fibrin persistence through multiple mechanisms, including 1) increased release of PAI-1, 2) shedding of thrombomodulin that enhances TAFI activation, and 3) suppression of tPA release, which compromises local mechanisms for limiting fibrin deposition [7, 85]. However, additional studies are required to better define the link between endothelial dysfunction in COVID-19 and perturbation of fibrinolysis.

The concept that COVID-19 patients show evidence of both robust plasmin generation potential in plasma while simultaneously displaying evidence of persistent fibrin deposits may relate to the deposition of fibrin in two distinct compartments (*i.e.*, intravascular and extravascular spaces). Increased levels of D-dimers are generally the end-products of coagulation followed by fibrinolysis [7]. However, the origin of D-dimers in patients with COVID-19 might be different. Degradation of fibrin in the intravascular compartment would be expected to be well represented in a plasma D-dimer analysis. However, the breakdown of fibrin in the alveoli and lung parenchyma may generate D-dimers that do not relocate to the bloodstream or relocate with a different pharmacokinetic pattern [7, 86]. Further, extravascular fibrin may be subject to modifications (*e.g.*, modified by unique reactive oxygen species) or may be in complex with proteins (*e.g.*, surfactants) that alter its susceptibility to lysis and/or change the composition of FDPs generated [87–89]. These non-traditional FDPs may be less susceptible to normal fibrin clearance mechanisms, leading to perturbed tissue healing and regenerative processes.

3. THERAPIES TARGETING COAGULATION AND FIBRINOLYTIC PROTEINS IN COVID-19

The emergence of SARS-CoV-2 variants presents a challenge for any therapeutic strategy directed specifically at the virus (*e.g.*, vaccines). Targeting host factors that play a central role in pathogenesis offers the potential significant benefit of maintaining efficacy for mitigating the manifestation of disease across variants. Accordingly, while the majority of ongoing clinical trials are testing antiviral drugs (*e.g.*, remdesivir and lopinavir) [90, 91], there is some experimental evidence that targeting fibrin in the airspace can preserve lung function.

Treatments with anticoagulants (*e.g.*, antithrombin, hirudin, factor Xa inhibitors), active site-inactivated factor VIIa, or TFPI to reduce thrombin generation are potential methods for blocking fibrin deposition [92–95]. Each of these treatments has demonstrated efficacy in animal models of acute lung injury *via* improved lung histology, preserved gas exchange, reduced edema formation, and prolonged survival time of challenged animals [43, 96, 97]. Investigation into the efficacy of such agents for COVID-19 patients is ongoing [98]. Ongoing studies of SARS-CoV-2 infection in mice carrying genetic deletion or mutation of fibrinogen may ultimately support a therapeutic strategy of targeting fibrinogen. To this end, it is notable that a selective fibrinogen-lowering agent was recently described and shown to successfully suppress a number of fibrin(ogen)-driven pathologies in mouse models [99]. These findings offer a tangible pathway forward for the translation of fibrinogen lowering as a possible treatment strategy for COVID-19.

Some studies have investigated the use of fibrinolytics, including uPA, tPA and plasmin, to clear existing fibrin from the airways [100]. The first recombinantly produced protein tPA (Alteplase), initially approved to treat acute myocardial infarction patients [101], has been investigated in phase 1 and 2 clinical trials (NCT04357730) for patients with COVID-19-induced respiratory failure in ARDS [102]. Bolus dosing of tPA followed by therapeutic heparin administration was found to be safe and improve oxygenation; however, differences

in clinical outcome could not be detected due to the low number of participants. A phase 3 trial has been initiated to determine the efficacy of tPA in treating respiratory failure in patients with COVID-19 (NCT04453371). Since systemic administration of tPA may increase bleeding risk, local administration of tPA to the lungs *via* a nebulizer may dissolve fibrin without enhancing bleeding risk. This may be particularly important in the late stages of the disease process [13, 98]. A phase 2 clinical trial of nebulized tPA for plastic bronchitis is ongoing (NCT02315898).

CONCLUSION

More than two years of thorough investigation of clinical parameters associated with patient outcome and autopsy studies have shed some light on the pathogenesis of COVID-19. Biomarkers have been identified to recognize patients with a worse prognosis for early treatment. Fibrinogen, fibrin deposition in intravascular and extravascular compartments, and FDPs all appear to be biomarkers of severe COVID-19 as well as active players in pathogenic mechanisms, leading to poor patient outcomes. The development of therapeutics targeting fibrin(ogen) and fibrinolysis is still in an early phase. Additional studies are required to define the causative mechanisms by which perturbations in fibrinogen, fibrin, and fibrinolytic pathways contribute to acute disease and the increasingly prevalent ‘long COVID’. Furthermore, new variants of SARS-CoV-2 may impose unique hemostatic changes and serious complications different than those manifested by the parental strain of the virus. Overall, given the consistent finding that changes in fibrin(ogen) accompany worse patient outcomes, a better understanding of changes in coagulation, inflammation, and fibrinolysis that accompany COVID-19 is required. Indeed, a fundamental understanding of the contribution of fibrinogen to parental SARS-CoV-2 will likely provide a significant benefit in defining the pathophysiology of new SARS-CoV-2 variants as well as completely new coronaviruses that emerge in the human population.

FUNDING

This paper was supported by a grant from the National Institutes of Health and National Heart Lung Blood Institute (R01 HL160046).

LIST OF ABBREVIATIONS

ALI	Acute lung injury
APR	Acute phase response
CAC	COVID-19-associated coagulopathy
COVID-19	Coronavirus disease 2019
DIC	Disseminated intravascular coagulation
ECMO	Extracorporeal membrane oxygenation
FDP	Fibrin degradation product
ICU	Intensive care unit

IL	Interleukin
MCP-1	Monocyte chemoattractant protein-1
MIP1α	Macrophage inflammatory protein-1α
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
TAFI	Thrombin-activatable fibrinolysis inhibitor
TFPI	Tissue factor pathway inhibitor
TNFα	Tumor necrosis factor α
tPA	Tissue plasminogen activator
uPA	Urokinase plasminogen activator

REFERENCES

[1]. Gorbalenya AE, Baker SC, Baric RS, et al. The species severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020; 5(4): 536–44. 10.1038/s41564-020-0695-z [PubMed: 32123347]

[2]. Dyson L, Hill EM, Moore S, et al. Possible future waves of SARS-CoV-2 infection generated by variants of concern with a range of characteristics. Nat Commun 2021; 12(1): 5730. 10.1038/s41467-021-25915-7 [PubMed: 34593807]

[3]. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: A systematic review. Ann Intern Med 2021; 174(5): 655–62. 10.7326/M20-6976 [PubMed: 33481642]

[4]. Wunsch H Mechanical ventilation in COVID-19: Interpreting the current epidemiology. Am J Respir Crit Care Med 2020; 202(1): 1–4. 10.1164/rccm.202004-1385ED [PubMed: 32402207]

[5]. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145–7. 10.1016/j.thromres.2020.04.013 [PubMed: 32291094]

[6]. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Med 2020; 46(6): 1089–98. 10.1007/s00134-020-06062-x [PubMed: 32367170]

[7]. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol 2021; 113(1): 45–57. 10.1007/s12185-020-03029-y [PubMed: 33161508]

[8]. Kaptein FHJ, Stals MAM, Grootenboers M, et al. Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave. Thromb Res 2021; 199: 143–8. 10.1016/j.thromres.2020.12.019 [PubMed: 33535120]

[9]. Jenner WJ, Gorog DA. Incidence of thrombotic complications in COVID-19: On behalf of ICODE: The international COVID-19 thrombosis biomarkers colloquium. J Thromb Thrombolysis 2021; 52(4): 999–1006. 10.1007/s11239-021-02475-7 [PubMed: 34047938]

[10]. Hadique S, Badami V, Sangani R, et al. Coagulation studies are not predictive of hematological complications of COVID-19 infection. TH Open 2022; 6(1): e1–9. 10.1055/s-0041-1742225 [PubMed: 35059556]

[11]. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. Res Pract Thromb Haemost 2020; 4(7): 1178–91. 10.1002/rth2.12439 [PubMed: 33043231]

[12]. Maiese A, Manetti AC, La Russa R, et al. Autopsy findings in COVID-19-related deaths: A literature review. Forensic Sci Med Pathol 2021; 17(2): 279–96. 10.1007/s12024-020-00310-8 [PubMed: 33026628]

[13]. Zanza C, Racca F, Longhitano Y, et al. Risk management and treatment of coagulation disorders related to COVID-19 infection. Int J Environ Res Public Health 2021; 18(3): 18. 10.3390/ijerph18031268

[14]. Hariri LP, North CM, Shih AR, et al. Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory sydrome and H1N1 influenza: A systematic review. Chest 2021; 159(1): 73–84. 10.1016/j.chest.2020.09.259 [PubMed: 33038391]

[15]. Campbell RA, Hisada Y, Denorme F, et al. Comparison of the coagulopathies associated with COVID-19 and sepsis. Res Pract Thromb Haemost 2021; 5(4): e12525. 10.1002/rth2.12525 [PubMed: 34027292]

[16]. Casini A, Neerman-Arbez M, de Moerloose P. Heterogeneity of congenital afibrinogenemia, from epidemiology to clinical consequences and management. Blood Rev 2021; 48: 100793. 10.1016/j.blre.2020.100793 [PubMed: 33419567]

[17]. Kamphuisen PW, Eikenboom JC, Vos HL, et al. Increased levels of factor VIII and fibrinogen in patients with venous thrombosis are not caused by acute phase reactions. Thromb Haemost 1999; 81(5): 680–3. 10.1055/s-0037-1614553 [PubMed: 10365736]

[18]. Maners J, Gill D, Pankratz N, et al. A Mendelian randomization of γ' and total fibrinogen levels in relation to venous thromboembolism and ischemic stroke. Blood 2020; 136(26): 3062–9. 10.1182/blood.2019004781 [PubMed: 33367543]

[19]. Prasad JM, Gorkun OV, Raghu H, et al. Mice expressing a mutant form of fibrinogen that cannot support fibrin formation exhibit compromised antimicrobial host defense. Blood 2015; 126(17): 2047–58. 10.1182/blood-2015-04-639849 [PubMed: 26228483]

[20]. Luyendyk JP, Schoenecker JG, Flick MJ. The multifaceted role of fibrinogen in tissue injury and inflammation. Blood 2019; 133(6): 511–20. 10.1182/blood-2018-07-818211 [PubMed: 30523120]

[21]. Miri C, Charii H, Bouazzaoui MA, et al. D-dimer level and diabetes in the COVID-19 infection. Clin Appl Thromb Hemost 2021; 27: 10760296211045902. 10.1177/10760296211045902 [PubMed: 34590493]

[22]. Chang R, Elhusseiny KM, Yeh YC, Sun WZ. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis. PLoS One 2021; 16(2): e0246318. 10.1371/journal.pone.0246318 [PubMed: 33571301]

[23]. Landini L, Leone A. Smoking and hypertension: Effects on clinical, biochemical and pathological variables due to isolated or combined action on cardiovascular system. Curr Pharm Des 2011; 17(28): 2987–3001. 10.2174/138161211798157694 [PubMed: 21861837]

[24]. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis 2020; 50(1): 54–67. 10.1007/s11239-020-02134-3 [PubMed: 32415579]

[25]. Wolberg AS, Campbell RA. Thrombin generation, fibrin clot formation and hemostasis. Transfus Apheresis Sci 2008; 38(1): 15–23. 10.1016/j.transci.2007.12.005

[26]. Doolittle RF. Fibrinogen and fibrin. Annu Rev Biochem 1984; 53(1): 195–229. 10.1146/annurev.bi.53.070184.001211 [PubMed: 6383194]

[27]. Kattula S, Byrnes JR, Wolberg AS. Fibrinogen and fibrin in hemostasis and thrombosis. Arterioscler Thromb Vasc Biol 2017; 37(3): e13–21. 10.1161/ATVBAHA.117.308564 [PubMed: 28228446]

[28]. Kattula S, Byrnes JR, Martin SM, et al. Factor XIII in plasma, but not in platelets, mediates red blood cell retention in clots and venous thrombus size in mice. Blood Adv 2018; 2(1): 25–35. 10.1182/bloodadvances.2017011890 [PubMed: 29344582]

[29]. Wolberg AS. Determinants of fibrin formation, structure, and function. Curr Opin Hematol 2012; 19(5): 349–56. 10.1097/MOH.0b013e32835673c2 [PubMed: 22759629]

[30]. Byrnes JR, Duval C, Wang Y, et al. Factor XIIIa-dependent retention of red blood cells in clots is mediated by fibrin α-chain cross-linking. Blood 2015; 126(16): 1940–8. 10.1182/blood-2015-06-652263 [PubMed: 26324704]

[31]. Davie EW, Fujikawa K, Kisiel W. The coagulation cascade: Initiation, maintenance, and regulation. Biochemistry 1991; 30(43): 10363–70. 10.1021/bi00107a001 [PubMed: 1931959]

[32]. Mast AE, Wolberg AS, Gailani D, et al. SARS-CoV-2 suppresses anticoagulant and fibrinolytic gene expression in the lung. eLife 2021; 10: e64330. 10.7554/eLife.64330 [PubMed: 33683204]

[33]. Shetty S, Padijnayayveetil J, Tucker T, Stankowska D, Idell S. The fibrinolytic system and the regulation of lung epithelial cell proteolysis, signaling, and cellular viability. Am J Physiol Lung Cell Mol Physiol 2008; 295(6): L967–75. 10.1152/ajplung.90349.2008 [PubMed: 18836029]

[34]. Landau N, Shoenfeld Y, Negru L, Segal G. Exploring the pathways of inflammation and coagulopathy in COVID-19: A narrative tour into a viral rabbit hole. Int Rev Immunol 2022; 41(4): 414–22. 10.1080/08830185.2021.1993211 [PubMed: 34678120]

[35]. Mosnier LO, Meijers JCM, Bouma BN. The role of protein S in the activation of thrombin activatable fibrinolysis inhibitor (TAFI) and regulation of fibrinolysis. Thromb Haemost 2001; 86(4): 1040–6. 10.1055/s-0037-1616531 [PubMed: 11686322]

[36]. Grobler C, Maphumulo SC, Grobbelaar LM, et al. Covid-19: The Rollercoaster of Fibrin(Ogen), D-dimer, von willebrand factor, P-selectin and their interactions with endothelial cells, platelets and erythrocytes. Int J Mol Sci 2020; 21(14): 21. 10.3390/ijms21145168

[37]. Jürgensen HJ, Silva LM, Krigslund O, et al. CCL2/MCP-1 signaling drives extracellular matrix turnover by diverse macrophage subsets. Matrix Biol Plus 2019; 1: 100003. 10.1016/j.mbplus.2019.03.002 [PubMed: 33543002]

[38]. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? Atherosclerosis 2000; 148(2): 209–14. 10.1016/S0021-9150(99)00463-3 [PubMed: 10657556]

[39]. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: The vasculature unleashed. Nat Rev Immunol 2020; 20(7): 389–91. 10.1038/s41577-020-0343-0 [PubMed: 32439870]

[40]. Fish RJ, Neerman-Arbez M. Fibrinogen gene regulation. Thromb Haemost 2012; 108(3): 419–26. [PubMed: 22836683]

[41]. Bouck EG, Denorme F, Holle LA, et al. COVID-19 and sepsis are associated with different abnormalities in plasma procoagulant and fibrinolytic activity. Arterioscler Thromb Vasc Biol 2021; 41(1): 401–14. [PubMed: 33196292]

[42]. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382(18): 1708–20. 10.1056/NEJMoa2002032 [PubMed: 32109013]

[43]. Guo Z, Sun L, Li B, et al. Anticoagulation management in severe coronavirus disease 2019 patients on extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth 2021; 35(2): 389–97. 10.1053/j.jvca.2020.08.067 [PubMed: 32994131]

[44]. Neethling C, Calligaro G, Miller M, Opie JJS. The evolution of clot strength in critically-ill COVID-19 patients: A prospective observational thromboelastography study. Thromb J 2021; 19(1): 83. 10.1186/s12959-021-00331-5 [PubMed: 34742307]

[45]. Rostami M, Khoshnegah Z, Mansouritorghabeh H. Hemostatic system (Fibrinogen Level, D-Dimer, and FDP) in severe and non-severe patients with COVID-19: A systematic review and meta-analysis. Clin Appl Thromb Hemost 2021; 27: 10760296211010 973.

[46]. Parzy G, Daviet F, Puech B, et al. Venous thromboembolism events following venovenous extracorporeal membrane oxygenation for severe acute respiratory syndrome coronavirus 2 based on CT scans. Crit Care Med 2020; 48(10): e971–5. 10.1097/CCM.0000000000004504 [PubMed: 32618700]

[47]. Vandenbriele C, Gorog DA. Screening for venous thromboembolism in patients with COVID-19. J Thromb Thrombolysis 2021; 52(4): 985–91. 10.1007/s11239-021-02474-8 [PubMed: 34019231]

[48]. Doyle AJ, Hunt BJ, Sanderson B, et al. A comparison of thrombosis and hemorrhage rates in patients with severe respiratory failure due to coronavirus disease 2019 and influenza requiring extracorporeal membrane oxygenation. Crit Care Med 2021; 49(7): e663–72. 10.1097/00003246-198607000-00021 [PubMed: 33861545]

[49]. Machlus KR, Cardenas JC, Church FC, Wolberg AS. Causal relationship between hyperfibrinogenemia, thrombosis, and resistance to thrombolysis in mice. Blood 2011; 117(18): 4953–63. 10.1182/blood-2010-11-316885 [PubMed: 21355090]

[50]. Wygrecka M, Birnhuber A, Seeliger B, et al. Altered fibrin clot structure and dysregulated fibrinolysis contribute to thrombosis risk in severe COVID-19. Blood Adv 2022; 6(3): 1074–87. 10.1182/bloodadvances.2021004816 [PubMed: 34861681]

[51]. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. EClinicalMedicine 2020; 24: 100434. 10.1016/j.eclinm.2020.100434 [PubMed: 32766543]

[52]. Congiu T, Demontis R, Cau F, et al. Scanning electron microscopy of lung disease due to COVID-19 - a case report and a review of the literature. Eur Rev Med Pharmacol Sci 2021; 25(24): 7997–8003. [PubMed: 34982463]

[53]. Fanni D, Cerrone G, Saba L, et al. Thrombotic sinusoiditis and local diffuse intrasinusoidal coagulation in the liver of subjects affected by COVID-19: The evidence from histology and scanning electron microscopy. Eur Rev Med Pharmacol Sci 2021; 25(19): 5904–12. [PubMed: 34661248]

[54]. Khismatullin RR, Ponomareva AA, Nagaswami C, et al. Pathology of lung-specific thrombosis and inflammation in COVID-19. J Thromb Haemost 2021; 19(12): 3062–72. 10.1111/jth.15532 [PubMed: 34538029]

[55]. Borczuk AC, Salvatore SP, Seshan SV, et al. COVID-19 pulmonary pathology: A multi-institutional autopsy cohort from Italy and New York City. Mod Pathol 2020; 33(11): 2156–68. 10.1038/s41379-020-00661-1 [PubMed: 32879413]

[56]. Aleman MM, Byrnes JR, Wang JG, et al. Factor XIII activity mediates red blood cell retention in venous thrombi. J Clin Invest 2014; 124(8): 3590–600. 10.1172/JCI75386 [PubMed: 24983320]

[57]. Kattula S, Sang Y, de Ridder G, et al. Novel venous thromboembolism mouse model to evaluate the role of complete and partial factor XIII deficiency in pulmonary embolism risk. J Thromb Haemost 2021; 19(12): 2997–3007. 10.1111/jth.15510 [PubMed: 34431201]

[58]. Duval C, Baranauskas A, Feller T, et al. Elimination of fibrin γ-chain cross-linking by FXIIIa increases pulmonary embolism arising from murine inferior vena cava thrombi. Proc Natl Acad Sci USA 2021; 118(27): 118. 10.1073/pnas.2103226118

[59]. Bouchard BA, Colovos C, Lawson MA, et al. Increased histone-DNA complexes and endothelial-dependent thrombin generation in severe COVID-19. Vascul Pharmacol 2022; 142: 106950. 10.1016/j.vph.2021.106950 [PubMed: 34871770]

[60]. Brown RE, Wolf DA, Hunter RL, Zhao B, Buja LM. Morphoproteomics and etiopathogenic features of pulmonary COVID-19 with therapeutic implications: A case study. Ann Clin Lab Sci 2020; 50(3): 308–13. [PubMed: 32581017]

[61]. Danics K, Pesti A, Törő K, et al. A COVID-19-association-dependent categorization of death causes in 100 autopsy cases. Geroscience 2021; 43(5): 2265–87. 10.1007/s11357-021-00451-w [PubMed: 34510338]

[62]. Günther A, Ruppert C, Schmidt R, et al. Surfactant alteration and replacement in acute respiratory distress syndrome. Respir Res 2001; 2(6): 353–64. 10.1186/rr86 [PubMed: 11737935]

[63]. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. Lancet Infect Dis 2020; 20(10): 1135–40. 10.1016/S1473-3099(20)30434-5 [PubMed: 32526193]

[64]. Flick MJ, LaJeunesse CM, Talmage KE, et al. Fibrin(ogen) exacerbates inflammatory joint disease through a mechanism linked to the integrin alphaMbeta2 binding motif. J Clin Invest 2007; 117(11): 3224–35. 10.1172/JCI30134 [PubMed: 17932565]

[65]. Steinbrecher KA, Horowitz NA, Blevins EA, et al. Colitis-associated cancer is dependent on the interplay between the hemostatic and inflammatory systems and supported by integrin alpha(M)beta(2) engagement of fibrinogen. Cancer Res 2010; 70(7): 2634–43. 10.1158/0008-5472.CAN-09-3465 [PubMed: 20233870]

[66]. Nasimuzzaman M, Arumugam PI, Mullins ES, et al. Elimination of the fibrinogen integrin $\alpha_M\beta_2$-binding motif improves renal pathology in mice with sickle cell anemia. Blood Adv 2019; 3(9): 1519–32. 10.1182/bloodadvances.2019032342 [PubMed: 31076408]

[67]. Negrón O, Hur WS, Prasad J, et al. Fibrin(ogen) engagement of S. aureus promotes the host antimicrobial response and suppression of microbe dissemination following peritoneal infection. PLoS Pathog 2022; 18(1): e1010227. 10.1371/journal.ppat.1010227 [PubMed: 35041705]

[68]. Flick MJ, Du X, Witte DP, et al. Leukocyte engagement of fibrin(ogen) via the integrin receptor alphaMbeta2/Mac-1 is critical for host inflammatory response in vivo. J Clin Invest 2004; 113(11): 1596–606. 10.1172/JCI20741 [PubMed: 15173886]

[69]. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol 2021; 17(1): 46–64. 10.1038/s41581-020-00357-4 [PubMed: 33077917]

[70]. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ 2021; 374(1648): n1648. 10.1136/bmj.n1648 [PubMed: 34312178]

[71]. Callard F, Perego E. How and why patients made long Covid. Soc Sci Med 2021; 268: 113426. 10.1016/j.socscimed.2020.113426 [PubMed: 33199035]

[72]. Crispo A, Bimonte S, Porciello G, et al. Strategies to evaluate outcomes in long-COVID-19 and post-COVID survivors. Infect Agent Cancer 2021; 16(1): 62. 10.1186/s13027-021-00401-3 [PubMed: 34717691]

[73]. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med 2021; 27(4): 626–31. 10.1038/s41591-021-01292-y [PubMed: 33692530]

[74]. Petersen MA, Ryu JK, Akassoglou K. Fibrinogen in neurological diseases: Mechanisms, imaging and therapeutics. Nat Rev Neurosci 2018; 19(5): 283–301. 10.1038/nrn.2018.13 [PubMed: 29618808]

[75]. Cortes-Canteli M, Mattei L, Richards AT, Norris EH, Strickland S. Fibrin deposited in the Alzheimer's disease brain promotes neuronal degeneration. Neurobiol Aging 2015; 36(2): 608–17. 10.1016/j.neurobiolaging.2014.10.030 [PubMed: 25475538]

[76]. Paul J, Strickland S, Melchor JP. Fibrin deposition accelerates neurovascular damage and neuroinflammation in mouse models of Alzheimer's disease. J Exp Med 2007; 204(8): 1999–2008. 10.1084/jem.20070304 [PubMed: 17664291]

[77]. Cajamarca SA, Norris EH, van der Weerd L, Strickland S, Ahn HJ. Cerebral amyloid angiopathy-linked β-amyloid mutations promote cerebral fibrin deposits *via* increased binding affinity for fibrinogen. Proc Natl Acad Sci USA 2020; 117(25): 14482–92. 10.1073/pnas.1921327117 [PubMed: 32518112]

[78]. Zamolodchikov D, Strickland S. Aβ delays fibrin clot lysis by altering fibrin structure and attenuating plasminogen binding to fibrin. Blood 2012; 119(14): 3342–51. 10.1182/blood-2011-11-389668 [PubMed: 22238323]

[79]. Davalos D, Ryu JK, Merlini M, et al. Fibrinogen-induced perivascular microglial clustering is required for the development of axonal damage in neuroinflammation. Nat Commun 2012; 3(1): 1227. 10.1038/ncomms2230 [PubMed: 23187627]

[80]. Schutte T, Thijs A, Smulders YM. Never ignore extremely elevated D-dimer levels: They are specific for serious illness. Neth J Med 2016; 74(10): 443–8. [PubMed: 27966438]

[81]. Rodelo JR, De la Rosa G, Valencia ML, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. Am J Emerg Med 2012; 30(9): 1991–9. 10.1016/j.ajem.2012.04.033 [PubMed: 22795996]

[82]. Thachil J The protective rather than prothrombotic fibrinogen in COVID-19 and other inflammatory states. J Thromb Haemost 2020; 18(8): 1849–52. 10.1111/jth.14942 [PubMed: 32588535]

[83]. Andrianto Al-Farabi MJ, Nugraha RA Marsudi BA, Azmi Y. Biomarkers of endothelial dysfunction and outcomes in coronavirus disease 2019 (COVID-19) patients: A systematic review and meta-analysis. Microvasc Res 2021; 138: 104224. 10.1016/j.mvr.2021.104224

[84]. Al-Tamimi AO, Yusuf AM, Jayakumar MN, et al. SARS-CoV-2 infection induces soluble platelet activation markers and PAI-1 in the early moderate stage of COVID-19. Int J Lab Hematol 2022; 44(4):712–721. 10.1111/ijlh.13829 [PubMed: 35266284]

[85]. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: Evidence from a single-centre, cross-sectional study. Lancet Haematol 2020; 7(8): e575–82. 10.1016/S2352-3026(20)30216-7 [PubMed: 32619411]

[86]. Hunt FA, Rylatt DB, Hart R-A, Bundesen PG. Serum crosslinked fibrin (XDP) and fibrinogen/fibrin degradation products (FDP) in disorders associated with activation of the coagulation or

fibrinolytic systems. Br J Haematol 1985; 60(4): 715–22. 10.1111/j.1365-2141.1985.tb07476.x [PubMed: 3896298]

[87]. Seeger W, Elssner A, Günther A, Krämer HJ, Kalinowski HO. Lung surfactant phospholipids associate with polymerizing fibrin: Loss of surface activity. Am J Respir Cell Mol Biol 1993; 9(2): 213–20. 10.1165/ajrcmb/9.2.213 [PubMed: 8338688]

[88]. Seeger W, Grube C, Günther A, Schmidt R. Surfactant inhibition by plasma proteins: Differential sensitivity of various surfactant preparations. Eur Respir J 1993; 6(7): 971–7. [PubMed: 8370446]

[89]. Ruppert C, Mahavadi P, Wygrecka M, et al. Recombinant production of a hybrid plasminogen activator composed of surfactant protein B and low-molecular-weight urokinase. Thromb Haemost 2008; 100(6): 1185–92. 10.1160/TH08-03-0142 [PubMed: 19132247]

[90]. Wadaa-Allah A, Emhamed MS, Sadeq MA, et al. Efficacy of the current investigational drugs for the treatment of COVID-19: A scoping review. Ann Med 2021; 53(1): 318–34. 10.1080/07853890.2021.1875500 [PubMed: 33706639]

[91]. Salasc F, Lahlali T, Laurent E, Rosa-Calatrava M, Pizzorno A. Treatments for COVID-19: Lessons from 2020 and new therapeutic options. Curr Opin Pharmacol 2022; 62: 43–59. 10.1016/j.coph.2021.11.002 [PubMed: 34915400]

[92]. Papaj K, Spychalska P, Kapica P, et al. Evaluation of Xa inhibitors as potential inhibitors of the SARS-CoV-2 Mpro protease. PLoS One 2022; 17(1): e0262482. 10.1371/journal.pone.0262482 [PubMed: 35015795]

[93]. Kharma N, Roehrig S, Shible AA, et al. Anticoagulation in critically ill patients on mechanical ventilation suffering from COVID-19 disease, The ANTI-CO trial: A structured summary of a study protocol for a randomised controlled trial. Trials 2020; 21(1): 769. 10.1186/s13063-020-04689-1 [PubMed: 32895056]

[94]. Ge J, Ma Y, Wu Z, Jin J, Sun X. Anticoagulation treatment for patients with coronavirus disease 2019 (COVID-19) and its clinical effectiveness in 2020: A meta-analysis study. Medicine (Baltimore) 2021; 100(47): e27861. 10.1097/MD.0000000000027861 [PubMed: 34964754]

[95]. Jorda A, Siller-Matula JM, Zeitlinger M, Jilma B, Gelbenegger G. Anticoagulant treatment regimens in patients with Covid-19: A meta-analysis. Clin Pharmacol Ther 2022; 111(3): 614–23. 10.1002/cpt.2504 [PubMed: 34862791]

[96]. Miller DL, Welty-Wolf K, Carraway MS, et al. Extrinsic coagulation blockade attenuates lung injury and proinflammatory cytokine release after intratracheal lipopolysaccharide. Am J Respir Cell Mol Biol 2002; 26(6): 650–8. 10.1165/ajrcmb.26.6.4688 [PubMed: 12034563]

[97]. Stroo I, Ding C, Novak A, et al. Inhibition of the extrinsic or intrinsic coagulation pathway during pneumonia-derived sepsis. Am J Physiol Lung Cell Mol Physiol 2018; 315(5): L799–809. 10.1152/ajplung.00014.2018 [PubMed: 30136609]

[98]. Mazilu L, Katsiki N, Nikolouzakis TK, et al. Thrombosis and haemostasis challenges in COVID-19 - Therapeutic perspectives of heparin and tissue-type plasminogen activator and potential toxicological reactions-a mini review. Food Chem Toxicol 2021; 148: 111974. 10.1016/j.fct.2021.111974 [PubMed: 33421462]

[99]. Juang LJ, Hur WS, Silva LM, et al. Suppression of fibrin(ogen)-driven pathologies in disease models through controlled knockdown by lipid nanoparticle delivery of siRNA. Blood 2022; 139(9): 1302–11. 10.1182/blood.2021014559 [PubMed: 34958662]

[100]. Liu C, Ma Y, Su Z, et al. Meta-analysis of preclinical studies of fibrinolytic therapy for acute lung injury. Front Immunol 2018; 9: 1898. 10.3389/fimmu.2018.01898 [PubMed: 30177934]

[101]. Marshall RS. Progress in intravenous thrombolytic therapy for acute stroke. JAMA Neurol 2015; 72(8): 928–34. 10.1001/jamaneurol.2015.0835 [PubMed: 26030910]

[102]. Barrett CD, Moore HB, Moore EE, et al. Study of alteplase for respiratory failure in SARS-CoV-2 COVID-19: A vanguard multicenter, rapidly adaptive, pragmatic, randomized controlled trial. Chest 2022; 161(3): 710–27. 10.1016/j.chest.2021.09.024 [PubMed: 34592318]

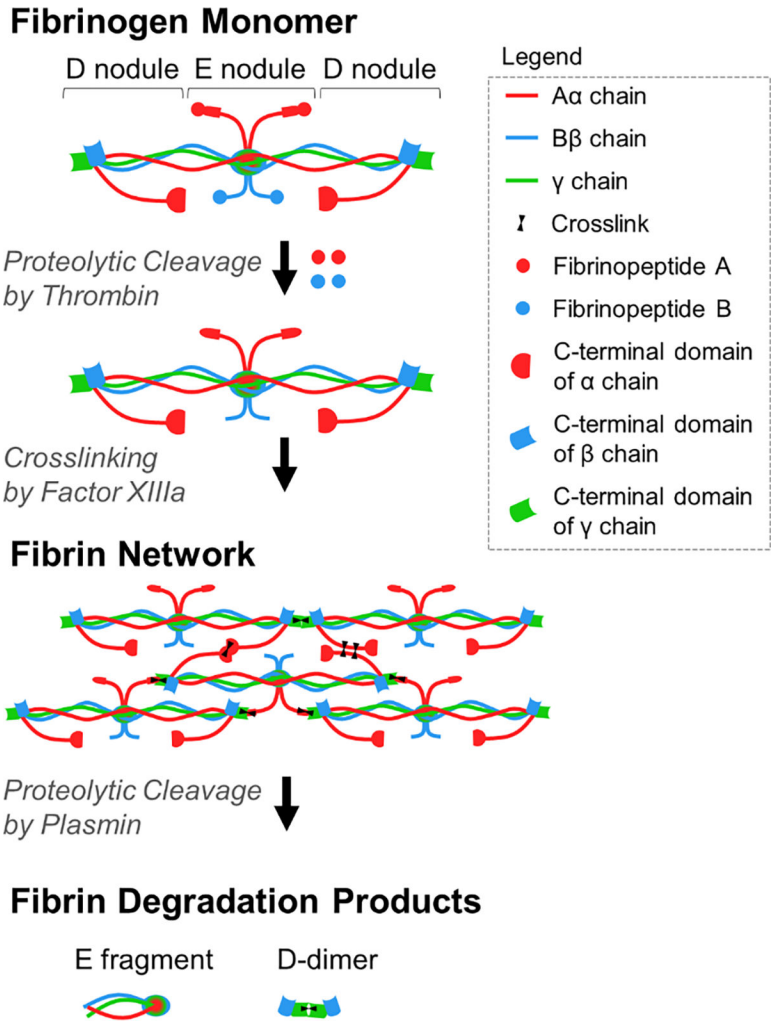

Fig. (1).
Summary of fibrinogen conversion to fibrin matrix and subsequent plasmin-mediated breakdown of fibrin polymer into fibrin degradation products (FDPs), including D-dimer. Figure produced with the assistance of Biorender.

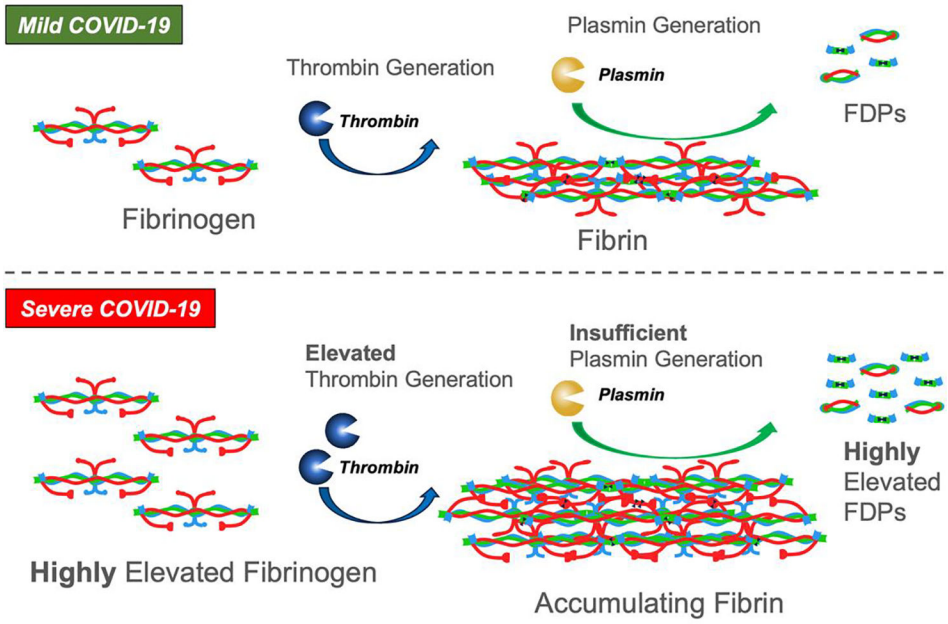

Fig. (2).

Molecular basis of the COVID-19 fibrin(ogen) paradox. Severe COVID-19 is marked by the accumulation of persistent intravascular and extravascular fibrin in tissues (*e.g.,* lung) and significantly elevated D-dimer in circulation. Current data indicate that patients suffering from COVID-19 have exuberant fibrinogen production, thrombin generation, and fibrin formation, but an insufficient counterbalance of plasmin generation necessary for fibrin clearance. Figure produced with the assistance of Biorender.

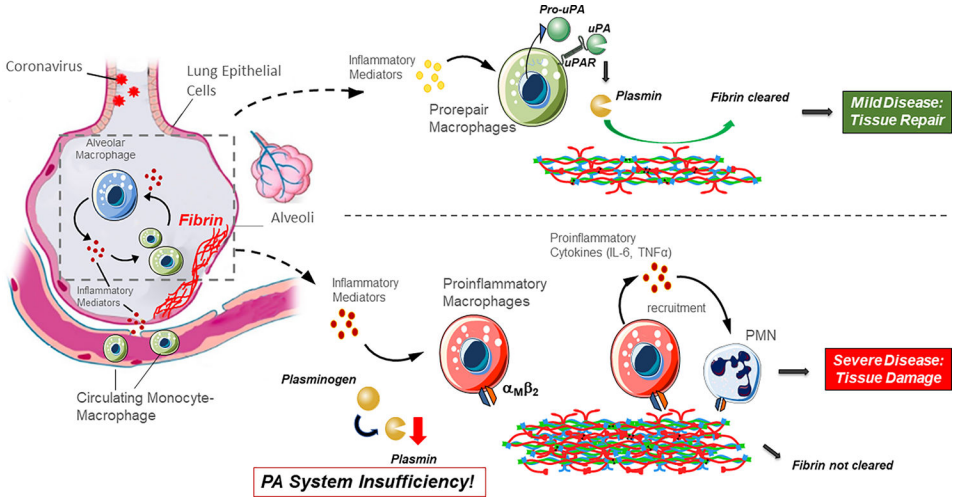

Fig. (3).

Possible mechanism of extravascular fibrin deposition and disease progression in mild and severe COVID-19. In patients who develop a mild or asymptomatic disease, fibrin is readily cleared by plasmin. In patients who develop severe COVID-19, persistent fibrin deposits lead to the activation of proinflammatory immune cells (*e.g.*, macrophages and neutrophils) that promote local tissue damage and destruction. Figure produced with the assistance of Biorender.