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Role of SARS-CoV-2-induced cytokines and growth factors in coagulopathy and thromboembolism

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ABSTRACT
Severe COVID-19 patients frequently present thrombotic complications which commonly lead to multiorgan failure and increase the risk of death. Severe SARS-CoV-2 infection induces the cytokine storm and is often associated with coagulation dysfunction. D-dimer, a hallmark of venous thromboembolism (VTE), is observed at a higher level in the majority of hospitalized COVID-19 patients. The precise molecular mechanism of the disproportionate effect of SARS-CoV-2 infection on the coagulation system is largely undefined. SARS-CoV-2-induced endotheliopathy and induction of cytokines and growth factors (GFs) most likely play important roles in platelet activation, coagulopathy, and VTE. Generally, viral infections lead to systemic inflammation and induction of numerous cytokines and GFs and many of them are reported to be associated with increased VTE. Most importantly, platelets play key thromboinflammatory roles linking coagulation to immune mediators in a variety of infections including response to viral infection. Since the pathomechanism of coagulopathy and VTE in COVID-19 is largely undefined, herein we highlight the association of dysregulated inflammatory cytokines and GFs with thrombotic complications and coagulopathy in COVID-19.

1. Introduction
COVID-19 is caused by a newly identified severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1,2]. SARS-CoV-2 infection is a huge challenge to the healthcare system due to the lack of immunity in the human population. There is no effective antiviral treatment so far available and effective immunization is the only option to combat this pandemic. The majority of SARS-CoV-2-infected individuals are either asymptomatic or develop mild to moderate symptoms like soar-throat, dry cough, fever, and fatigue. However, some cases present severe respiratory conditions like acute respiratory distress syndrome (ARDS) and pneumonia resulting in severe hypoxic conditions and progressive respiratory failure [3,4]. A relatively higher incidence (35–45%) of venous thromboembolism (VTE, thrombi formation followed by dissolution in veins) is reported in critically ill COVID-19 patients [5,6].

Acute respiratory disease progression includes an early infection phase, a pulmonary phase, and a severe hyper-inflammation phase [7]. The binding of SARS-CoV-2 to angiotensin-converting enzyme-2 (ACE2) promotes alveolar epithelial damage that in turn triggers a local immune response by recruiting macrophages and monocytes [8]. Inflammatory cells recruitment help minimizing the infection in the lung and limit immune response, and ultimately help the patient recover. In contrast, a dysfunctional immune response triggers a cytokine storm which induces an extensive inflammatory reaction in the lung of severe cases. The hospitalized COVID-19 patients requiring intensive care mostly present elevated levels of plasma inflammatory cytokines like interleukin-2 (IL-2), IL-6, IL-10, macrophage inflammatory protein 1α (MIP1α) and tumor necrosis factor (TNF) [9]. Most importantly, IL-6 levels in severe cases continue to increase as the disease progresses and are observed comparatively at a higher level in non-survivors vs. survivors [10]. Evolving datasets indicate that cytokines like IL-1β, IL-6, IL-17A, IL-9, transforming growth factor-β (TGF-β) and C-C chemokine ligand 2 (CCL-2) promote thrombosis, and other cytokines such as IL-8, IL-10 and TNF-α help in thrombus resolution [11]. Moreover, growth factors (GFs) including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin growth factor-1 (IGF-1) and TGF-β play critical roles in coagulation dysfunction and are reported to be dysregulated in severe COVID-19.

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Post-viral and other types of infections, endothelial cells release inflammatory markers like TNF, IL-1 and IL-6 which in turn induce tissue factor (TF) expression on the endothelial lining. TF plays a critical role in the activation of the extrinsic coagulation pathway including activation of downstream clotting factors VII, X, II and, protease-activated receptors (PARs) that ultimately trigger pro-inflammatory response [12]. Viral endotoxin-induced TF and plasminogen activator inhibitor-1 (PAI-1) expression on endothelium likely provide a stimulus to thrombin generation which activates PARs and ultimately contribute to thrombosis [13,14]. Moreover, activated endothelial cells expose P-selectin and secrete procoagulant components like thromboxane A2 (TXA2) and von Willebrand factor (VWF) and, antifibrinolytic components like PAI-1 [15,16] which are linked to inflammation. Viral infections like dengue and influenza are also reported to induce inflammation and platelet activation [17]. Not only SARS-CoV-2-infected but also previously reported SARS-CoV-1 or MERS-infected patients displayed thrombi formation in the lung vasculature [18]. Platelets have long been known for their pro-adhesive function and later studies revealed their pro-coagulant roles [19,20]. Besides these, platelets are increasingly recognized as circulating immune cells and identified to play proinflammatory roles particularly upon endothelial damage or activation [21]. A variety of platelet characteristics including surface receptors and secretion of immunoregulatory chemokines, cytokines and GFs help perform this function [22]. Platelets play critical roles in the progression of COVID-19 pathogenesis, however, it is largely unknown how precisely platelet communicate with inflammatory markers and contribute to SARS-CoV-2-mediated inflammation and coagulopathy. In this review, we highlight the cross-talk between platelets, coagulation factors and inflammatory markers and, establish a potential molecular mechanism of thromboembolism in COVID-19.

2. Association of inflammation and coagulopathy in viral pandemics

Coagulation and inflammation are highly connected pathways and work closely in the event of pathogenesis such as injury and invasion of pathogens [23,24]. A variety of severe infections are often associated with excessive inflammation and dysregulated hemostatic balance that promote coagulation dysfunction and thrombosis. Inflammation-induced coagulation activation is characterized by disseminated intravascular coagulation (DIC) which is associated with enhanced intravascular fibrin generation and deposition, and impaired fibrin degradation [25,26]. Such excessive activation of the coagulation pathway is accompanied by inhibition of anticoagulant thrombomodulin, protein S, protein C and components of the fibrinolytic pathway [26].

Early reports suggest patients with severe COVID-19 frequently present DIC [27,28] and severe inflammatory response (cytokine storm) [29]. The coagulopathy in COVID-19 is characterized by elevated levels of fibrinogen and D-dimer with mild prolongation in prothrombin and activated partial thromboplastin times [27,30]. Studies suggest that induction of inflammatory response likely plays critical roles in the modulation of coagulation factors expression which possibly induces VTE. Therefore, a correlation between the pattern of inflammatory markers dysregulation and aberrant coagulation factor levels in a variety of viral pandemics is required.

2.1. SARS-CoV-1 and MERS-CoV –induced cytokine and growth factor dysregulation and coagulopathy

Similar to COVID-19 pathogenesis, SARS-CoV-1 also induces a cytokine storm, coagulopathy and deep vein thrombosis (DVT) [18, 31–33] though limited clinical data is available in comparison to COVID-19. The postmortem analysis revealed that the SARS-CoV-1 induces prothrombotic effects mainly in the pulmonary vasculature [18, 31,32]. The pulmonary thrombosis in SARS-CoV-1 infected patients was accompanied by a low count of CD4 and CD8 positive T cells which were likely associated with disease severity and adverse outcomes [31]. Studies employing in vitro model revealed the increased expression of procoagulant genes including factors II, III and X, fibrinogen, and serine protease inhibitors (SERPINs) in SARS-CoV-1 infected peripheral blood mononuclear cells (PBMCs) [34]. Interestingly, dysregulation of coagulation factors was accompanied by upregulation of chemokines including CCL4, CCL20, CCL22, CCL25, and CCL27, and their receptors (CCR4 and CCR7) along with IL8 and IL17. Additionally, the thromboxane synthase (TBXAS) gene and Toll-like receptor 9 (TLR9) were also found to be upregulated in the infected cells [34]. Consistent with these observations, SARS-CoV-1 infected hepatoma cells displayed an increased expression of tissue factor pathway inhibitor 2 (TFPI2), PAI1, THBS1 and phospholipid scramble 1 (PLSCR1) which were accompanied by induction of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), TGF-β, TNF-α, IL-1β, IL-8 and a variety of chemokine ligands CXCL1, −2, −3, −5, −6, and −10 [35]. Studies with SARS-CoV-1 infected mice models further validated the abnormal expression of procoagulant genes such as thrombin, VII, XI, XII, and plasminogen activators especially in those who had fatal consequences [36,37]. Moreover, SARS-CoV-1 infection induces the expression of well-known pro-inflammatory markers IL-1β, IL-6 and TNF-α [36]. Another in vitro study revealed the dysregulation of inflammatory markers in SARS-CoV-1 infected primary macrophages. This study reported a minimal induction of beta-interferon (IFN-β), however, elevated expression of chemokines such as CXCL10/IFN-γ-inducible protein-10 and CCL2/monocyte chemotactic protein-1 (MCP-1) [38]. In contrast, Okabayashi et al., [39] reported that SARS-CoV-1 induces the expression of a variety of IFN isoforms in CACO2 cells. Additionally, SARS-CoV-1 mediated induction of cytokine IL6 and, TLR4 and TLR9 was also observed in CACO2 cells [39] and, CCL3, CCL5, CCL2, and CCL10 in infected airway epithelial cells [40]. Patients infected with SARS-CoV-1, particularly the severe ones, have shown the cytokine storm which includes induction of pro-inflammatory cytokines TGF-β, IFN-γ, IL-1, IL-6 and IL-12, and chemokines IL-8, CCL2, CXCL9, and CXCL10 [33,41,42]. Moreover, an anti-inflammatory cytokine, IL-10 was profoundly downregulated in severe SARS patients [43]. Interestingly, a higher level of IFN and IFN-stimulated chemokines (CCL2, and CXCL10) was correlated with SARS-CoV-1-mediated deaths [44,45]. Though none of these inflammatory markers (IFN, CCL2, and CXCL10) are reported to be directly associated with coagulopathy, SARS-CoV-1 infected PBMCs, as stated above, have shown increased levels of procoagulant proteins along with pro-inflammatory markers [34,46].

Inflammatory response to MERS-CoV was largely similar to SARS-CoV-1 infection. As observed in SARS-CoV-1 infection, the expression levels of cytokine IL-1β, IL-6 and IL-8 were also upregulated in the MERS-CoV infected alveolar cells [47]. Clinical studies revealed the induction of pro-inflammatory markers IL-6, IL-8, IFN-γ, CXCL-10, and CCL5 which were associated with an increased number of neutrophils and monocytes particularly in severe MERS cases [48,49]. These studies have clearly shown the higher levels of some common serum pro-inflammatory markers both in SARS as well as MERS cases. Dysregulated pro-inflammatory cytokines play important roles in the activation of the coagulation system and inhibition of important physiological anticoagulants [50]. As discussed above induction of pro-inflammatory markers particularly, IL-1β, IL-6 and IL-8 have been consistently identified as an important SARS and MERS infection. It was also observed that roles are quite prominent in the modulation of coagulation profile and dysfunction of platelets and erythrocytes. All three ILs have been reported to increase platelet activation and spreading. Moreover, erythrocytes distortion and apoptosis were observed particularly in the presence of IL-8. Studies have shown that IL-8 had the most prominent effect on coagulation compared to IL-1β and IL-6 in thromboelastography [51,52]. Another study has shown that IL-6 may activate coagulation but have a minimum effect on fibrinolysis [53]. When it comes to
IL-1β, it regulates platelets aggregation through its receptor IL-1R1 expressed on platelets [54].

3. SARS-CoV-2 induced inflammation and coagulopathy

SARS-CoV-2 primarily invades alveolar epithelial cells and induces early immune reactions which subsequently orchestrate inflammatory and coagulation processes. Early immune response to the virus and virus-derived products including secretion of type 1 interferons (IFNs) eventfully trigger the host inflammatory responses [55]. This leads to activation and infiltration of various innate and adaptive immune cells to the site of infection leading to hyper inflammation. Production and release of proinflammatory mediators by the epithelial, endothelial, and infiltrated immune cells eventually contribute to lung tissue damage and coagulopathy (Fig. 1). Several inflammatory mediators are linked to coagulation factor regulation, thereby interplay between these two factors play a critical role in COVID-19 disease manifestation and severity.

a. SARS-CoV-2 mediated alveolar epithelium and endothelial damage, and inflammation

Infection of alveolar epithelial cells by SARS-CoV-2 triggers the production of proinflammatory mediators including chemokines and cytokines. Chemokines promote infiltration of innate monocyte/macrophages, natural killer (NK) cells, dendritic cells and neutrophils, and adaptive immune cells (CD4+ and CD8+ T cells) to the site of infection [56], thereby contributing to the cytokine storm in severe COVID-19 patients [13,57]. One of the early pro-inflammatory cytokines released by the epithelial cells is recognized by the inflammatory myeloid cells such as monocyte/macrophages and dendritic cells leading to inflammasome activation to trigger an inflammatory cascade.

Epithelial cells are severely damaged by the virus as well as inflammatory mediators produced by immune cells in the lung. Some of the major cytokines such as IL-1α and IFNs are released to extracellular space, and that further damage adjacent microvascular endothelial cells. Therefore, the crosstalk between epithelial and endothelial cells seems to play a vital role in lung tissue damage [57]. SARS-CoV-2 is efficiently replicate in the lung epithelial cells resulting in high viral load, inflammation, and cell damage. In addition, SARS-CoV-2 damaged alveolar epithelium releases urokinase and PAI-1 to activate coagulation pathways leading to fibrin deposition [58]. Other inflammatory mediators such as TGF-β, PDGF and IL-6 released by the virus-infected epithelium, immune cells, and myofibroblast may contribute to lung fibrosis.

The major functions of endothelium include serving as a mechanical barrier between circulating blood and the basement membrane, controlling the vascular tone, and immunomodulation. SARS-CoV-2 has been shown to infect vascular endothelial cells both in vivo and ex vivo [59], thus affect multiple organs through virus dissemination after entering the systemic circulation. Virus infection of vascular endothelial cells has been confirmed recently in an autopsy case study [60]. It suggests that these cells are susceptible to virus infection and contribute to inflammation either directly or

![Fig. 1. SARS-CoV-2 -induced inflammation and thromboembolism: The schematic diagram shows the alveolar epithelial cell damage-induced secretion of cytokines and chemokines orchestrated immune reactions including infiltration of various immune cell types including macrophages (MP), neutrophils (NP), natural killer cells (NK) and T-cells to the site of infection or inflammation. Moreover, in addition to infection of alveolar epithelial cells, SARS-CoV-2 can also activate immune cells in general. The infiltration and activation of immune cells enhance the release of inflammatory mediators which are mainly responsible for causing the cytokine storm. Induction of inflammatory reaction activates endothelial cells as well, and triggers the tissue factor (TF) expression on a variety of cells and, at the same time, attenuates the level of plasma tissue factor pathway inhibitor (TFPI) which induces TF pathway activation and thrombin generation. SARS-CoV-2-induced systemic inflammation can trigger the release of P-selectin and soluble CD40 ligand (sCD40L) which, along with thrombin, activates platelets that further enhances the levels of thrombin, P-selectin and sCD40L and provide positive feedback to the platelet activation and thrombus formation. The attenuated level of factor XIII (FXIII) in severe COVID-19 can destabilize the clot and induce venous thromboembolism (VTE). Moreover, induction of tissue plasminogen activator (tPA), a known regulator of thrombus dissolution (fibrinolysis), potentially leads to hyperfibrinolysis and excessive D-dimer formation as observed in COVID-19 patients.](https://example.com/fig1.png)
indirectly via inflammatory mediators released by other cells such as epithelial and immune cells [61].

Similar to epithelial cells, endothelial cell function is significantly affected by SARS-CoV-2 in multiple ways [62,63]. Some of the major endothelial dysfunction involves reduced endothelium-dependent vasodilation leading to proinflammatory, procoagulant and hyperproliferation [64,65]. Notably, inflammation may also trigger the release of endothelial PAI-1 to inhibit urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) leading to attenuated fibrin degradation [66]. However, viral replication within endothelial cells may result in activation of the extrinsic coagulation pathway or the recruitment of platelets to the site of endothelial injury that further contributes to hypercoagulability. Among the key factors of endothelial cell dysfunction include reduced nitric oxide (NO) production, increased reactive oxygen species (ROS) generation, decreased anticoagulant heparin and dipeptidyl peptidase-4, and elevated VWF, TF, ICAM-1, E-selectin and P-selectin. Moreover, early production of proinflammatory cytokine IL-1α by endothelial cells, monocytes and activated platelets is reported to bridge the coagulation process and inflammatory response [67,68]. Also, IL-1α is suggested to promote infiltration of granulocytes and inflammation-mediated thrombosis [69]. Given the role of the endothelium in regulating fibrinolysis, endothelial dysfunction can induce immunothrombosis and subsequently hypercoagulopathy in COVID-19 patients [70]. That means damaged alveolar epithelial cells and the pulmonary endothelial cell can activate platelets and induce intravascular microthrombi formation [58,71]. The above changes appear to contribute to impaired hypoxemic vasoconstriction and the clinical phenotype of happy hypoxemia [72].

b. SARS-CoV-2 infection-specific inflammatory cytokine and growth factor dysregulation

SARS-CoV-2 induces the production and release of inflammatory mediators including cytokines and chemokines. Proinflammatory mediators secreted by the damaged epithelial and endothelial cells and infiltrated innate immune cells immensely contribute to the cytokine storm, a hallmark of COVID-19. Most commonly identified inflammatory factors including IL-2, IL-6, IL-7, IL-8 (CXCL8), TNF-α, granulocyte-colony stimulating factor (G-CSF), chemokine interferon-γ inducible protein-10 (IP-10, CXCL10), CCL2 (MCP-1), MIP1α/CCL3 and CRP, procalcitonin (PCT), and ferritin [10,73–75] secreted by the infected cells and, immune cells recruit both innate and adaptive immune cells to the site of infection, thereby, exacerbating inflammatory responses [76]. In addition, a recent study highlighted the induction of hepatocyte growth factor (HGF) as counter-mechanism to resist pro- cytokine-mediated inflammation in severe COVID-19 [77].

Among the proinflammatory cytokines, IL-6 has been identified as the most common and predominant cytokine causing the cytokine storm [13], a phenomenon behind acute lung injury and ARDS in severe COVID-19 cases. IL-6 is also reported to induce expression of TF on endothelial cells and monocytes, increases platelet activation, and endothelial dysfunction [78]. Notably, the levels of IL-6, D-dimer, lactate dehydrogenase (LDH), and transaminases are considered crucial factors to identify high-risk COVID-19 patients who can potentially be benefited from anti-IL-6 (tocilizumab) therapy [79]. Similarly, IFN-γ also increases platelet production and vascular endothelial growth factor (VEGF) to deliver proangiogenic effects. Another important pro-inflammatory cytokine IL-8 (CXCL8), a well-known chemoattractant that activates and controls the infiltration of neutrophils to the site of infection, is highly elevated in COVID-19 patients. In addition to regulating neutrophil infiltration, IL-8 also induces neutrophil extracellular traps (NETs) formation, a process called NETosis that is triggered during microbial infections. A recent study has shown a gradual increase in inflammatory cytokines and chemokines such as IL-6, CXCL10 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in COVID-19 [80]. In addition to chemokines, their receptors have also been implicated in COVID-19. For example, the severity of COVID-19 with genotype-inferred CCR2 expression in the lung shows strong evidence of myeloid cells contribution to immunopathology as CCR2 is highly expressed on monocytes/macrophages [81]. In addition, several myeloid cell growth factors such as macrophage-CSF (M-CSF), G-CSF and GM-CSF known to regulate myeloid cells growth and differentiation are also found to be significantly elevated in COVID-19 patients [9,82].

Furthermore, significant activation of the complement system, a key component of the innate immune system, found to be associated with terminal complement complex C5b-9 and mannose-binding protein-associated serine protease 2 (MASP2) deposition in the lung lesions of COVID-19 patients [83,84]. Other studies also support the role of the complement system in COVID-19 as blocking of C5a and C5a receptor signaling and C3 deficiency reported to attenuate neutrophil infiltration and disease severity in animal models of SARS and MERS virus infection [85,86]. These studies suggest that complement activation is a key component of the innate immune defense triggered early on by the SARS-CoV-2 infection. Besides cytokine and chemokines, elevated levels of serum CRP, PCT, erythrocyte sedimentation rate (ESR), and ferritin were also observed in severe COVID-19 patients [10]. In addition, some of these key coagulation factors associated with inflammation in COVID-19 are discussed below.

c. Association of dysregulated cytokines and growth mediators with coagulation factors

The worse clinical outcome in COVID-19 is associated with endothelial dysfunction observed in the autopsy series [63,87]. In addition to triggering a cytokine storm [13], SARS-CoV-2 activates the coagulation pathway through vascular endothelial cells damage as discussed above. Among the key biomarkers of the coagulation including fibrinogen and D-dimer, CRP and ferritin, and their levels were found elevated in severe COVID-19 cases [30, 88–90]. An increasing body of evidence points towards the association of abnormal coagulation parameters with increased levels of inflammation markers. In this regard, we and others have recently described the elevated levels of fibrinogen, D-dimer, and IL-6 in COVID-19 patients with ARDS [91,92]. However, another study has shown an association of elevated levels of D-dimer, PT and IL-6 with COVID-19 mortality [10]. In particular, the D-dimer was found positively associated with CRP, serum ferritin, PCT, and IL-2R. However, the elevated ferritin level was reported to promote a hypercoagulable state in COVID-19 [93].

In the context of coagulopathy, IL-6 potentially induces megakaryopoiesis and coagulation factors including TF, fibrinogen and factor VIII. Therefore, the level of TF may increase in the lungs of COVID-19 patients through virus-damaged epithelial cells as well as by the IL-6. Moreover, IL-6 also induces endothelial cells secretion and increases vascular permeability through the release of VEGF [94]. Besides these, the clinical trials in sepsis patients revealed that IL-6 is a predominant inflammatory mediator of cytokine-driven coagulation than both TNF-α and IL-1 that are strongly upregulated during SARS-CoV-2 infection [95]. Concerning growth factors, a recent study has shown an association of a high level of HGF with severity and mortality of COVID-19 patients [77]. These findings indicate the existence of a possible interplay between Inflammation and coagulation during SARS-CoV-2 infection. Further studies are required to identify the specific regulators to precisely define the association of coagulation and inflammation in COVID-19 patients.

d. Correlation of dysregulated coagulation factors with the COVID-19 severity

Viral infections lead to inflammation, initiated by the primary target such as epithelial cells and subsequently by the immune cells, also observed in SARS-CoV-2 infection. This event could stimulate
the coagulation system [96,97]. The findings from several studies describe a dysregulated coagulation process and the relationship between dysregulated fibrinolytic factors with COVID-19 severity, ARDS development and death. In context to the association between coagulation and inflammation, D-dimer, SIC score, and DIC score positively associate with the infectious and inflammatory markers. In particular, D-dimer was shown to correlate with the severity and mortality in the ongoing COVID-19 pandemic [9].

Another important phenomenon associated with COVID-19 is sepsis-associated coagulopathy which is believed to be primarily linked to proinflammatory cytokines. For example, IL-6 is reported to play a central role in activating coagulation by crosstalk with protein C, protein S, and antithrombin systems [53,98]. SARS-CoV-2 associated sepsis remains the leading cause of DIC, a process observed before COVID-19 patients’ death. A recent study has reported the association of dysregulated PT, aPPT, fibrinogen degradation product (FDP), and D-dimer in fatal DIC [99]. However, in another study on a large cohort of critical COVID-19 patients, D-dimer and PT appear to be associated with disease severity and death [10,100]. In an interesting observation, COVID-19 patients with pneumonia presented higher levels of D-dimer and FDP and, longer PT in non-survivors as compared to survivors [27]. These clinical observations suggest a potential association of dysregulated coagulation factors with the severity of COVID-19 and consideration of assessing coagulation markers in the management of coagulopathy.

4. Cross talk between platelet activation and inflammation in COVID-19

Platelets interact with other cells including immune cells during infection, thus actively participate in the process of inflammation. These tiny, non-nucleated cells respond precisely to pathogenic infection by undergoing morphological and biological changes and release various components including pro-coagulant and inflammatory mediators which eventually contribute to the thrombotic and immune system. Severe COVID-19 patients have shown a peculiar complication of thromboinflammation [101]. Recent literature suggests the role of platelets in inflammation and thrombosis in severe COVID19 patients [102–104]. The following sections discuss the role of activated platelets in thromboinflammation observed in COVID19.

a. Platelets in immunity:

Platelets play a major role in controlling blood loss and are important contributors to hemostasis and thrombosis. In addition, platelets are essential components of the immune system and play a pivotal role in inflammation by releasing active mediators that are necessary for inflammatory response [105]. Platelets can participate both in innate and adaptive immunity and, the ability of platelets to participate in immunity is due to the presence of storage granules and receptor-rich plasma membrane. Plasma membrane expresses multiple receptors through which platelets crosstalk with immune cells such as lymphocytes, neutrophils and monocytes. Storage granules (alpha- and dense-granules) are packed not only with adhesion and activation molecules but also with other molecules such as chemokines, cytokines and bioactive amines [106]. As a result of bacterial/viral infections, platelets alter their morphological and biological features to facilitate their participation in the defense mechanism. Pathogens bind to platelets either directly or indirectly via surface recognizing receptors, plasma proteins, bacterial toxins, etc. The infection triggers the release of chemokines, such as CXCL4 and β-thromboglobulin (CXCL7) from platelets. The chemokine, CXCL4 is known to involve in the regulatory functions of inflammation, also, serves as a prognostic marker of viral infections such as SARS-CoV-2 infection [107].

The role of chemokines, secreted by platelets, in other viral infections such as dengue, has also been documented recently [108]. In some viral diseases, infection and inflammation are associated with the development of prothrombotic complications. Since platelets are procoagulant and have the nature of spreading, adhesion, secretion and aggregation, these cell particles contribute to thrombotic development. Platelet-derived thrombosis during infection, also called immunothrombosis, occurs as a result of cross-talk between platelets and inflammation [109]. Along with the activated platelets, tissue factors, antimicrobial peptides activated monocytes and endothelial cells contribute to the development of immunothrombosis. Complement components and NETs are also key contributors to immune-mediated thrombosis [110].

Immunothrombosis enhances the recognition and destruction of pathogens, however, excessive thrombus formation leads to adverse events such as tissue damage as observed in SARS-CoV-1 infection [111]. Recently, several evidences have been reported about the complications associated with immunothrombosis in COVID19 [112–114].

b. Role of activated platelets in COVID19:

Activated platelets serve as mediators of inflammation and thrombosis in many clinical conditions [115–118]. Platelet activation triggers inside-out signaling and activate surface receptors that bind to the ligand on other cells, de-granulates and secretes contents into the plasma [119]. The release of granular contents such as adhesive proteins, coagulation factors, chemokines and numerous other biologically active molecules not only promote a hypercoagulable state but also promote the inflammatory process utilizing immune cells. Pro-inflammatory mediators such as CD40 ligand (CD40L) and TLRs are synthesized and expressed on the surface of the activated platelets that help crosstalk with other cells like monocytes and neutrophils. The interaction between platelets and other cells results in the formation of platelet-leukocyte aggregates which leads to the pathological condition of thrombosis [120]. Release of granular contents, surface expression of certain key receptors and platelet-leukocyte aggregates are the strong markers of activated platelets. When such features are associated with viral, bacterial and inflammatory diseases, the risk of occurrence of immunothrombosis is also increased. Patients with COVID19 manifest with thromboembolic complications as a result of inflammation, platelet activation and hypercoagulation [102,121]. It is identified that the activated platelets play an important role in SARS-CoV-2 associated thrombus formation as platelets coordinate between inflammation and thrombosis which lead to thromboinflammation [122].

Increased expression of P-Selectin, a marker of activated platelets, has been reported in patients with COVID19. Additionally, TBXβ2, platelet factor 4 (PF4) and PDGF were also found to be increased in patients with COVID19 [107]. The soluble form of P-Selectin (sP-Selectin), a reliable marker of in vivo platelet activation found linked with increased severity and in-hospital mortality of COVID19 patients [123]. There was a positive correlation between the increased levels of sP-Selectin and inflammatory markers such as CRP which suggests the association of platelets with inflammation. Platelets are potential regulators of expressions of receptors/ proteins on the other cells via either direct cell-cell interaction (PSGL-1/P-Selectin mediated) or binding of platelet releasate (soluble proteins) with the surface of other cells [124]. Platelet-leukocyte aggregates were observed only in severe but not in mild or asymptomatic COVID19 patients. The existence of platelet-neutrophil and platelet-monocyte aggregates in severe COVID19 patients suggests the role of inflammation in the platelet signaling mechanism [125]. Platelet-leukocyte aggregation triggers the expressions of proteins necessary for inflammation and thrombosis, for example, Mac-1 on neutrophils, COX-2 and PSGL-1 on monocytes, ICAM-1 on endothelial cells; all these proteins are key for the thromboinflammation [124]. Apart from these, platelet microparticles have emerged as a prognostic marker in severe COVID19 patients as the
increased level of microparticles has been observed in these individuals [126].

Thrombocytopenia, a condition marked by low platelet count may serve as a potential biomarker to guide the disease severity in viral diseases. Thrombocytopenia in viral diseases such as Dengue, Chikungunya, Japanese Encephalitis, Hepatitis B, Human Immunodeficiency Virus (HIV) and many other viral infectious diseases have been reported in the past. Platelets are activated by the direct binding with either the viral particle or immune complexes that are produced as a result of infection. For example, infection by the dengue virus activates platelets via either C-type lectin receptor-2 (CLEC2) or anti-non-structural protein-1 IgG [127]. A recent study identified thrombocytopenia as a potential biomarker of severity in COVID19 patients [128]. An aberrant megakaryocyte maturation, increased platelet destruction and consumption in thrombi formation could be the possible cause of thrombocytopenia in severe COVID19. However, the existence of comorbidities may contribute to the coincidence of thrombocytopenia in COVID19 as severe platelet reduction is not observed in all the patients with COVID19. All the above studies strongly support the role of activated platelets in the pathophysiology of COVID19 as the activated platelets are known to take part in the process of thrombosis and inflammation through releasing proinflammatory and procoagulant mediators.

5. Role of SARS-CoV-2 mediated inflammation in thromboembolism and aberrant fibrinolysis

The viral and bacterial infection enhances the risk of thromboembolic diseases including DVT and pulmonary embolism (PE) [129–131]. Such thromboembolic complications are a major contributing factor to increased morbidity and mortality [132]. SARS-CoV-2 infection induces not only immunothrombosis but also thrombocytopenia and inhibits fibrinolysis [133,134]. Thromboembolism in hospitalized COVID-19 patients is more commonly reported in veins [135] and it has been extensively reviewed previously [136–138]. The main focus of this review is to establish a potential association between inflammatory markers and thromboembolism in COVID-19. Studies suggest that systemic inflammatory response causes VTE which in turn further enhances the inflammatory reaction. The dysregulated coagulation factors particularly, thrombin/fibrin and FXIII, were reported to modulate thrombus stability and embolization [20]. Therefore, we sought to establish a potential association between SARS-CoV-2 –induced inflammatory markers and dysregulation of coagulation factors which ultimately regulate fibrin generation and polymerization. Fibrin generation is regulated by both extrinsic as well as intrinsic coagulation pathways and potentiated by additional thrombin generation contributed by activated platelets.

Table 1

| Cytokines Function | Associated coagulation factors | References |
|-------------------|--------------------------------|------------|
| IL-6 Proinflammatory | TF Fibrinogen Factor VIII VEGF PAI-1 | [139] [140] [141] [142] [143–145] |
| IL-1 Proinflammatory | TF VEGF PAI-1 Platelet activation | [146,147] [148] [149] [146,150] |
| TNF-α Proinflammatory | TF u-PA PAI-1 upregulation Platelet | [147,151] [152] [144,153] [154,155] |
| IL-8 Proinflammatory | TF Factor VII via NET Platelet | [139] [110] [156] |
| IFN-y Proinflammatory | TF | [147,157] |
| IL-2 Proinflammatory | TF PAI-1 tPA | [147] [159] |
| IL-10 Anti-inflammatory | TF VEGF PAI-1 | [161,162] [163] [164] |

a. Association of inflammatory mediators with thromboembolism:

Uptregulation of proinflammatory markers in COVID-19 including IL-1, IL-2, IL-6, IL-8, TNF-α, CRP and IFN-y has previously been identified as a critical regulator of coagulation factors and platelet activity (Table 1). Of these, an association was established between increased levels of IL-6, IL-8, TNF-α, and CRP with increased risk of VTE in systemic inflammation [11,132]. These inflammatory markers potentially play critical roles in thrombin/fibrin generation by modulating the coagulation system. Though mentioned proinflammatory markers likely enhance thrombin/fibrin generation in COVID-19 which is consistent with the finding that showed the presence of fibrin-rich thrombi in the lung vasculature of patients who died due to COVID-19 [165]. The question, how thrombus in severe COVID-19 destabilizes and embolizes even in the presence of an adequate amount of fibrin, remains unanswered and is an area of extensive research. The most likely cause of VTE in the COVID-19 is the downregulation of FXIII, particularly in severe cases, which attenuates the fibrin polymerization (Fig. 1). FXIII facilitates the cross-linking of fibrin and increases the thrombus stability during platelet accumulation on growing thrombus [166]. Studies employing the ferric chloride-induced venous thrombosis model have displayed a significantly increased level of thrombus embolization in FXIII deficient mice [167]. In contrast, supplementation of FXIII stabilizes the deep vein thrombi in mice and limits PE [168]. A recent study has shown that COVID-19 is associated with acquired FXIII deficiency [169]. Consistently, we recently observed that the level of FXIII gradually decreases with the progression of COVID-19 severity [92]. These findings indicate that FXIII deficiency could be a major driving factor of thromboembolism in COVID-19 though further investigation and validation are required. Existing evidence suggests for a link between FXIII and inflammatory markers and it is reported that CXCR3 expression in the lung directly correlates with the FXIII levels in diseases condition [170]. Importantly, the level of CXCR3 expression in mild and severe COVID-19 patients was comparable to healthy controls [171]. Therefore, down-regulation of the FXIII level in COVID-19 is possibly independent of CXCR3. Interestingly, in vitro studies in macrophages have demonstrated that the induction of the classical activation pathway by IFN-y downregulates the catalytic A subunit of FXIII both at mRNA and protein levels [172]. The polymorphonuclear (PMN) leukocytes activate FXIII by releasing human neutrophil elastase which likely promotes fibrin cross-linking at an inflammatory site. However, within the fibrin clot, PMN leukocytes become activated and proteases released by these cells inhibit FXIII to prevent the formation of over-cross-linked fibrin [173]. Therefore, an increased leukocyte number and IFN-y particularly in severe COVID-19 cases [92,174] may play important roles in the modulation of FXIII and fibrin cross-linking and cause thromboembolism in the severe COVID-19.

b. Association of inflammatory mediators with aberrant fibrinolysis in COVID-19:

The elevated level of D-dimer in the COVID-19 suggests the activation of the coagulation system and hyperfibrinolysis. Fibrinolysis is a physiological process required for thrombus dissolution governed by plasmin, plasminogen, tPA, and PAI-1. Studies suggest that
SARS-CoV-2 infection dysregulates the fibrinolysis process by modulating the level of tPA and PAI-1 likely through inducing the inflammation \[175–178\]. Recently, we and others have reported the increased level of PAI-1, a fibrinolytic inhibitor, in COVID-19 patients \[92,179\]. Importantly, we observed a higher level of PAI-1 in the moderate vs. severe COVID-19 cases which indicates diminished thrombus dissolution in moderate cases and possibly promotes COVID-19 severity. Interestingly, we observed an elevated level of tPA particularly in severe COVID-19 patients which indicates the activation of hyperfibrinolysis. Similarly, other studies have also reported an elevated level of PAI-1 in COVID-19 patients \[180\]. Moreover, an elevated level of tPA in hospitalized COVID-19 patients was reported to be associated with higher mortality \[179\].

Inflammation can trigger the release of PAI-1 from vascular endothelial cells (reviewed in \[66\]). Like t-PA, PAI-1 is normally produced and released from the vascular endothelium, but also by mast cells and adipose tissue \[181\]. Proinflammatory cytokines are thought to be one of the major factors in inducing tPA and PAI-1 either directly or through indirect activation of endothelial cells \[182\]. In addition to inflammatory mediators, SARS-CoV-2 infection can also trigger the release of tPA and PAI-1 from endothelial cells \[70\]. Some of the key mediators of the cytokine storm such as IL-1, IL-6 and TNF-α are also linked to PAI-1 dysregulation \[183\]. Notably, IL-6, a key predictor of COVID-19 severity activates PAI-1 production in endothelial cells \[143\]. Another COVID-19 associated innate inflammatory molecule C5a \[83\] increases the expression of PAI-1 in mast cells \[184\]. The contribution of TNF-α and IL-1β mediated regulation of PA-1 \[185\] is well supported by the observation of non-occurrence of thrombosis in endotoxin-treated PAI-1 knockout mice \[186\]. In contrast to PAI-1, the most common inflammatory mediator CRP decreases the tPA expression in human aortic endothelial cells \[187\]. Likewise, tPA expression was found downregulated by other common pro-inflammatory mediators such as IL-1β, TNF-α as well as endothelin-1, and ROS \[188–190\]. Although the majority of these studies do not show a direct association with COVID-19, the strong link among inflammatory mediators, in particular, those constituting the cytokine storm (IL-1β, IL-6, TNF-α), and the regulation of PAI-1 and tPA indicate the existence of an association between inflammation and aberrant fibrinolysis in COVID-19 that needs further investigation.

6. Conclusions

The cytokine storm and coagulation dysfunction appear to be the major cause of venous thrombosis and thromboembolism in COVID-19 that significantly contribute to the severity of disease and death rate. The pattern of coagulation dysfunction in COVID-19 seems to be different than the traditional coagulation pathway. The inflammation induction mediated by a plethora of cytokines and growth factors in COVID-19 potentially regulate procoagulant mechanisms partly through enhancing the TF expression on immune and endothelial cells which is crucial for TF-FVIIa pathway activation. Though no direct association between inflammatory mediators and coagulation factors dysregulation in COVID-19 is established yet, studies strongly suggest that cytokines and growth factors induction might play important roles in coagulation dysfunction. In the experimental model, inhibition of the endogenous activity of cytokines has revealed the key roles of TNF-α in fibrinolysis however, IL-1 and IL-6 were found to be associated with the coagulation system activation. Interestingly, inflammatory response in COVID-19 was identified to be largely similar to as seen in MERS and SARS-CoV-1 infections where higher levels of IL-1, IL-6, and TNF-α were also observed. The molecular mechanisms of inflammation-induced coagulation dysfunctions in the viral pandemics including COVID-19 appear to be largely similar though the precise cause is undefined. Since all the said inflammatory mediators are the critical regulator of the components of the coagulation system, effective management of such cytokines in the COVID-19 potentially limits the coagulopathy and severity of the disease. Moreover, combination therapy could be an effective therapeutical approach to minimize the thrombotic events in the COVID-19. Based on observations, thromboembolic events in severe COVID-19 patients could be minimized when treated with recombinant FXIII in combination with an antplatelet and/or low molecular weight heparin. Such combinational therapy needs to be validated in preclinical models.

Declaration of Competing Interest

None.

Acknowledgments

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