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# Review of Laboratory Investigations Associated With COVID-19 Induced Coagulopathy

**Shyreen Chitani[1], Dharmendra Kumar Dubey[2]**

[1]Student of MSc Clinical Research, School of Allied Health Sciences, Sharda University, Greater Noida, Uttar Pradesh, India. Email: reenchitani74[at]gmail.com

[2]Associate Professor, Department of Clinical Research, School of Allied Health Sciences, Sharda University, Greater Noida, Uttar Pradesh, India. Email: dubey. dharm[at]gmail.com

Corresponding Author

**Dr. Dharmendra Kumar Dubey**, Associate professor, Department of Clinical Research, School of allied health sciences, Sharda University, Greater Noida, Uttar Pradesh, India. Email: dubey. dharm[at]gmail.com

**Abstract:** ***Background: Coronavirus disease (COVID-19), a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has currently infected millions of people and remains a threat to many more. Even though most cases are asymptomatic, severe cases of COVID-19 can cause health threatening complications, multi organ damage and death in some cases. COVID-19 is also very much associated with a high prevalence of coagulopathy and thrombotic embolisms that further contribute to the weakening of the respiratory system. Coagulation disorders as a result of COVID-19 are said to be caused by interaction between coronaviruses and endothelial cells, the local and systemic inflammatory response, and the coagulation system. Understanding the pathophysiology of COVID-19 associated coagulopathy is important in order to determine appropriate treatment and monitoring of these complications. Objective: This article will focus on the laboratory tests that are performed to confirm coagulopathy in COVID-19, provide a summary of key characteristics of other coagulopathies, their differences and similarities with the intention of clearly stating the uniqueness of COVID-19 associated coagulopathy (CAC). Methods: Publicly available Pubmed, England Journal of Medicine, Sage Journals, National Library of Medicine database have been searched from 2019-2021. Search results were restricted to articles that were in English and the following article types: case control studies, retrospective reviews, cohort studies. Conclusion: COVID-19 associated coagulopathy has a unique clinical and pathophysiologic challenge with distinct laboratory traits. It is of great importance to monitor its progression in order to properly treat it to avoid severe complications and death.***

**Keywords** COVID-19, coagulopathy, Coronavirus, COVID, SARS-COV-2, coagulation, endothelial, thrombosis, anticoagulation, thromboembolism, Deep Vein Thrombosis

## 1.Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a betacoronavirus, one of the four genera of coronaviruses. It causes of a coronavirus disease (COVID-19) and has resulted in an ongoing pandemic. The increasing number of cases and deaths worldwide has generated a global effort to fully understand the pathophysiology of the disease (1). While the majority of critically ill patients with COVID-19 have isolated respiratory failure, multiple organ failure and dysfunction occurs in some patients with critical illness and more often in fatal cases (2). It is a known fact that hematologic findings, such as mild to moderate thrombocytopenia and lymphopenia, are associated with COVID-19; however, the most significant and concerning vascular aspect of this disease its association with coagulation disorders (2). A number studies have been conducted to understand COVID-19 and its association with coagulopathies. In early retrospective studies, cohorts of COVID-19 patients in Wuhan, China were found to have disturbances in coagulation parameters including elevated D-dimer levels and prothrombin time (PT) (1). Similar findings were observed in early case series in China and New York City and were proven to be associated with increasing COVID-19 severity and mortality (2). Thromboembolic complications have been consistently reported in almost all publications involving patients' populations from different countries. Due to the undeniable role of coagulation dysfunction in the initiation of several complications, assessment of coagulation parameters and the platelet count would be helpful in early diagnosis and also timely prediction of disease severity. In addition to the disturbances in laboratory markers of coagulation, COVID-19 infection has been associated with both venous and arterial thrombosis. It has been suggested that the SARS-Cov2 virus uses angiotensin converting enzyme-2 (ACE-2) as its main receptor; this membrane protein is expressed in the blood vessels, lungs, heart, kidneys, and numerous other tissues. There is reason to believe that SARS-CoV-2 binding to ACE-2 leads to local and systemic inflammatory response, endothelial injury, and an imbalance in pro-and anticoagulant signals, with resultant macro-and microvascular thrombosis (1).

## 2.Literature Review

### Laboratory Abnormalities in COVID-19 Patients

#### D-Dimer

D-Dimer is one of the protein fragments produced when blood clots are dissolved in the body. It can be detected in blood of humans and is a marker of possible coagulopathy. Extensive amount of research has shown that patients who died from COVID-19 had significantly high D-dimer levels, pro-thrombin time (PT) and fibrinogen on admission as compared to survivors of

COVID-19 infection. In a retrospective analysis of 343 patients from Wuhan, China, high levels of D-dimer were associated with mortality (18% vs.0.4%), with 92.3% sensitivity and 83.3% specificity. The dynamic association between D-dimer level and COVID-19 disease prognosis has been repeatedly demonstrated (3). Multiple studies also demonstrate a relationship between the trend of D-dimer levels and COVID-19 disease progression. Initial studies equated the elevation in D-dimer level with DIC, but ongoing work has suggested that COVID-19 associated coagulopathy is its own kind of disorder (4). Another study done in Wuhan china on 183 patients had an overall mortality of 11.5%, the non-survivors revealed significantly higher D-dimer and fibrin degradation product (FDP) levels, longer prothrombin time and activated partial thromboplastin time compared to survivors on admission; 71.4% of non-survivors and 0.6% survivors met the criteria of disseminated intravascular coagulation during their hospital stay (5).

Abnormally high D-dimer level is a marker for venous thromboembolism (VTE) in the ideal clinical setting. In COVID-19 patients, elevated D-dimer levels have been shown to be predictive of VTE development (6). This therefore shows that D-dimer level potentially has a role in clinical decision making for patients with COVID-19 infection. It is worthwhile to note that different institutions and laboratories vary in unit of measurements for D-dimer levels, with the most common measurements being ng/mL, µg/ml, and µg/dL. The ISTH has recommended admission testing and monitoring of D-dimer, prothrombin time (PT), platelet count, and fibrinogen in all hospitalized COVID-19 patients (1).

**Thrombocytopenia**

Thrombocytopenia is a condition in which there is low blood platelet count in the body. It has been found to be a significant finding in prognosis of COVID-19. A study was done on 466 patients admitted to hospital from Jan 23 to Feb 23, 2020, 380 patients with COVID-19. The incidence of thrombocytopenia in patients with critical disease was significantly higher than in those who had moderate symptoms (7). There are also reports of a phenomenon known as delayed phase thrombocytopenia (occurring 14 days after symptom onset). The delayed-phase thrombocytopenia in COVID-19 is prone to develop in elderly patients or patients with low lymphocyte count on admission. It is significantly associated with increased length of hospital stay and higher mortality rate (8). A retrospective study from Wuhan, China showed that 32 of 271 patients developed thrombocytopenia at 14 days after symptom onset, and the mean time from symptom onset to thrombocytopenia was 28.3 days (8). The majority of thrombocytopenic patients in this study were older with worse outcomes, including increased hospital length of stay and increased rate of mortality. It is thought that COVID-19 leads to bone marrow suppression through suppression which delays development of blood components (9). Even though thrombocytopenia is certainly not present in the majority of COVID-19 patients, it has been associated with poor prognosis at various stages in the disease process. Platelet count should thus be checked on admission and monitored in hospitalized COVID-19 patients (10).

**Von Willebrand Factor**

Studies have shown that patients with COVID-19 have significantly raised levels of VWF antigen and activity, likely contributing to a high risk of thrombosis seen in CAC. The high levels of both VWF antigen and activity have been clinically correlated with worse outcomes (11). Von Willebrand factor is a blood glycoprotein involved in the normal blood coagulation process. There is a deficiency and in some cases, a malfunction of VWF in von Willebrand disease and is involved in many other diseases, including thrombotic thrombocytopenic purpura. Endothelial injury which is caused by COVID-19 induced inflammation is thought to contribute to hypercoagulation because of elevated level of VWF (12). In a case report study done by Escher et al showed that markedly elevated plasma VWF antigen and Factor activity levels in a critically ill COVID-19 positive patient on hospital day 21, indicative of endothelial cell injury (13). Measurement of VWF level and activity is very unusual in the clinical setting, these data back up the suggestion that the coagulopathy of COVID-19, is as a result of endothelial injury (1).

**Antiphospholipid Antibodies**

Antiphospholipid syndrome occurs when your immune system mistakenly produces antibodies that make your blood much more likely to clot. APLs have been associated with other systemic viral illnesses but typically are not associated with an elevated thrombotic risk (4). COVID-19 infection is associated with an overall hypercoagulable state, but it is unclear whether the presence of APLs contributes to this coagulopathy or represents cross-reactivity between the virus and host cell receptors. It has been proposed that host B2-GP1 domains are exposed as a result of SARS-CoV-2 induced endothelial cell injury and give rise to cross-reactive anti-B2-GP1 antibodies or anti-cardiolipin antibodies (14). Further investigation is needed to elucidate the potential role of APLs within the schematic of COVID-19 associated coagulopathy. Current ISTH guidelines advocate for testing and diagnosis of anti-phospholipid antibody syndrome, if clinically indicated, with confirmatory testing 12 weeks following initial detection, even in patients with multiple positive APLs (15).

**Other Coagulopathies**

**Sepsis-Induced Coagulopathy (SIC) and Disseminated Intravascular Coagulation (DIC)**

In patients with sepsis, the imbalance in clot generation (coagulation) and clot breakdown (fibrinolysis) is an important response that occurs due to host defense mechanisms but is often linked to the development of organ dysfunction (16). In SIC/DIC, fibrinolysis is often inhibited due to the over-production of plasminogen activator inhibitor, with progressive fibrin clot formation within the tissue microcirculation leading to organ

dysfunction (17). To detect this type of coagulation disorder, a decrease in the platelet count and increase in prothrombin time (PT) the two laboratory parameters used in the SIC and are the most useful indicators (18). There is no increase in D-dimer levels with increasing SIC/DIC severity due to suppression of fibrinolysis, also known as fibrinolytic shutdown. Fibrinolytic shutdown is an acute impairment of fibrinolysis and it has been known to be a risk factor for increased mortality (19). In COVID-19, the D-dimer level is generally high according to research and usually greater than five times the upper limit of the normal range. Also, in SIC/DIC, anticoagulant proteins such as antithrombin decrease significantly because of increased vascular permeability and other mechanisms of coagulation (17).

**Antiphospholipid Syndrome (APS)**

Secondary antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia defined by the development of arterial and venous thromboses in the presence of antiphospholipid antibodies (20). Decrease in platelet count and a prolonged activated partial thromboplastin time (aPTT), are findings often are the clues to confirm this syndrome (21). Antiphospholipid syndrome (APS) is defined by clinical manifestations that include thrombosis and/or fetal loss or pregnancy morbidity in patients with antiphospholipid antibodies (aPL). Antiphospholipid antibodies are among the most common causes of acquired thrombophilia, but unlike most of the genetic thrombophilias are associated with both venous and arterial thrombosis (22). Non-thrombotic stenosis is frequently caused by attacks from autoimmune antibodies, with a pathological characteristic of vasculitis and without common vascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, or smoking. According to available literature, APS-related-non-thrombotic venous stenosis is rather rare and never reported before due to the misclassification or ambiguous classification of APS thrombotic complications when patients are combined with other multiple vascular risk factors in clinical settings (23).

**Heparin-Induced Thrombocytopenia (HIT)**

Heparin-induced thrombocytopenia (HIT) is a prothrombotic complication that can occur following treatment with heparin as the name itself suggests. Typically, heparin-induced thrombocytopenia begins with the appearance of thrombocytopenia about a week after the start of heparin therapy (24). In HIT, the most significant laboratory marker is a decrease in the platelet count. Heparin-induced thrombocytopenia (HIT) is a profoundly dangerous, potentially lethal, immunologically mediated adverse drug reaction to unfractionated heparin or, less commonly, to low-molecular weight heparin. Some patients with HIT develop serious thrombotic complications like limb ischemia and gangrene, while others may not develop such complications. Current laboratory diagnostic tools incur significant time delays before confirming HIT, therefore upon clinical suspicion, treatment of HIT should start immediately (25).

**Deep Vein Thrombosis (DVT)**

In the early months of COVID-19, a number of retrospective studies from Wuhan, China showed that hospitalized COVID-19 patients had a DVT rate ranging from 25-46% (26). In multiple studies, increased D-dimer levels were significantly associated with DVT. The incidence of VTE in patients with severe Novel Coronavirus Pneumonia (NCP) was 25%, which is believed to be related to poor prognosis. The significant increase of D-dimer in severe NCP patients is a good index for identifying high-risk groups of VTE (27) (28). When they were compared to 141 COVID-19 negative patients presenting with similar signs and symptoms, there was a 6.1% rate of DVT in COVID-19 patients compared to a 3.5% rate patients without COVID-19 (29). An abnormally high incidence of venous thromboembolism (VTE) has been reported among critically ill patients with COVID-19 assisted in the intensive care unit (ICU). However, VTE burden among non-ICU patients hospitalized for COVID-19 that receive guideline-recommended thromboprophylaxis is unknown (30). Increased D-dimer concentrations of more than 1.0 μg/ml predict the risk of venous thromboembolism. D-dimer level-guided aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies (31).

## 3.Methods

Publicly available Pubmed, England Journal of Medicine, Sage Journals, National Library of Medicine database were searched from 2020-2021. The following keywords were utilized: COVID-19, coagulopathy, Coronavirus, COVID, SARS-COV-2, coagulation, endothelial, thrombosis, anticoagulation, thromboembolism, Deep Vein Thrombosis, hypercoagulable, pulmonary embolism. Search results were restricted to articles written or translated in English and the following article types: retrospective reviews, cohort studies.

**Table 1:** Inclusion and exclusion criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Articles in English | Clinical Trials |
| Retrospective reviews, Prospective studies, Cohort, Case Series | |
| Articles with CAC laboratory markers | |

A review was done and articles were selected based on the PRISMA guidelines. Main focus was on published articles with adequate data on CAC and laboratory markers and also articles with data on other coagulation disorders.

**Table 2:** Search strategies

| Search Strategies | Number of Articles |
|---|---|
| COVID-19, coagulopathy, Coronavirus, COVID, SARS-COV-2, coagulation, endothelial, thrombosis, anticoagulation, thromboembolism, DVT, hypercoagulable, pulmonary embolism | 766 |
| Total number of articles excluded because of eligibility criteria | 730 |
| Articles excluded because they were not full reviews | 24 |
| Total number of studies accepted and reviewed | 12 |

**Table 3:** Summary of Relevant Lab Findings in COVID-19

| Study article | Country of origin | Design | COVID-19 Participants | Relevant findings |
|---|---|---|---|---|
| Artifoni et al. (31) | France | Retrospective cohort | 71 | Increased D-dimer concentrations of more than 1.0 µg/ml predict the risk of venous thromboembolism |
| Cho et al. (6) | NY, USA | Retrospective | 1170 | D-dimer levels are uniformly elevated in patients with COVID-19 |
| Rieder et al. (29) | Germany | Prospective | 190 | The maximum level of D-dimers during follow-up was associated with disease severity in COVID-19 |
| Cui et al. (27) | China | Prospective | 81 | The incidence of VTE in patients with severe NCP is 25% |
| Santoliquido et al. (30) | Italy | Retrospective | 84 | DVT may occur among non-ICU patients hospitalized for COVID-19, despite guideline-recommended thromboprophylaxis |
| Goshua et al. (12) | USA | Cross sectional study | 68 | Our findings show that endotheliopathy is present in COVID-19 and is likely to be associated with critical illness and death |
| Chen et al. (26) | China | Retrospective | 88 | D-dimer were 4ignificantly independent risk factors of DVT |
| Chen et al. (8) | China | Retrospective | 450 | |
| Tang et al. (5) | China | Retrospective | 183 | The present study shows that abnormal coagulation results, especially markedly elevated D-dimer and FDP are common in deaths with NCP |
| Yang et al. (32) | China | Retrospective | 1476 | Thrombocytopenia is common in patients with COVID-19, and it is associated with increased risk of in-hospital mortality. |
| Escher et al. (13) | Switzerland | Case series | 3 | Increased VWF and Factor VIII with normal ADAMSTS13 and platelet count |
| Helms et al. (33) | France | Prospective | 150 | 85% of tested with increased lupus anticoagulant |

## 4.Conclusion and Recommendations

COVID-19 associated coagulopathy has a unique clinical presentation with its very own laboratory characteristics. CAC results from complex interactions between regulators of inflammation and coagulation in the body. Consequent venous and arterial thrombosis in the vasculature leads to severe complications in COVID-19. The ISTH currently recommends that all hospitalized COVID-19 patients receive prophylactic dose low-molecular weight heparin in the absence of contraindications (10). Many of the papers reviewed in this article were case series, retrospective studies. It is vital that ongoing clinical research is to continue in order to determine pharmacologic strategies that will aid in improving the prognosis and thereby improving outcomes. As seen by these articles, checking for possible coagulopathy in COVID-19 patients should be part of a routine. This can aid in reducing the burden of disease and death that comes with it. CAC resembles other coagulopathies explained in this paper in some features but has a uniqueness that may be have it defined as a new category of coagulopathy. The clinical and laboratory features of COVID-19-associated coagulopathy (CAC) partially overlap with sepsis-induced coagulopathy (SIC) /disseminated intravascular coagulation (DIC), hemophagocytic syndrome (HPS) /hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome

(APS), and thrombotic microangiopathy (TMA); however, it does not completly match with any of these other coagulopathies.

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