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Review

Role of D-Dimer as a Marker of Severity and Long COVID-19

Sura Al-Shamma

Department of pathology, University of Warith AL-Anbiyaa, Karbala, Iraq

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Correspondence: Maryam Mahdi Salman
Email: sura.am2003@yahoo.com

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Abstract

D-dimer is a soluble byproduct of fibrin degradation. It's well known for its role in the exclusion of venous thromboembolism (VTE) and other thromboembolic disorders. Recently with the emergence of COVID-19, D- dimer used as an indicator of disease severity and outcome in acute phases. However, there is limited data regarding the significance of D-dimer in long-term COVID-19. This review tried to elaborate on the significance and mechanism of prolonged D- dimer in long-term COVID-19.

Keywords: D-dimer; Long COVID-19; COVID-19 coagulopathy; Laboratory changes

Introduction

Coronavirus disease (COVID-19) caused by the beta coronavirus SARS-Cov2 was first diagnosed in Wuhan in December 2019. It first presented as pulmonary symptoms, with fever cough, shortness of breath, and loss of smell and taste sensation. Mortality due to multi-organ failure was high among patients with severe fulminant disease who had respiratory failure that required intubation and ventilation [1].

D-dimer, the soluble fibrin degradation by-product, was reported to be elevated along with other inflammatory biomarkers in hospitalized COVID-19 patients, indicating a hypercoagulability state. Its high level was correlated with poorer prognosis [2-4]. However, the underlying pathophysiological mechanism is not clear. Many hypothesis was postulated suggesting the underlying mechanism. In addition to the classic risk factors of thromboembolism, COVID-19-related factors may play a role like inflammation and lung injury [5-6]. The "cytokine storm theory "was recently suggested as one of the most accepted theories explaining the mechanisms. All the above theories were studied and conducted on Acute COVID-19 syndrome. However, data regarding chronic or post-COVID-19 syndrome were scarce. Few reported high levels of plasma D-dimer among outpatient COVID-19 who were diagnosed more than three months ago. Whether the underlying mechanism for this elevation is the same as for acute or not, still not clear [7- 8].

For better understanding, a detail of the D-dimer structure, factors affecting its elevation, and association with COVID-19 will be discussed in this review aiming to explore the pathophysiology of elevated D-dimer in long COVID-19.

What is D-dimer?

D-dimer is the soluble product of fibrin degradation resulting from the action of plasmin on the cross-linked fibrin, which in turn resulted from the conversion of fibrinogen to fibrin by the action of thrombin on the N-terminal region of A α and Bβ chain at the E domain. The resulting fibrin monomers interact with each other through the D domain to form the fibrin polymer, which is further cross-linked by the action of Factor XIIIa (FXIIIa) [9]. The main sites of action of FXIIIa on fibrin are between the γ chain in the D -dimer of the adjacent fibrin monomers and between the carboxy-terminal ends of α- chains of fibrin monomer [10-11].

The activation of fibrinolysis started with the conversion of plasminogen to plasmin. Plasmin acts on the cross-linked fibrin polymer degrading it into different molecular weight soluble fragments including D-dimers. Therefore D-dimer will not be generated in the absence of cross-linked fibrin [9]. Thus D-dimer is an indication of both coagulation and fibrinolytic activity [11]. The resulting D-dimer produces a neo-epitope that is detected by specific antibodies used in the different assay methods [9]. There are more than 30 commercially available tests for D-dimer detection. All depend on the principle of applying specific monoclonal antibodies against the D-dimer epitope. Different techniques are used to detect these antibodies including latex agglutination immunoassays,

enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunofluorescence assay (ELIFA), chemiluminescent enzyme immunometric assay, and latex-enhanced immunoturbidimetric assay. In addition to the point of care (POC) test it is a qualitative technique mainly. Each of these methods has its considerations and restrictions [12].

Factors affecting D-dimer results

1) Issues of standardization

Due to the presence of many different methods for D-dimer estimation, and hence many commercially available kits, there is a tremendous variability between the reported results from different laboratories, which creates confusion and general errors. This issue has been studied thoroughly and many trials for standardization have been attempted. However, till now there is no consistent method for reporting D-dimer due to the following issues [13-14].

1. The presence of different cut-off values due to the presence of different methods of estimation and calibration [13-14].
2. The use of different units: The results of D-dimer are expressed using two different units; fibrinogen equivalent units (FEUs) that compare the mass of D-dimer to the mass of fibrinogen 340 kDa; and D-dimer units (DDU) that compare the mass of D-dimer alone 195 kDa. This makes a 1.75-fold difference between the two results [9].
3. The variation in the magnitude of unit (eg, ng/mL, or mcg/mL) recommended by different assays, in addition to the variation between the results from different laboratories. It has been reported that 33% of labs give the results in a different unit from that recommended which could result in a further discrepancy between the results [14-15].
4. The difference in proprietary monoclonal antibodies specificity [9, 16].

2) Pre and post analysis factors

According to the ISO International Organization for Standardization, the preanalytical phase is any process involved before the sample reaches the lab and starts processing. For the hemostatic lab, preanalytical errors affect the results more than the analytical and postanalytical errors and it is identified in 5.5% of all coagulation samples collected [17]. It is recommended for the D-dimer to be collected in straight needles with a diameter ranging from 19 to 22 gauge (G), as collection by butterfly may induce clotting and affect the results. However, most of the data collected from different studies showed no significant effect of butterflies on the results of D-dimer. The same applied to the use of plastic tubes. Although it recommended to use of glass tubes for the collection of samples, no significant effect were reported on using plastic ones [18]. On the other hand, the proper use of anticoagulants with the proper ratio is of grave importance for accurate results. The Clinical Laboratory Standards Institute (CLSI), as well as the World Health Organization, recommend the use of collection tubes containing 3.2% (105–109 mmol/L) buffered sodium citrate anticoagulant with a blood-to-anticoagulant ratio of 9/1 because the sodium citrate anticoagulant can be used only in a liquid form. The use of another additive, heparin or EDTA may affect the clotting results mainly prothrombin time (PT), partial thromboplastin time (PTT), and another clotting factor. The effect of these additives may be less pronounced in D-dimer however the issue of dilution is still a concern [18-19]. Even though, several D-dimer assays (including POC tests) allow the use of citrated, heparinized, or EDTA plasma. A correction factor of 0.84 was recommended by a few studies when using heparin to take into account the dilution of the citrate anticoagulant, a process that may be confusing in routine practice [19]. In one study heparin collected blood reported higher levels of D-dimer compared to citrated blood. However, these findings didn't reach statistical significance [20]. *In vitro*, hemolysis is still a source of error in coagulation lab accounting for 30-70% of the preanalytical issues [18]. Turnaround time (TAT) is a critical aspect of D-dimer reporting because this test is mostly used in urgent clinical conditions. The Italian consensus document has recently set an overall TAT of less than one hour for effective reporting [21]. Few reports have examined heterophilic antibody interference with D-dimer assays [22-24]. Recently, such cases were also reported in coronavirus disease 2019 (COVID-19) patients [25].

3) Age, Gender and associated morbidity

Many co-factors affect the results of D-dimer. A higher level of D -dimer is seen in older age, female gender, African American, chronic disease, diabetes, hypertension, active malignancies, surgery, and pregnancy [5-6, 26-31].

Significance of D-dimer

D-dimer is known to be elevated in different clinical scenarios. It is used as a valuable marker of coagulation and fibrinolytic activity as well as inflammation. A large data implying its significance in many conditions mainly in excluding the risk of venous thromboembolism (VTE), determining the optimal duration for

anticoagulant, diagnosing and monitoring disseminated intravascular coagulation (DIC) in addition to monitoring bleeding and thrombosis [29,32]. Recently with the emergence of COVID-19, D-dimer was widely used as a marker of inflammation indicating the severity of the disease activity as well as a prognostic tool for the outcome [1-2].

D-dimer and COVID-19

Since the emergence of COVID-19, many data relate the association of coagulopathy with the disease activity [1]. D-dimer, PT, and PTT were reported to be elevated [3]. In addition, the data reports a positive correlation between the level of D-dimer and the level of morbidity and mortality [4]. D-dimer namely was elevated in many studies and the level of increment was related to more severe disease course and high mortality [6-7, 33-34]. Furthermore, the level of D-dimer was used to assess treatment strategy regarding those who may benefit from anticoagulant therapy [34-35]. One study reported that a D-dimer level of greater than 1360 ng/ml at day 5 of admission could predict a poor prognosis at an early stage of COVID-19 [36]. Other study shows that serial measurement of D-dimer helps in predicting the outcome of the disease [6, 37]. Many Hypothesis was postulated to explain the mechanism of the increase in D-dimer in the acute phase. These include increased inflammation, hypoxia, endothelial inflammation, DIC, and other mechanisms [6].

Many reports have linked the increased D-dimer to the "cytokine storm "theory in which the level of pro-inflammatory cytokines IL6, IL7 G-CSF, TNF-α, and IL1 were reported to be elevated especially in severe cases. This was evident by the reported high level of CRP [24, 38]. TNF-α, and IL1 in specifically known to cause suppression of endogenous anticoagulant pathways. In addition, activation and proliferation of mononuclear cells (T-cells, macrophages, and natural killer) induce endothelial injury through the release of hundreds of cytokines. This effect is exacerbated by hypoxia and tissue anoxia resulting from COVID-19 infection. Together the net results are spread to small vessel vasculitis and microthrombi [6, 26, 39]. The post-mortem findings of platelet-rich microthrombi in the lungs and kidneys of patients with COVID-19 in the absence of features of hemolysis and thrombocytopenia confirm the above findings [39]. However, the presence of the microthrombi in this organ only raises the concern of restricted microangiopathy [34]. In addition, dysregulation of the immune system may underlie the pathogenesis of elevated D-dimer levels. This was confirmed by the reported presence of positive antiphospholipid (APL) in addition to complement activation in cases of severe COVID-19 which may explain the coagulopathy [40]. APL is known to be associated with viral infection. Its association with hepatitis C is well confirmed however in the case of COVID-19, there are few studies that reported positive APL in COVID-19 which didn't exceed 20% [41]. More data is needed to confirm this relationship [35, 40-42]. Activation of the complement system is another theory explaining the immune dysfunction in COVID-19. It was stated that" viral mediated endothelial injury may stimulate excessive production of thrombin, fibrinolysis inhibition, and continuous activation of the complement pathways resulting in prolonged dysfunction of the microvascular system and formation of microthrombi" [43]. Association with DIC was another hypothesis that proposed for the elevated D-dimer in acute COVID-19. This is confirmed by the findings of thrombocytopenia with elevated PT and D-dimer; However, the thrombocytopenia is less profound than the DIC in sepsis and D-dimer elevation is remarkable in COVID-19 patients. Therefore, the patient was not diagnosed as having DIC according to the DIC score of the International Society on Thrombosis and Haemostasis [39, 42, 44-45]. On the other hand, other studies report an elevation in D-dimer without an increase in PT or thrombocytopenia [35]. Other studies assessed the von Willebrand factor vWF, p selecting, and CD40 level in both critically ill and non-critically ill. Level was raised in both groups indicating that endotheliopathy and platelet activation play a role in the mechanism underlying the pathology of the disease [46-47]. Another theory was the genetic mutation induced by the infection which led to elevated D-dimer. Data reveals a molecular link connecting key genes to the coagulation process. Single nucleotide polymorphisms (SNPs) that strongly affect D-dimers are mainly associated with fibrinogen gamma (FGG), fibrinogen alpha (FGA), and factor V (F5) [48].

D-dimer and Long COVID-19

Many researchers worked to define what is long COVID-19. Fernández-de-las-Peñas *et al.* classifies COVID-19 into 4 phases. The National Institute for Health and Care Excellence guideline (United Kingdom) classified COVID-19 into long COVID-19 in which symptoms persist between 4-12 weeks and post-COVID-19 syndrome in which symptoms last more than 12 weeks with symptoms not explained by another diagnosis. World Health Organization (WHO) defines long-term COVID-

19 as symptoms persisting more than 3 months after the onset of COVID-19 that cannot explained by other diagnoses [49]. The prevalence of long-term COVID-19 varies in different studies ranging between 7-30%, being higher in patients who presented with severe acute infection and patients with poor health baseline [50-52]. The exact underlying pathogenesis for long COVID-19 was not clear however many mechanisms may play a role including; persistence of viral infection and immune activation (T-cell activation) [53], autoimmunity, microclots, persistent vascular inflammation, re-activation of latent infection, and dysbiosis and residual tissue damage [35, 43].

Again, an elevated D-dimer was also reported in many cases of long COVID-19 with about 15%-25 % of these cases reported to have elevated D-dimer [42, 54-55]. However, the mechanism of this elevation remains obscure and seems to be different from that of acute COVID-19. Many data have related the pathogenesis of convalescent or post-COVID-19 to the continuation of inflammatory response that results in continuous organ system damage and prolonged inflammation [56-58]. This was proved by the high CRP found in many studies [38,59], and the chronic elevation of IL-1b, IL-6, and TNF plasma levels reported by Christoph Schultheiß *et al*. [60]. However other studies found that CRP gets to baseline level three months post-infection despite a high level of D-dimer [61-62] and that even if it remains elevated this elevation has no significant relationship with the elevated D-dimer [63]. Of interesting findings is that there is no relation between D-dimer elevation and with previous peak of D-dimer during acute illness reported by Townsend *et al*. These findings suggest another mechanism of elevation from acute phase infection [62]. However, the possibility of asymptomatic re-infection in vaccinated patients cannot be excluded [54].

Other coagulation parameters like platelet PT PTT and fibrinogen level were also reported to be normal in long COVID-19 excluding low-grade DIC as the pathogenesis of elevated D-dimer [62]. Dysregulation of the immune system may underlie the pathogenesis of elevated D-dimer levels both in the acute and chronic phases. Data reported a persistent T-cell dysfunction in patients with chronic COVID-19. It was also reported that patients with long COVID-19 have higher levels of autoantibodies [53, 64]. Both the prolonged inflammation and the immune dysregulation may induce a hypercoagulable state and increase D-dimer [53]. Extravascular pulmonary fibrinolysis may play a role in the mechanism of elevated D-dimer [59, 62].

Conclusion

D-dimer is a test that helps in the diagnosis of coagulopathy. A high level of D-dimer indicates the activation of both coagulation and fibrinolysis. D-dimer is a valuable tool in excluding venous thromboembolism (VTE) rather than diagnosing it. This is due to the presence of many confounding factors that affect its level, in addition to the issue of standardization, the sensitivity, specificity, and predictive values (positive predictive value, PPV or negative predictive value, and NPV) vary with different cut-off values.

With the pandemic of COVID-19, data reported a correlation between the level of D-dimers and disease activity in the acute phase. Many hypotheses for the mechanism of this elevation have been proposed. The most accepted one was the cytokine storm theory. D-dimer was reported to be elevated in long-term COVID-19 as well. The mechanism for this elevation seems to be different from that of the acute phase. The theory of cytokine storm does not seem to be applied to the chronic phase. Many hypotheses were proposed like immune mechanisms, continuation of the acute phase, or even re-infection. The possibility of a combination of more than one mechanism may exist. Whether this elevation is of clinical significance or not is still not well known. Further investigations are recommended on this issue. The best recommendation for the time being is close observation of patients with elevated D-dimer with an individual assessment of each case.

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