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Utility of D-dimer as a Prognostic Factor in SARS CoV2 Infection: A Review

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Abstract

Coronavirus Disease-2019 (COVID-19) is currently a public health emergency and has been listed by the World Health Organization (WHO) as a pandemic. It has commonly been associated with pulmonary manifestations and there is a growing body of evidence of multisystem involvement of the virus. As evidenced by various case reports and cohort studies, COVID-19-associated coagulopathy has been a common manifestation amongst the critically ill and has been associated with increased mortality. The presence of venous thromboembolic events in patients who are critically ill due to COVID-19 has prompted the adoption of anticoagulation regimens aimed at preventing thromboembolic phenomena. Coagulation abnormalities have also been implicated in the progression and the severity of COVID-19 related acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC). There is strong evidence that D-dimer levels help predict which patients are at risk of thromboembolic events, progression to ARDS, DIC, immune dysregulation and mortality. We will review the utility of D-dimer as screening tool and in the risk stratification of COVID-19 patients prone to developing thromboembolic events, DIC, immune dysregulation and death. To date, the studies that have been published show the presence of elevated D-dimer levels in both the adult and pediatric populations and the measured level correlates with disease severity. Studies have also shown the relative increase of D-dimer levels in non-survivors compared to survivors. The elevation of D-dimer levels has shown to guide clinical decision making, namely the initiation of therapeutic anticoagulation and mortality benefit in patients with severe COVID-19 pneumonia compared to severe non COVID-19 pneumonia. Although the current body of literature suggested the use of D-dimer as a risk stratification tool and as a test to augment clinical judgement regarding the initiation of anticoagulation, randomized control trials are needed to fully understand the relationship between COVID-19 infection and the efficacy of D-dimer assays in clinical decision making.

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Keywords

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The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 virus) resulting in Corona virus disease 2019 (COVID-19) infection was first reported in late December 2019 in Wuhan, China and soon after human to human transmission was confirmed [1,2]. Early investigations suggested that the origin of SARS-CoV-2 may have come from bats. Zhou et al. demonstrated that SARS CoV-2 possesses 96% nucleotide identity with a bat coronavirus [2,3]. The acute worsening of clinical status, rapid progression to end organ failure and death, and the rapid transmission rate provoked public health concerns regarding the current outbreak [2,4,5,6,7]. The World Health Organization declared that the COVID-19 epidemic is a public health emergency of international concern on January 31, 2020. As of April 25, 2020, COVID-19, has been spreading worldwide, causing over 2.9 million cases and over 200 thousand deaths. [2] In the existing cases, some patients with SARS-CoV-2 pneumonia developed acute respiratory distress syndrome (ARDS), and a part of them worsened in a short period of time and died of multiple organ failure [8]. Angiotensin-converting enzyme 2 receptor (ACE2R) appears to be the surface receptor for SARS-CoV-2 receptor binding domain, to which the spike-like protein of the virus holds a very high affinity [9]. ACE2R is widely expressed in various organ systems, including the epithelium, cardiovascular system, kidneys, lungs, intestines, islet cells of pancreas and brain, which might provide an explanation to why some COVID-19 patients develop multiple organ failure. [7,8,10,11,12]

Coagulopathy is known to occur in the majority of patients who succumb to COVID-19 [6,8,13], as evidenced by presence of both microvascular and macrovascular thrombosis [14–19]. An Italian study directly measured inflammatory markers and components of clotting cascade in COVID-19 ICU patients and determined that the baseline is that of an increased clot strength, which in 100% of the patient population was related to high fibrinogen levels, and in about 60% to an elevated platelet contribution to clot strength. From an interpretative perspective, this pattern is consistent with a model of interaction between inflammation and coagulation [15]. A Brazilian autopsy study of deceased COVID-19 patients demonstrated high frequency of pulmonary microthrombi as well as small fibrinous thrombi in the glomeruli and superficial dermal vessels [17]. In addition to microvascular thrombosis, COVID-19 infection has been associated with a high prevalence of venous thromboembolism such as deep vein thrombosis (DVT) and central line thrombosis [20–26]. Hospitalization and infection carry inherent risk factors for the development of venous thromboembolism (VTE) due to immobilization and inflammatory processes. However, it appears that in COVID-19 there are additional mechanisms that might contribute to increased VTE risk, including endothelial damage, microvascular thrombosis and occlusion, or even autoimmune mechanisms [14,27]. Reported prevalence of VTE in ICU patients with COVID-19 is higher compared to patients admitted in ICUs for other disease conditions [28,29]. Pulmonary Embolism (PE) in the setting of COVID-19 has already been reported in literature [30]. In a recent report from EuroELSO, 20% of patients under extracorporeal

membrane oxygenation had PE [13,31]. Vascular occlusive events such as ischemic limbs, strokes and myocardial infarctions have been seen as well. [13,21,22,23,24,25,26,32]

Acute respiratory distress syndrome (ARDS) is one of the commonest complications of COVID-19 infection. ARDS/respiratory failure remains the leading cause of death (70%), followed by sepsis/multiorgan failure (28%), heart failure (15%), hemorrhage (6%), and renal failure (4%) [33]. Coagulation ranks among the top three leading causes of death [34]. Activation of the coagulation system has been shown to be relevant in the pathogenesis of ARDS, suggestive that these patients likely carry a concomitant diagnosis of disseminated intravascular coagulation (DIC), although it is noteworthy to mention that this is not a bleeding diathesis but rather a predominantly prothrombotic variant where the prothrombotic state is not seen to convert into a usual pro-hemorrhagic pattern [12,13,15,16,31,35]. Two studies revealed that intubated COVID-19 patients exhibit DIC features based on increased biomarkers such as greatly elevated D-dimer (1.2–16.9 μg/mL) [13,15]. Given that ARDS and DIC carry a high mortality rate, it is not surprising that 71.4% of patients who die of COVID-19 meet the International Society of Thrombosis and Hemostasis (ISTH) criteria for DIC while only 0.6% of patients who survive meet these criteria [13,36].

D-dimer is a biomarker of fibrin formation and degradation, typically used in risk stratification of VTE. However, the accumulating evidence in COVID-19 implies that D-dimer can be used not only for the prediction of VTE, but as a prognostic tool for risk stratification and disease progression to ARDS, DIC, cytokine storm and death [13,14,15,21,33,37–45]. During the inflammatory storm, the D-dimer increases significantly. In the early stage, this is the result of inflammation activating plasmin. However, as inflammation progresses in the presence of hypoxia, hypoxia-induced molecules can activate thrombin directly, and the activation of monocyte-macrophages would also secrete a mass of tissue factors and activate the exogenous coagulation pathway, which lead to an overall hypercoagulable state or even DIC [38]. Multiple studies have suggested that elevated D-dimer in severe COVID-19 is independently associated with higher mortality [6,8,13,20,22,31,43,44,46,47,48,49].

Several studies demonstrate elevated D-dimer values in both adult and pediatric patients with COVID-19 [21,42,50,51], with one meta-analysis demonstrating that 25.9 % of all COVID-19 positive patients had elevated D-dimer levels [52]. More severe COVID-19 infection requiring hospitalization tends to present more often with elevated D-dimer, which continues to increase with disease severity, as seen in a study whereg hyper-fibrinolysis, reflected by elevated serum D-dimer levels, was present in 97% of COVID-19 patients at admission and increased further in all patients prior to death while decreasing to control levels in survivors or non-ARDS patients [34]. Another study revealed that 75% of deceased COVID-19 patients had an increase in D-dimer compared to admission levels [37]. Higher D-dimer levels are further associated with development of complications leading to mortality. D-dimer values in COVID-19 ARDS have been shown frequently be higher than upper limit of normal and range from 0.46 – 5.37 μg/mL and are associated with 49% mortality, while remain significantly lower in patients who do not progress to ARDS, range 0.33 – 0.93μg/mL and are associated with 9% mortality [15,36,44,46]. When comparing survivors vs. non-survivors of COVID-19, D-dimer concentrations were markedly greater

in deceased patients (2.29–4.6 μg/mL) than in recovered patients (0.6μμg/mL). [46,53], with D-dimer levels (>1μμg/mL) appearing to be an independent risk factor for mortality, some studies specifying death at 2–3 weeks after admission (43, 44, 48). D-dimer >1.5 μg/mL is predictive of VTE in COVID-19, which has an overall 25% prevalence in non-anticoagulated patients admitted to ICU with COVID-19 pneumonia and carries a 40% mortality [14]. Tang et al reported that, among subjects with severe COVID19 infection not treated with heparin, mortality raised according with D-dimer levels [13,20,49]. One study found significantly higher D-dimer levels in diabetic patients with COVID-19 when compared to non-diabetics, indicating that diabetics are more prone to a hypercoagulable state in setting of COVID-19 infection, underscoring the predictive value of D-dimer for progression toward severe disease in that patient population [7]. It is useful to note that D-dimer best correlated with progression to severe disease and death. It may be less useful in mild COVID-19 cases, as suggested by a small study from China where no correlation between D-dimer values was found in patients who did not meet criteria for ICU, intubation or ARDS [54].

The early identification of high-risk patients based on D-dimer values could prevent progression to ARDS, DIC, cytokine storm and their associated increase in mortality, if anticoagulation is initiated [31,33,38,55]. In a study of 449 patients with severe COVID-19, anticoagulant therapy with mainly low molecular weight heparin (LMWH) was associated with lower mortality in a sub-population meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer [14,55]. Tang et al. showed that the use of heparin for 7 days or more resulted in decreased mortality in severe cases, especially the ones with sepsis induced coagulopathy (SIC) score > 4 or D-dimer > 6 fold of upper normal limit (greater than 3.0 μg/mL) [20,55]. A Chinese study of over 500 patients comparing outcomes in severe COVID-19 pneumonia vs. severe non- COVID-19 pneumonia found that use of prophylactic doses of enoxaparin in COVID-19 positive group with D-dimer levels greater than 3.0 μg/mL was associated with significantly lower mortality. This mortality benefit was not seen in severe non COVID-19 pneumonia group. [46] A meta-analysis noted that adjunctive treatment with LMWH within the initial seven-day onset of ARDS reduces the risk of 7-day mortality by 48% and the risk of 28-day mortality by 37% in addition to significantly improving PaO2/FiO2 ratio (the improvement was particularly important in the subgroup receiving high-dose LMWH of ≥ 5000 units/day) [56]. The possible need for higher doses was also noted in a study of critically ill patients with sepsis who ‘failed’ thromboprophylaxis [57].

In conclusion, the current literature seems to point to the utility of D-dimer as a screening tool for disease severity as well as a predictor of disease progression to end organ failure and mortality in ARDS. The utilization of heparin therapy based on the clinical picture and D-dimer levels can improve outcomes and prevent mortality in severely ill COVID-19 patients. While randomized controlled studies are needed to confirm these findings, we hope that this article can provide some guidance to clinicians battling the COVID-19 pandemic on the front lines.

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