# Analysis of Coagulation Profile and Possible Mechanism of Coagulation Activation in COVID-19 Patients: A Systematic Literature Review

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## ABSTRACT

The ongoing COVID-19 pandemic has caused a global health crisis with serious impacts that extending beyond the acute infection stage. This comprehensive review of literature looks at the mechanism of coagulation activation during COVID-19 as well as the examination of coagulation profile in infected patients. Prolonged prothrombin time (PT), higher D-Dimer, thrombocytopenia, and altered coagulation factors activity are indicators of hypercoagulability in severe cases. Long-term COVID-19 sequelae indicated persistent difficulties, such as psychological and physical disorders, that are revealed throughout the post-recovery phase. Multiple studies have shown a correlation between the severity of the disease and coagulation issues, highlighting the importance of a thorough coagulation profile investigations in COVID-19 patients after recovery.

Mechanistically, the inflammatory response initiates a cytokine storm that activates monocytes, platelets, and endothelial cells. The viral spike protein interacts with the ACE2 receptors of endothelial cells, causing endothelial damage and activating procoagulant pathways. In addition, alterations in the renin-angiotensin system (RAS) intensify vasoconstriction, inflammation, and pro coagulation. Recognizing these intricate biochemical processes, it is essential to predict and manage chronic consequences related to coagulation factors. In patients who have recovered, early examinations of coagulation parameters may help with early medications, which could prevent thrombotic incidents.

**KEY WORDS:** COAGULATION FACTORS, COVID-19, D-DIMER, ENDOTHELIAL DYSFUNCTION, VENOUS THROMBOEMBOLISM,

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global health crisis that emerged in Wuhan City, China on December 3, 2019, and is still an ongoing pandemic worldwide. According to data from the Indian Government, India is ranked second in the world, with 44,996,963 confirmed COVID-19 cases and had the third highest number of 531,928 COVID-19 deaths (Ritchie et al. 2022). Although the patients recovered from infection, after effects of COVID-19 do not end with infection resolution, as reported in studies (Del Rio, Collins and Malani, 2020), patients after 12 weeks of COVID-19 recovery experienced a wide range of mental and physical complications with specific organ dysfunctions involving heart, lung and brain, and stated that major consequences of COVID-19 increased the incidences of heart failure in young population and athletes and also decline in lung functions and neurological manifestations. Studies also support the hypothesis of severe major consequences reported earlier due to long COVID-19 sequelae by examining blood samples from 70 South African long COVID-19 patients, (Pretorius et al., (2021).

All the results showed platelet pathology and substantial fibrin amyloid microclots which can be linked to chronic symptoms that persisted even after the subsidence of acute COVID-19. Coagulopathy is an emerging hallmarks of COVID-19 induced by the hyperinflammatory response. The authors also found that elevated coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, and thrombocytopenia are associated with higher mortality from COVID-19. Hence, examination of these factors is important to determine the level of coagulopathy, (Wang et al 2020).

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The major issue that needs to be addressed is the emergence of mysterious clots that result in coagulation irregularities and thrombosis. An earlier detection of thrombotic events will be possible by the increased knowledge of thrombotic consequences in recovered individuals. The primary objective of this literature review is to analyze studies investigating coagulation parameters in COVID-19 patients and to provide an overview of the mechanisms underlying COVID-19-associated coagulopathy.

## MATERIAL AND METHODS

**Search Strategy:** PubMed, Scopus, Web of Science, and Google Scholar databases were searched to identify relevant articles. Following key words were used for the search ensuring an extensive search strategy, literature search performed using COVID-19 and coagulopathy related keywords such as "COVID-19", "coagulation factors", "coagulopathy", "thrombosis", "D-Dimer", "coagulation mechanism".Inclusion and exclusion Criteria: In order to assure relevance to recent advances in the understanding of COVID-19 associated coagulopathy, only peer reviewed articles written in English between 2019 and 2023 are taken into consideration. Articles that did not meet the inclusion criteria were also excluded.

**Selection of studies: Screening:** The titles and abstracts if retrieved papers were examined to determine their relevance to the goal of the study.

**Full-text Review:** To ascertain eligibility in accordance with the inclusion and exclusion criteria, potentially relevant papers were subjected to a full-text review.

**Extracting data:** Relevant information about COVID-19-associated coagulopathy, thrombosis risk, population characteristics, study design, and measured coagulation parameters were gathered from a subset of selected studies.The publications that offered significant insights into COVID-19-associated coagulopathy and its clinical consequences are included and served as the foundation for our review and can help to unfold later pathological manifestations. The included papers' references were taken out and subjected to additional examination and analysis. This made it possible to find other information sources and to investigate similar studies that might advance our grasp of the subject matter.

## RESULTS AND DISCUSSION

The level of coagulation parameters changes due to the COVID-19 severity (Teimury, Khameneh and Khaledi, 2022). They reported that patients with severe COVID-19 had decreased lymphocytes, reduced platelet count (thrombocytopenia), high fibrinogen and fibrin degradation products (FDP), highly increased D-dimer, higher factor VIII activity, lower factor V and VII activity, elevated PT and APTT, and low antithrombin III (AT III).

To investigate the difference between survivors and non-survivors, coagulation parameters of consecutive novel coronavirus pneumonia (NCP) cases were studied in Tongji Hospital, Wuhan China, and vigorous fluctuations in parameters were traced. They reported the D-dimer range 0.22-21.00 µg/ml and the FDP range of 4.0-150.0 µg/ml and concluded that significantly higher coagulation parameters could be associated with the development of coagulation disorders (Wang et al., 2020).

Analysis of coagulation parameters performed to determine the consumption of coagulation factors and found normal median PT, and APTT but particularly elevated D-dimer (median 450 ng/ml), and mean fibrinogen levels were also above the upper limit. Workers (Martín-Rojas et al., 2020) also observed that 11 out of 206 patients met the criteria for overt DIC (disseminated intravascular coagulopathy) with elevated D-dimer levels (median 2812 ng/ml). Prolonged PT (median 16.5 S), lower platelet count (median 98×103 µl), decreased level of protein C and antithrombin, lower level of factor II, X and XII .

A study (Cui et al., 2020) explored the incidence of venous thromboembolism (VTE) in ICU patients with severe NCP and investigated the difference between VTE and non-VTE patients. Patients with VTE had higher D-dimer, longer APTT, and lower lymphocyte counts, and these parameters were also consistent with those of older patients. Researchers (McFadyen, Stevens and Peter, 2020) reported that, patients with COVID-19 have markedly increased rates of venous thromboembolism (VTE) and pulmonary embolism. In addition, arterial thrombosis, acute myocardial injury, and microvascular thrombosis commonly complicate the condition of patients. Elevated acute-phase reactants such as C-reactive protein (CRP) and fibrinogen and abnormal coagulation parameters such as prolonged APTT, PT, D-dimer, thrombocytopenia (<100×10^9/L) are prognostic markers in COVID-19.

Whole blood samples from 24 COVID-19 patients were analyzed to evaluate parameters by Thromboelastography (TEG), an in vitro device used to assess the viscoelastic properties of native whole blood upon stimulation of hemostasis by an exogenous trigger (kaolin); they concluded that COVID-19 patients show hypercoagulability, which could develop pulmonary embolism or deep vein thrombosis of the lower limbs (Panigada et al., 2020). They also observed other parameters of hemostasis such as normal or slightly prolonged PT and APTT, greatly increased fibrinogen and D-dimer levels, and suggested that patients with COVID-19 do not have DIC; rather they support hypercoagulability together with a severe inflammatory state.

Their findings are also supported by a study (Levi et al., 2020), which reported that patients with COVID-19 coagulopathy not have many hemorrhagic complications and excessive thrombin generation, which is the characteristic feature of DIC. The clinical and laboratory features of coagulation changes in COVID-19 did not match the DIC score of the International Society on Thrombosis and Haemostasis (ISTH). Therefore, they concluded that COVID-19 coagulopathy is distinctly different from DIC. The proportion of abnormalities was higher in the severe group than in the mild group, and significant coagulopathy

was correlated with the degree of disease severity to some extent (Zou et al., 2020). This analysis inferred by studying coagulation parameters in 303 COVID-19 patients in Shanghai, China. The abnormal parameters were fibrinogen in 64.3% patients, D-dimer in 42.6% patients, prolonged prothrombin time in 18.5% patients, abnormal activated partial thromboplastin time in 21.8% patients, and elevated fibrinogen degradation products in 6.3% patients.

The study js also supported by the findings of Abd El-Lateef et al., (2022) who analyzed the differences in coagulation markers and biochemical and inflammatory markers in the severe and non-severe patients and found increased PT, INR, APTT, D-dimer, fibrinogen, C-reactive protein (CRP), factor VIII, VWF and ristocetin cofactor (RiCoF) and decrease lymphocyte count in severe patients but with not any variation in platelet counts.

However, there were significant differences between survivors and non-survivors. All the biochemical inflammatory and coagulation markers were greatly increased in non-survivors, with a decreased lymphocyte and platelet counts. They also found RiCoF was a novel predictor of COVID-19 severity. RiCoF forms complexes with VWF and induces platelet aggregation by conformational change in VWF. Another study by Al Nafea et al., (2023) also depicts coagulopathy associated with severe COVID-19 patients by assessing coagulation profile of survivors and non-survivors and concluded that non-survivors exhibited higher level of D-Dimer (36.8%), PT (31.5%) and PTT (10.5%), demonstrating a strong association between coagulopathy and disease severity.

Coagulation profile of 455 hospitalized COVID-19 patients analyzed in Addis Ababa, Ethiopia, of which 46% showed prolonged PT and variation in INR values. Prolonged PT were more frequent (51.3%) in older people (> 55 years) and males (49.8%) than in females (41%), and 22.1% of total patients had thrombocytopenia. Venous thromboembolism (VTE), arterial thrombosis, and thrombi in vessels of the lung, kidney, and other organs have been reported in critically ill patients with COVID-19 (Araya et al., 2021).

Another study by Larsen, Pasalic and Hvas, (2020) also reported that patients with COVID-19 frequently have minor thrombocytopenia; nonetheless, it is uncommon and should be considered as a sign of either existing or emerging thrombocytopenia when the platelet count is <100×109 /L. They also reviewed the mechanism behind it, which may be adhesion and activation of platelets and this is due to direct influence of virus on hemostasis. In an investigation by Bilaloglu et al., (2020) conducted on 3334 consecutive COVID-19 hospitalized patients, the authors stated that higher D-dimer levels were related to a thrombotic event and that 533 (16.0%) patients experienced such occurrences.

D-dimer level in 119 COVID-19 patients who recovered within the last 6 months were assessed by Lehmann et al., (2021), and elevated D-dimer levels were found in 15% of the patients who had severe COVID-19 that required hospitalization. Of these, when CT scan performed in 79% patients showed elevated D-dimer levels, 13% patients had thrombotic complications. Therefore, D-dimer could be a potential biomarker for post-COVID-19 conditions. Their hypothesis was also supported by another study that assessed the coagulation profile of 75 children below 18 years of age and had confirmed COVID (Di Gennaro et al., 2022).

Tests were performed after 8-12 months of recovery. The coagulation profile of children with post-COVID conditions (PCC) who had at least three or more persisting symptoms compared with the control group of children fully recovered post-SARS-COV-2. They found that the majority of children displayed a coagulation profile that was near normal or within normal range but had significantly elevated D-dimer levels in children with post-COVID conditions compared to those fully recovered from infection.

**Mechanism of coagulation activation in patients with COVID-19:** COVID-19 coagulopathy also referred to as immuno-thrombo inflammation is the consequence of disturbance of various biological pathways. Mechanisms include an inflammatory response to COVID-19, activation and damage of endothelial cells due to the binding of the spike protein of SARS-CoV-2 with ACE2 receptors on endothelial cells, platelet activation, aggregation, and deregulation of rennin-angiotensin system. Disturbances in these biological pathways leads to various long-term complications, including venous thromboembolism (VTE), disseminated intravascular coagulopathy (DIC), pulmonary embolism (PE), and arterial thromboembolism.

Endothelium is required for normal coagulation, and it is well recognized that endothelial cell destruction induces both intrinsic and extrinsic coagulation pathways, which in turn cause vessel occlusion. Inflammatory responses of COVID-19 such as high levels of interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF), and other inflammatory cytokines described as a "cytokine storm" alter fibrinolysis and natural anticoagulant pathway and activate endothelial cells, platelets, monocytes and tissue factors (Varga et al., 2020).

Another study (Levi et al., 2020) also found that severely affected COVID-19 patients have cytokine storm profiles characterized by high concentrations of proinflammatory cytokines, such as TNF-α and interleukins (IL-1 and IL-6), which activate coagulation pathway by inducing tissue factor (TF) and inactivating natural anticoagulant pathway. Endothelial cell injury due to this inflammation results in massive release of plasminogen activator, which induces fibrinolytic system, and high concentration of D-dimer and fibrin degradation product (FDP) is detected in patients with severe COVID-19.

Grover and Mackman, (2018) further stated that tissue factor (TF) is the high-affinity receptor for factor VIIa and is expressed on epithelial cells. The VIIA-TF complex activates the extrinsic pathway of coagulation by converting inactive protease factor X into active protease factor Xa. Under pathological conditions, inducible TF can trigger arterial and venous thromboses, leading to disseminated

intravascular coagulation. Another study of Cacciola et al., (2022) found that TF expression in monocytes occurs as a result of proinflammatory cytokine and thrombin production in moderate COVID-19 cohort. They also measured IL-6 and TNF-α levels, which reflect a higher inflammatory state.

Angiotensin-converting enzyme 2 (ACE2) functions as a receptor for SARS-CoV-2 (Varga et al., 2020). ACE2 is expressed on the endothelial cells of heart, kidney, intestine, liver, testis, adipose tissue, and central nervous system. They also stated that endothelial dysfunction causes vasoconstriction, inflammation, and a procoagulant state. This statement is well supported by the study of Escher, Breakey and Lämmle, (2020), who concluded that ACE2 present on endothelial cells are receptors for SARS-COV-2 and responsible for endothelial destruction and release of Von Willebrand factor (vWF) into blood which is stored in Weibel-palade bodies of endothelial cells.

Endothelial cell injury triggers primary hemostasis by activating events, such as platelet activation, aggregation, and adhesion to generate primary platelet plugs (Zhang et al., 2020). ACE2 and transmembrane serine protease 2 (TMPRSS2) are expressed on the platelet surface through which spike protein of virus binds via spike/ACE2 interactions, triggers the release of clotting factors and inflammatory mediators, and generates the leukocyte-platelet aggregates.

Derangement of hemostasis described by a study (Lippi et al., 2021) stated that primary hemostasis is triggered by the binding of SARS-CoV-2 on receptor ACE2 expressed on the surface of endothelial cells. Endothelial injury, followed by activation, adhesion, and aggregation of platelets, generate a platelet plug. This platelet plug is stabilized by fibrin generated by activation of coagulation cascade due to release of tissue factor (TF) from macrophages, and activation of macrophages occurs as a result of cytokine storm characterized by high interleukin values.

They also provided an overview of derangement of fibrinolysis, antiphospholipid antibodies, and renin-angiotensin-aldosterone system and concluded that COVID-19 has developed an immuno-thrombo-inflammatory thrombotic process which is most likely the result of numerous biological pathways, including endothelial damage, macrophage/monocyte activation, and neutrophil activation, which are all made worsened by continuous immobilization and the development of antiphospholipid antibodies.

It has been concluded that SARS-CoV-2 injured the vascular wall of blood vessels by binding with ACE2 expressed on the endothelium. Vascular injury causes vasoconstriction; high expression and secretion of Von Willebrand factor (VWF) promotes platelet aggregation at the site of vascular injury, reduces the expression of thrombomodulin and fibrinolytic heparin, and activates the coagulation cascade.

After the endothelial cells are injured, platelets stick to the vascular proteins, become degranulated, and release prothrombin activator, serotonin, adenosine diphosphate (ADP), and thromboxane A2 for their activation and mechanism of clot formation that start sequentially at the site of injury (Biswas et al., 2021).

Another report of Hess, Eldahshan and Rutkowski, (2020) revealed that angiotensin-converting enzyme 1 (ACE1) and angiotensin II (ATII) contribute to vasoconstriction, proinflammatory, and procoagulation effects. The renin-angiotensin system (RAS) is a hormone system in which angiotensinogen, produced by the liver, is cleaved into angiotensin I (ATI) by rennin secreted from juxtaglomerular cells in the kidney. ACE1 cleaves angiotensin I into angiotensin II. ATII induces tissue factor (TF) and plasminogen activator inhibitor-1 (PAL-1) expression and worsens endothelial function.

By directly cleaving ATII to angiotensin (1-7), ACE2 counteracts the harmful effects of ACE1 and ATII and protects endothelial function. During COVID-19 SARS-CoV-2, the spike protein interacts with ACE2, resulting in the depletion of ACE2. The unavailability of ACE2 favors the action of ACE1/AT2, which leads to a pro-inflammatory and pre-coagulation effect and contributes to endothelial dysfunction, tissue injury, and stroke.

**Understanding COVID-19-associated Coagulopathy:** A growing number of studies are showing that COVID-19 infection and coagulopathy are significantly correlated. Abnormalities in multiple coagulation measures, such as higher D-Dimer levels, extended prothrombin time (PT) and activated partial thromboplastin time (APTT) are indications of coagulopathy in COVID-19 patients. There exists a definite correlation between abnormalities in blood coagulation and the intensity of the COVID-19 disease. Patients who present with more severe manifestations of the illness tend to display more prominent deviations in their blood clotting measurements when compared to those with milder or moderate symptoms (Lin et al., 2021).

In particular, elevated levels of D-dimer have consistently been associated with greater disease severity and unfavourable clinical outcomes (Yao et al., 2020). This knowledge emphasises how crucial it is to keep updated on coagulation markers in COVID-19 patients in order to determine their risk of thrombosis and to direct treatment decisions. The coagulopathy linked with COVID-19 has complicated several pathophysiological processes.The hypercoagulable state seen in COVID-19 patients is thought to be caused by endothelial dysfunction, virally-induced proinflammatory cytokine release, and deregulation of the host immunological response. Furthermore, endothelial cell invasion by direct infection and coagulation cascade activation raise the risk of thrombosis (Iba, Connors and Levy, 2020).

**Clinical Implications of COViD-19-associated Coagulopathy:** Significant clinical consequences, such as an elevated risk of venous thromboembolism (VTE),

disseminated intravascular coagulation (DIC), and mortality are associated with coagulopathy in COVID-19 patients. Improving patient outcomes and preventing thrombotic consequences need the early detection and treatment of coagulopathy. Prophylactic and therapeutic anticoagulation have been used as strategies to reduce the risk of thrombosis in COVID-19 patients.

**Challenges in Managing COVID-19-associated Coagulopathy:** There are still a number of difficulties in managing COVID-19-associated coagulopathy, despite progress in our understanding of its etiology. Clinicians face difficulties in optimising anticoagulant medication due to variation in coagulation profiles, inconsistency in clinical presentation, and a lack of evidence-based guidelines. In addition, worries about bleeding complications linked to strong anticoagulation tactics emphasize the necessity of customized risk assessment and treatment. Studies available in the literature differ in their definitions of disease severity and the measurements used to evaluate outcomes, thereby emphasizing the necessity for standardized criteria to classify disease severity and uniformly assess clinical outcomes across various studies.

**Further Direction and Research Implications:** Moving forward, more investigation is necessary to clarify the best ways to treat COVID-19-associated coagulopathy. To support evidence-based practice, prospective studies assessing the effectiveness and safety of various anticoagulation regimens as well as the function of novel therapeutic medicines are required. Furthermore, coordinated efforts to standard treatment algorithms and diagnostic criteria would make it easier to provide high quality care to COVID-19 patients who are at risk of thrombotic problems.

Additionally, there is a need to analyze the coagulation profile of recovered COVID-19 patients so that early examination can be used for timely treatment, and early antithrombotic medication for prevention and treatment of thrombosis associated with COVID-19 will lead to enhanced results for recovered COVID-19 patients. The mechanisms that explain the link between blood coagulation abnormalities and disease severity are not fully understood, thus necessitating further investigations into the underlying pathophysiological pathways involved.

## CONCLUSION

The literature review acknowledged close link between COVID-19 infection and coagulopathy with elevated coagulopathy markers such as D-Dimer levels, PT and APTT, especially in those patients who experienced severe manifestations of COVID-19 illness. It also underscores the clinical implications related to COVID-19 coagulopathy such as deep vein thrombosis (DVT), venous thromboembolism (VTE), disseminated intravascular coagulation (DIC) and increased mortality. However, there are several challenges in managing COVID-19-associated coagulopathy. Diverse coagulation profiles, uneven clinical presentations, and worries about bleeding side effects from anticoagulant medication are among challenges that clinicians must overcome. In summary, COVID-19-associated coagulopathy poses a serious clinical problem that affects patient outcomes and care. To optimize patient care and guide therapeutic strategies, a thorough understanding of the etiology and clinical symptoms of coagulopathy in COVID-19 patients is essential. In order to lessen the effect of coagulopathy on COVID-19 morbidity and mortality, research efforts must be sustained with the goal of filling up knowledge gaps and improving therapeutic approaches.

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