D dimer as Biomarker for Covid-19 severity

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Abstract: Coronavirus infectious disease 2019 (COVID-19) infections, a highly coagulative and inflammatory state, predispose patients to arterial and venous thrombotic events due to platelet activation, endothelial dysfunction, and stasis. There are several reasons why elevated levels of D-dimer indicate the severity of the disease. This review paper aims to revise the significance of D-dimer levels in the covid-19. Thus, according to the studies, the increase in D-dimer level was significantly associated with the severity of the disease's course and the mortality rate. Moreover, in the case of mortality of hospitalized patients, a very high level of D-dimer is detected, which confirms that D-dimer can be used as a valuable biomarker for evaluating clinical outcomes in patients with Covid-19.

Keywords: COVID-19, Biomarkers, Severity, Comorbidity, Mortality

Introduction

Biomarkers are quantitative values that mirror the pathogenesis of the disease and help physicians identify the prognosis of the disease. They help public health specialists to develop treatment algorithms, accordingly differentiate the moderate to severely ill patients, and permit the adequate and appropriate allotment of healthcare resources and funds to eliminate the disease. Coronavirus infectious disease 2019 (COVID-19) infections, a highly coagulative and inflammatory state, predispose patients to arterial and venous thrombotic events due to platelet activation, endothelial dysfunction, and stasis. Recent evidence of a highly inflammatory condition during severe COVID-19 infection has encouraged investigations for specific biomarkers and their relationship with disease evolution. There are several reasons why elevated levels of D-dimer indicate the severity of the disease. Possible theories suggest the aggravated inflammatory response and inadequate anti-inflammatory response, which could cause a dysfunctional endothelial state leading to a prothrombotic state or simply the fact that patients with severe COVID-19 were often older aged and had co-morbidities which again created a hypercoagulable state (Wong et al., 2021). 58% of COVID-19 patients' autopsy have shown death due to pulmonary embolism or venous thrombosis, while 70% of patients died due to DIC ((Tang, Li, et al., 2020),(Wichmann et al., 2020)). In current clinical practice, dimer levels are used as a biomarker for DIC and for estimation and early diagnosis of Deep Vein Thrombosis (DVT). Average D Dimer levels in infected patients are 0.9mg/l and 36% of COVID-19-infected patients have a value greater than mentioned (Guan et al., 2020). In this article, we explore D dimer levels and its relation to comorbidities, prognosis, mortality, and future scope as a biomarker in clinical settings. D-Dimer is a fibrin degradation product used as a biomarker for the pro thrombotic state. Its levels were not used as a biomarker previously for

bacterial or viral infections. Since the outbreak of Covid 19, D dimer has been used as a potential biomarker for prognosis and treatment management in clinical settings. D dimer levels are significantly increased in critical or severe patients compared to mild/moderate patients indicating markedly high inflammation and consumptive coagulation state (J. Zhang et al., 2020). Based on the abovementioned, in this review paper, we aimed to revise D-dimer's significance level in the covid-19.

Comorbidities associated with D dimer levels

Patients with severe COVID-19 associated with co-morbidities (such as hypertension, heart disease, diabetes etc.) often had induced coagulopathy and excessive fibrinolysis, leading to increased blood-dimer levels. D-dimer levels increased up until the death of the patient. This was also accompanied by reduced platelet counts (Y. Li et al., 2020). Similarly, patients admitted to the hospital with coronavirus infection and with D-dimer levels >2.0μg/mL had a higher prevalence of the abovementioned co-morbidities. They also reported increased levels of C-reactive protein, neutrophils, prothrombin time, and reduced haemoglobin levels, lymphocyte, and platelets. And more than 90% of patients with levels >2.0μg/mL died (L. Zhang et al., 2020). Thus, elevated D-dimer levels have now become a common feature that can correlate with the severity and mortality associated with the disease and could be used as a marker to differentiate between COVID-19 patients. It can also serve as an independent biomarker to predict the course of the disease. Diabetes is one of the gravest and most common co-morbidity in the world. When uncontrolled hyperglycemia is combined with COVID-19, the debilitating effects of both these diseases could possibly synergize and create a poor outcome for the patient. This is due to the fact that diabetes patients often have a deficient immune system and its responses. Apart from this, the ongoing slow rate inflammation makes the patients very likely to have a cytokine storm which in turn could lead to a thrombotic event. D-dimer levels can help us assess the criticality of COVID-19 infected diabetic patients (Apicella et al., 2020). In an observational study, the analysis of D-dimer levels was compared between diabetic and non-diabetic patients. Both groups included COVID-19 infected patients with a moderate to severe level

of the infection. D-dimer levels in patients with moderate COVID-19 infection were found to be statistically significant (p=0.041) (Mishra et al., 2020). Henceforth, it is very likely that moderate to severe infections could lead to coagulopathy and miserable outcomes in diabetic patients.

An excellent example of adverse outcomes and comorbidities of raised D dimer is illustrated by Berger et al., a retrospective study of 2377 Covid 19 infected patients admitted in 4 New York hospitals from March 2020- May 2020. D dimer levels are measured at admission and routinely for admitted patients. Results noted are as follows, At admission, 76% (1823) patients had D dimer levels more than 0.23 μg/ml (230 ng/ml) and among them 37.8% (899) of study patients had critical illness requiring ICU (intensive care unit) admissions, 26.1% (620) required mechanical ventilation, 17.2% (410) suffered from a thrombotic event such as Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE), myocardial infarction, ischemic stroke and lastly 36.8% (871) developed acute kidney injury (AKI). Hence comparing patients with elevated D dimer levels to normal levels, increased risk of mechanical ventilation (29.9% vs 13.9%), AKI (42.4% vs 19.0%) and greater risk of thrombotic event (19.4% vs 10.2%) were noted. This concludes patients having initial elevated D dimer levels i.e., 43.9% of patients are at greater risk of developing of adverse outcomes compared to patients with normal levels (18.5%) at admission.

The same study also concludes that D dimer elevated levels at admission is found to be independently associated, irrespective of age, gender, sex, and preexisting illness, with adverse clinical outcome risk. This can be noted for two significant and serious complication, AKI, and thrombotic events. The higher the levels of D dimer in Covid 19 patients at admission, the higher the risk of AKI and thrombosis while admitted. Another trend this study noticed is fluctuating D dimer levels with disease progression. D dimer levels initially rises until Day 5 of admission, where it peaks and then progressively plateaus at higher levels than at admission but lower than peak during course of illness. For example, average D dimer levels at admissions were 0.387 μg/ml (387 ng/ml) with peak of about 0.767 μg/ml (767 ng/ml) at 5th day of admission. Hence the magnitude of

peak is also an independently associated with comorbidities.

Relationship of D dimer levels and clinical outcomes can also be studied. Regardless of factors such as age, sex, preexisting illness, mortality rates were much higher with higher D dimer readings. Risk of mortality were as follows, Patients with levels 0.23-0.50 µg/ml (230-500 ng/ml) were 1.7 times more at risk, levels at range 0.5-2.0 µg/ml (500-2000 ng/ml) were at 2.3 times at risk and very high levels of > 2.0 µg/ml (2000 ng/ml) were at maximum risk of about 4.2 times compared to patients with normal admission levels. With higher peak D dimer, mortality risk also increases proportionately. 301 Patients with highest peak D Dimer levels during the study (> 10.0 µg/ml (10,000 ng/ml)), 60% (182 patients) died. Hence Mortality rate was much higher in patients with high D dimer levels at admission (29.9%) than patients with normal D dimer levels (10.8%) and proving levels of D dimer is independently linked with risk of mortality and poor outcome (Berger et al., 2020).

D dimer and DIC development

Liu et al. suggested that the development of viral sepsis plays a pivotal role in the COVID-19 mechanism. SARS-CoV-2 could induce sepsis independently of secondary bacterial or fungal infections (Li et al., 2020). Patil et al. proposed that the virus itself is likely responsible for inducing a sepsis syndrome through various potential mechanisms, such as 1) immune system dysregulation, 2) respiratory dysfunction leading to hypoxemia, and 3) metabolic acidosis resulting from circulatory problems.(Patil et al., 2021) Liu et al. emphasized that severe infections of COVID-19 lead to varying degrees of damage to organs along with laboratory abnormalities such Lymphocytopenia, thrombocytopenia, elevated levels of D-dimer, CRP, liver and myocardial enzymes, and increased cytokine levels. These similarities to bacterial infection-induced sepsis led to suggestions that severe COVID-19 exhibits all the characteristic features of sepsis, including a specific viral pathogen, thereby warranting its consideration as viral-induced sepsis.(Koçak Tufan et al., 2021). Most cases of coronavirus infection develop into sepsis, causing a widespread organ damage. This sepsis in turn leads to a cytokine storm leading to the activation of endothelial cells which causes excessive activation of platelets and fibrinolysis and eventually leads to DIC (Kitchens, 2009). A similar study in Asia concluded that patients who died due to coronavirus infection had higher levels of D-dimer, Fibrin degradation product (FDP), longer Prothrombin time (PT) and activated partial thromboplastin time (aPTT) when compared with the alive and infected patients on admission to the hospital (p<.05). Not only that, a large chunk of patients who died had met the criteria for disseminated intravascular coagulation (DIC) in the hospital. DIC criteria are based on platelet count, D-dimer levels, fibrinogen and prolonged PT time. More than 85% of the patients who met the DIC criteria had levels >3.0 µg/mL. The patients had a median age of 54.1 years. The levels of D-dimer were measured for 14 days at an interval of 3 days during the patient's hospital stay. In the later stages of coronavirus infection, D-dimer levels were mild to severely elevated, which indicated that there was activation of coagulation and fibrinolysis secondary to viral infection that led to the death of the patients. D-dimer levels could possibly help us assess the prognosis of the disease when measured during the initial stages of the infection (Tang, Li, et al., 2020).

D dimer and Thrombotic Complications

Levels at admission can predict those at high risk for developing venous thromboembolism and help strategically reduce and early manage such patients (Nauka et al., 2021). It is proposed that D dimer levels greater than 1.5mg/L may serve as a biomarker to detect the occurrence of Venous Thromboembolism (VTE) in infected patients with a sensitivity of 85% and specificity of 88.5% (Bikdeli et al., 2020).

Sepsis and Pneumonia

Sepsis is a medical condition characterized by a dysregulated response to infection, traditionally associated with bacterial and fungal pathogens. Historically, viruses have not been as prominently linked to the development of sepsis. However, this paradigm has shifted recently due to the emergence of the COVID-19 pandemic, resulting in a significant impact on the medical literature and the discourse surrounding sepsis. The COVID-19 pandemic has prompted a reassessment of existing

medical definitions and concepts, particularly in the context of sepsis. This reevaluation is necessitated by the identification of a novel etiologic agent, the SARS-CoV-2 virus. (Koçak Tufan et al., 2021)

In recent times, there has been a notable emphasis on the association between sepsis and COVID-19. Some researchers argue that individuals with severe and critically ill COVID-19 meet the diagnostic criteria for sepsis and septic shock as outlined in the Sepsis-3 International Consensus. (Singer et al., 2016, Li et al., 2020) Consequently, use of the term 'viral sepsis' rather than the terms 'severe and critical illness' is more accurately describing these cases. This terminology shift underscores the importance of acknowledging SARS-CoV-2 as a causative agent in sepsis and highlights the need to adapt our understanding of sepsis in the face of evolving medical knowledge. D dimer levels can be used in COVID-19 patients as a biomarker for sepsis and pneumonia. In a cohort study done in Colombia, Patients with high admission day D dimer levels above 2409 ng/mL and suffering from sepsis had higher 28-day mortality proving as an independent indicator for mortality (Rodelo et al., 2012). Similar observation was noted for severe community-acquired pneumonia; higher levels may predict severity (Bikdeli et al., 2020). Majority of the COVID-19 patients who suffered from pneumonia developed acute respiratory distress syndrome (ARDS) and presented with dyspnea, cough, fever and existing co-morbidities. The median age of the patients were 51 years and a larger part were men. Amongst them, more than 50% of the patients reported mortality due to ARDS. The risk factors leading to ARDS's development and progression were increased age, neutrophil count and deranged coagulation profile (elevated D-dimer levels). Therefore, all these factors created a greater risk for the patient, resulting in a weak immunologic response. Also, there was a statistical difference of D-dimer levels in between ARDS patients who died and survived (difference, 2.10 μg/mL; 95% CI, 0.89-5.27 μg/mL; P=.001). As patients who died due to ARDS had significantly elevated D-dimer levels, measuring D-dimer levels in the early stage of the disease can be an inexpensive way to predict the severity and the mortality associated with the disease (Wu et al., 2020).

Hematological aspects of D dimer

The value of D-dimer is often considered as the most sensitive markers to identify the hematological aspects associated with COVID-19 infection. These levels indicate a high chance of development and activity of a thrombus. Consequently, the prophylactic use of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) is associated with lower deaths in severe COVID-19 patients (Tang, Bai, et al., 2020). The International Society of Thrombosis and Hemostasis (ISTH) advocates the usage of prophylaxis for thrombolysis in patients with COVID-19 infection who need to be admitted to the hospital (Thachil et al., 2020). Han et. Al. reported that the levels of D-dimer, fibrin degradation products (FDP), and fibrinogen (FIB) was significantly higher in coronavirus-infected patients than compared to the healthy control (5.02 vs. 2.90 g/L, p< 0.001). Also reported that severe COVID-19 cases had a higher level of D-dimer when compared with milder COVID-19 cases (5.59 vs. 5.10 g/L, p< 0.01). The controls also reported a lower prothrombin time activity and Antithrombin values (p <0.001). Overall, routinely monitoring D-dimer levels can help us identify the deranged values of the coagulogram in patients infected with coronavirus (Han et al., 2020).

Therefore, it can be concluded that, (a) D dimer testing can be helpful for triaging Covid 19 patients in hospital settings and (b), monitoring levels during first few weeks of hospital admission can improve clinical outcomes.

Serial D-dimer measurements can help us triage the coronavirus infected patient, providing ease of follow up and treatment for the patient. This was demonstrated by an observational study conducted in China. The levels of D-dimer were measured serially on Day 1,3 and 28 since the day of the patient's hospital admission. When D-dimer levels were measured on Day 1 and compared with the mortality after Day 28; it was reported that the levels had a survival sensitivity of 87% (95% CI = 86% to 89%) and a positive predictive value of 93% (95% CI = 92% to 95%). Similarly, the D-dimer levels on Day 3 showed a strong correlation of normal D-dimer values with that of the patient's survival. The sensitivity 76% (95% CI = 75% to 77%), positive predictive value was 98% (95% CI = 96% to 99%), specificity was

83% (95% CI = 72% to 91%), and the negative predictive value was 28% (95% CI = 24% to 30%). Thus, a normal D-dimer value can help us predict the patient's mortality and guide us in triage of the patient, which can help us in smooth and frictionless patient surveillance (C. Li et al., 2020).

Although the concrete evidence of elevated D-dimer levels associated with coronavirus remain yet to be elucidated. More newer studies from North America and Europe have displayed that retrospectively analyzing the D-dimer levels in post COVID-19 patients can help us understand some patterns of D-dimer as an important biomarker. In a study of 150 patients who were diagnosed with positive SARS-COV-2, with majority being females, white ethnicity, mean age of 47.3 years and with a median comorbidity count of 1 (interquartile range [IQR] 0–2); It was noted that 25% of the patients had elevated D-dimer levels even 4 months post the infection. These higher levels were associated with patients who required admission to the hospital during severe coronavirus infection compared to the milder disease and were aged >50 years (p < .001) and in those patients who had existing co-morbidities (comorbidity count - z 2.03 p < .001). All in all, constant elevated D-dimer levels are often associated with severe acute illness and in elderly patients (Townsend et al., 2021). Investigation of Sakka et al., recommended that levels of D-dimer could be useful in sorting the COVID-19 patients at the time of admission, which can be more helpful in efficiently managing clinically severe patients (Sakka et al., 2020).

D dimer levels and Mortality Risk

In a meta-analysis by Shah et al demonstrated that, D dimer levels more than 0.5mg/l had twice high risk of developing the serious clinical disease (P < 0.001) and four times higher risk of mortality compared to patients with lower levels (Shah et al., 2020). Studies have shown that patients with high admission day D dimer levels are at high risk for in hospital mortality and poor prognosis (Poudel et al., 2021). With D dimer levels >1 μg/mL patients have showed significant mortality (18 times) compared to survivors with lower levels (Zhou et al., 2020). Abnormal D-dimer levels and the biomarkers mentioned above were independently associated with below par outcomes in patients infected with coronavirus. Higher D-dimer levels

of ≥0.5 mg/L were corelated with three times the risk for poor outcomes (pooled-OR: 3.39; 95% CI: 2.66–4.33; p<0.00001). These poor outcomes were defined as intensive care unit admission (ICU), very low oxygen saturation (<90%), hospital admission, use of mechanical ventilation and even death. Henceforth, we can demonstrate that biomarkers such as D-dimer are beneficial and can help us see the adverse outcomes associated with COVID-19 infection (J. Zhang et al., 2020).

Furthermore, covid infection increases the risk of a thrombotic event in patients. Thus, D dimer levels can be used to monitor disease progression in high-risk prothrombotic complications such as pulmonary and venous thromboembolism, thus initiating early treatment. D Dimer testing is a relatively inexpensive laboratory testing and, with many clinical studies, has proved to be a sufficient biomarker in predicting outcomes; thus, its incorporation in routine testing can be proven helpful in managing high-risk patients and reducing high-risk mortality.

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D-димер як біомаркер тяжкості Covid-19

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Анотація: коронавірусна інфекція 2019 (COVID-19), гіперкоагуляція та запальні процеси, схиляють пацієнтів до артеріальних і венозних тромботичних подій через активацію тромбоцитів, ендотеліальну дисфункцію та стаз. Існує кілька ознак, за якими підвищений рівень D-димеру свідчить про тяжкість захворювання. Ця оглядова стаття має на меті переглянути значення рівнів D-димеру при COVID-19. Таким чином, згідно з дослідженнями, підвищення рівня D-димеру було суттєво пов'язане з тяжкістю перебігу захворювання та рівнем смертності. Крім того, у випадку смертності госпіталізованих пацієнтів виявляється дуже високий рівень D-димеру, що підтверджує, що D-димер може бути використаний як цінний біомаркер для оцінки клінічних результатів у пацієнтів з Covid-19.

Ключові слова: COVID-19, біомаркери, тяжкість, супутня патологія, смертність