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D-dimer, an important pathophysiological factor of deadly diseases including SARS

Chandan Kumar[1], Praveen Katiyar[2,*], Shashwat Katiyar[3], Ajay Kumar Gupta[4], Rakesh Kumar Dixit[5]

[1,2]University Institute of Health Sciences, Chhatrapati Shahu Ji Maharaj University Kanpur-208024
[3]Institute of Bioscience and Biotechnology, Chhatrapati Shahu Ji Maharaj University Kanpur-208024
[4]Institute of Pharmacy, Chhatrapati Shahu Ji Maharaj University Kanpur-208024
[5]Dept. of Pharmacology & Therapeutics, King George's Medical University, Lucknow-226003

*Corresponding Author. Email-drpraveenkatiyar@gmail.com

Abstract

Coronavirus 2019 (COVID-19) is an infectious viral disease with high grade of infectivity, caused by SARS (COV-2). COVID 19 infection was the first reported in Wuhan China. D-dimer is an important predictive tool often recommended for patients with severe Corona virus (COVID19) infection. In this systematic review, we aim to investigate the significance of D-dimer prediction in patients with COVID -19. We used research materials from PubMed, Medline, Embase to learn about D-dimer levels in COVID-19 patients and their effect on mortality.

Key words-COVID-19, SARS-CoV-2, D-dimer, Fibrinogen degradation product, Disseminated intravascular coagulation, Heart disease

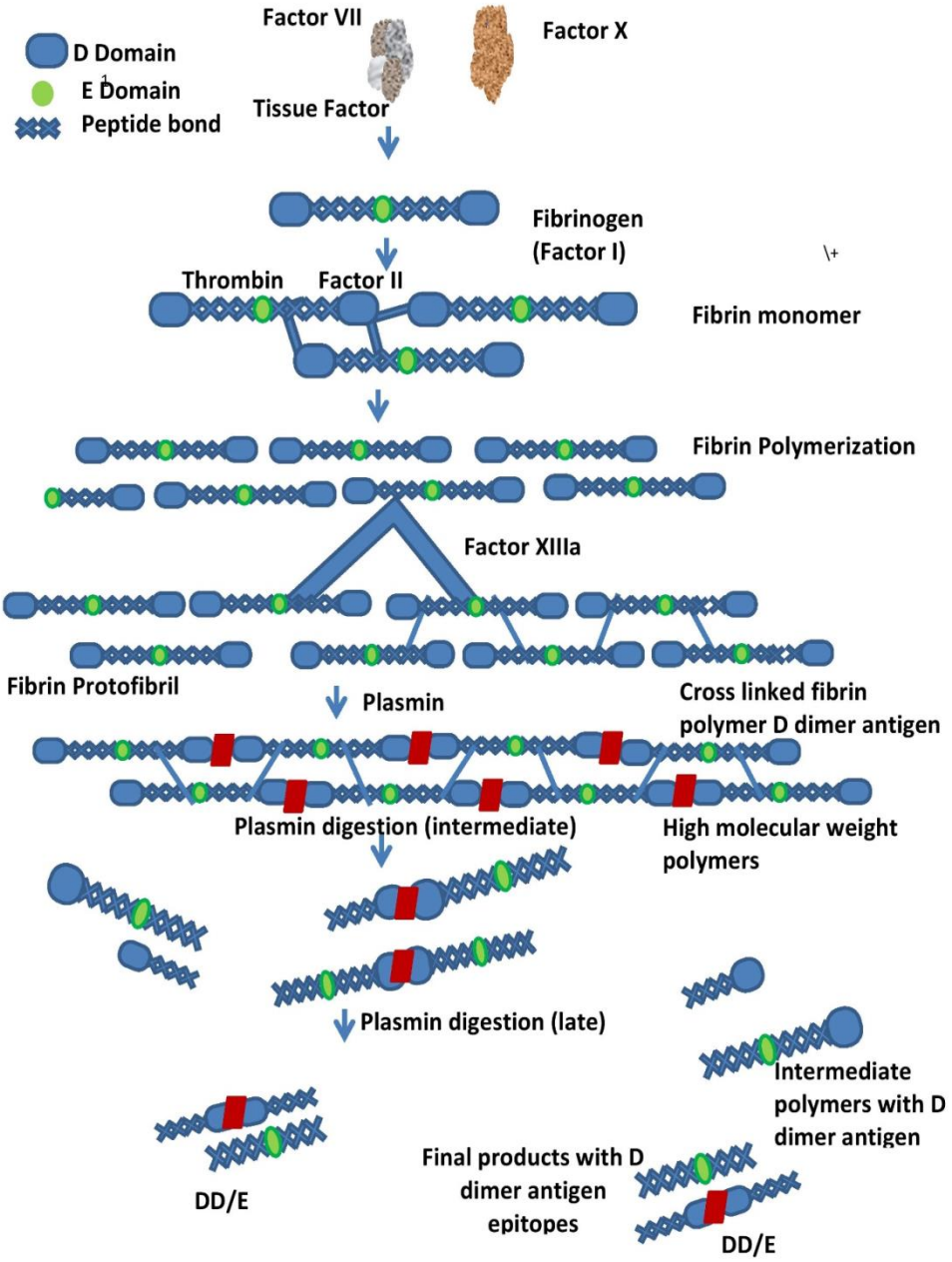
Introduction

Coronavirus 2019 (COVID-19) is an infectious disease caused by SARS (COV-2). Infection with COVID19 was first reported in Wuhan China (Seyed et al., 2021). Corona viruses (CoVs) are single-stranded RNA viruses which cause infections in humans and animals. Coronavirus belongs to the family Coronaviridae which includes alpha, beta, delta, and gamma coronaviruses with large RNA genomes and a different mode of replication. The new SARS-CoV-2 has been identified as a beta-coronavirus (Huang et al., 2020).

SARS-CoV-2 is transmitted through respiratory droplets and enters the target cell via the angiotensin-converting enzyme (ACE2) receptor. After incubation for 2–14 days, an asymptomatic stage may be seen, with fever, shortness of breath, cough, and progression of pneumonia, respiratory dysfunction, and global degeneration (Vidali et al., 2020). Over the past few years, Human-CoVs have often been found to be associated with high-risk and upper respiratory tract infections (RTI). Two human coronaviruses have been identified that cause high pathogenic effects, including corona-associated respiratory infections (SARS-CoV-2) and Middle Eastern respiratory infections (MERS-CoV) from different regions of the world (Bilian et al., 2020). In some patients, severe lung and extra-pulmonary complications can lead to respiratory failure and life-threatening events (Bilian et al., 2020).

Severe disease is associated with conditions such as Acute Respiratory Distress Syndrome (ARDS) and laboratory abnormalities including leukopenia, thrombocytopenia, and hypercoagulative state D-dimer elevation (Vidali et al., 2020, Mehrdad et al., 2020). Prolonged outbreaks of coronavirus 2019 (COVID19) has posed a serious threat to international health and the economy. It has been reported that approximately 50% of patients have increased D-dimer levels, as well as unusual D-dimer levels are associated with worse prognosis. D-dimer antigen is a unique sign of fibrin degradation formed by the sequential action of 3 enzymes: thrombin, factor XIIIa, and plasmin.

First, thrombin separates fibrinogen that produces fibrin monomers, which polymerize and act as a catalyst for factor XIIIa and plasmin formation. Second, thrombin activates plasma factor XIIIa bound to fibrin polymers to produce the active transglutaminase, XIIIa factor. Factor XIIIa promotes the formation of strong bonds between D-domains in polymerized fibrin. Finally, plasmin degrades connective fibrin to free up the degrading fibrin products and expose D-dimer antigen. D-dimer antigen may be present in fibrin degradation products found in soluble fibrin prior to its insertion of the fibrin gel, or after the fibrin clot has been reduced by plasmin (Soheir et al., 2009).



D-Dimer Antigen

There are 3 major steps of D-dimer antigen formation:

- The fibrinogen molecule is cleaved by thrombin to produce fibrin monomers. These monomers associate with fibrinogen or fibrin to form protofibrils. They are held together by noncovalent forces shown as dotted lines between the intermolecular D-domain and D-E domains.
- Factor XIIIa formed by thrombin on fibrin polymers then covalently attaches D domains and inserts a covalent intermolecular linkage designated by the diamond-shaped figure.

- Plasmin must degrade fibrin at multiple sites to release fibrin degradation products, which then expose the D-dimer antigen epitope. The initial fragments are high-molecular-weight complexes followed by further degradation to produce the terminal D-dimer–E complex, which contains the dimer antigen. The 3 phases of this process are labelled on the right side of the diagram, and the different molecular forms of fibrinogen and its subsequent transformation by thrombin, factor XIIIa, and plasmin are shown on the left side of the diagram. This is a schematic representation of just one protofibril. Multiple protofibrils are aligned side by side and undergo branching to make a fibrin gel.

Increase D-dimer marker of provoked coagulation process as fibrin formation is followed by fibrin degradation by plasmin the result in an increase in the FDP concentration in blood stream. Fibrinogen clotting underlies in the pathogenesis of many disorders and therefore elevated level of D-dimer have been found in the blood of patients with deep vein thrombosis, pulmonary thromboembolism, atherosclerosis, disseminated intravascular coagulation, sepsis, cancer and other disease as well as of major surgery (Al exender et al., 2016). Due to the injury to vascular endothelial cells caused by toxins released from fast growing tumour cells and the fibrinolytic activator on the surface of tumour cells, cancer patients often exhibit abnormal coagulation and fibrinolytic activities and their D-dimer levels tend to be higher than those in non-neoplastic populations.

The D-dimer levels of almost all cancer patients exceed the recommended limits according to the existing reference range (0–0.5 mg/L). Therefore, the high risk of DVT according to this range might be overestimated (Baboolall et al., 2019). Pregnancy is associated with gradual increase in levels of coagulation factors and decrease in natural anticoagulants. There occurs a significant decrease in fibrinolysis during pregnancy, which is in disagreement with the gradual rise in D-Dimer showing that although depressed, fibrinolysis remains an active process.

The overall effect of hypercoagulability and hypo fibrinolysis induced by pregnancy is rise in intravascular thrombosis and FDPs which include D-Dimer. Several studies investigated whether pregnancy related complications such as preeclampsia (PE), gestational diabetes (GDM) and pre-labour rupture of membranes (PROM) are associated with changes in the haemostatic system. Increase in D dimer could therefore occur before appearance of hypertension (Jeffrey et al., 2017).

D-Dimer in Cancer Patients

Patients with cancer are at increased risk of thrombosis, and VTE **(**Venous thromboembolism) is the second leading cause of death in cancer patients (Jeffrey et al., 2017, Prandoni et al., 2002).

Thromboprophylaxis has the potential to reduce the burden of VTE in cancer patients, but needs to be targeted to those at highest risk. A validated risk assessment tool that includes the site of the cancer, platelet count, white blood cell count, and haemoglobin level before chemotherapy, use of erythropoiesis stimulating agent, and body mass index has been used to assess the risk of VTE in cancer patients (Khorana et al., 2008; Khorana et al., 2014). Adding measurement of D-dimer levels to this scoring system may improve VTE risk prediction. Therefore, prospective management studies are needed to determine the benefit–risk of primary thromboprophylaxis in cancer patients identified using these risk assessment models (Ay et al., 2010).

D-Dimer in Pulmonary Embolism (PE)

A pulmonary embolism refers to a blood clot located within the pulmonary vasculature resulting in a decrease in blood flow downstream of the clot. While some patients can have small pulmonary emboli that cause few symptoms, others can have large pulmonary emboli blocking the main pulmonary artery or arteries. When a pulmonary embolism is located in the main pulmonary arteries bilaterally, it is referred to as a saddle embolus. A patient with a saddle embolus is at high risk of cardiopulmonary arrest and death. Obtaining a D-dimer can help in exploring the differential diagnosis in patients who present with symptoms or signs such as chest pain, shortness of breath, or hypoxia.

Based on the Wells Criteria, patients can be risk-stratified into low-risk, moderate-risk, or high-risk for PE. The Wells Criteria takes into various risk factors or symptoms of PE, including signs or symptoms of deep vein thrombosis (DVT), clinical suspicion for PE, the presence of tachycardia, recent immobilization (recent surgery), previously diagnosed PE or DVT, haemoptysis, and malignancy. Another scoring system is the Geneva Score or revised Geneva Score (r Geneva). It classifies patients as low-risk, intermediate-risk, or high-risk for PE. This score takes into account patient age (if older than 65 years), previous PE or DVT, recent surgery or lower extremity fracture, active malignancy, haemoptysis, unilateral extremity subjective pain, unilateral extremity tenderness to palpation, and elevated heart rate (Gando et al., 2016)

D-Dimer in Deep Vein Thrombosis (DVT)

A DVT is a blood clot located in the deep venous system in the arms or legs. They are most commonly located in the legs. Symptoms of DVT can include erythema, pain, swelling, and increased warmth of the affected extremity. There is also a risk-stratification score for DVT, which is the Wells Criteria for DVT. This scoring system considers recent malignancy, recent immobilization (including recent surgery), asymmetric leg swelling, the presence of collateral veins, tenderness along the location of suspected vein, previously diagnosed DVT, and high clinical suspicion for DVT. With this scoring system, one can either be classified as DVT “likely” or “unlikely” or further divided into low-risk, moderate-risk, or high-risk. Either way, a DVT can be ruled out with a negative D-Dimer in the low-risk or “unlikely” groups. In the moderate-risk, high-risk, or “likely” groups, a positive D-Dimer necessitates imaging with Ultrasound to evaluate for DVT. Again, however, if there is high clinical suspicion for DVT, one can order an ultrasound without obtaining a D-Dimer (Gando et al., 2016, Emily et al., 2021)

D-Dimer in Disseminated Intravascular Coagulation (DIC)

DIC is a common disease with high morbidity and mortality; it is characterized by systemic activation of the hemostatic system with intravascular thrombin generation, fibrin formation, and increased fibrinolysis. If untreated, it can lead to a depletion of platelets, clotting factors, and inhibitors, resulting in life-threatening bleeding and/or thrombosis. It is most common in hospitalized patients with infectious/inflammatory diseases, malignant neoplasms, trauma, or obstetric diseases. Recent classifications of DIC divide it into non symptomatic (pre-DIC), organ failure, bleeding, and massive bleeding subtypes. DIC is characterized by a consumptive coagulopathy as a result of increased thrombin generation and enhanced fibrinolysis. DIC can complicate an array of disorders and patients with DIC

may present with thrombosis, bleeding, or both depending on the cause and the extent of the Coagulopathy (Brenner et al., 2004).

D-Dimer in pregnancy

A normal pregnancy is characterized by changes in blood coagulation and fibrinolysis with a thrombotic nature, often referred to as physiological hypercoagulability. The results of many studies have shown that increased thrombotic activity during pregnancy is characterized by significant hyperfibrinogenemia, an increase in the activity of plasma coagulation factors, mainly VII, VIII, IX, X, and XII; a decrease in the concentration of the natural clotting inhibitor protein S; and by intensification of the processes of adhesion and platelet aggregation (Brenner et al., 2004, Hellgren, 2003)

The consequence of high procoagulation activity is increased fibrin turnover, as indicated by increasing concentrations of D-Dimers (D-D), recognized as the most sensitive markers of secondary fibrinolytic activation, with successive trimester (Szecsi et al., 2017). Changes in hemostatic systems occur gradually in normal pregnancy, reaching the highest degree of hypercoagulability in the third trimester and disappearing slowly during puerperium (Hellgren, 2003). They should be considered an adaptive mechanism protecting a pregnant woman against delivery hemorrhage and generally do not have any clinical implications. However, the risk of pulmonary embolism (which often results from VTE) has been found to be higher and occurs 4-6 times more often than in nonpregnant women of similar age (Duhl et al., 2007).

An increase in thrombotic risk occurs most often in pregnant women with cardiovascular risk factors (nicotinism, diabetes, hypertension, and overweight/obesity), with prolonged immobilization, use of hormonal oral contraception before pregnancy, and/or with pathological pregnancy factors (premature placental abruption, preeclampsia) (Simcox et al., 2015). Nicotinism and diabetes, in combination with hypoestrogenism, are particularly strong risk factors for VTE (Cheng et al., 2013).

Venous thromboembolism is manifested most often as deep vein thrombosis (DVT) of the lower limbs, or as pulmonary embolism (PE), or both together. Pulmonary embolism remains the main cause of perinatal mortality in developed countries and accounts for around 10-20% of pregnancy-related deaths (Gando et al., 2016). The occurrence of VTE is associated with a significant risk of serious complications in pregnant women, such as massive hemorrhage or post thrombotic syndrome.

The diagnosis of VTE in pregnant women is particularly difficult due to nonspecific clinical symptoms (limb oedema, shortness of breath) as well as the lack of standard diagnostic procedures for the exclusion of VTE based on low D-Dimer levels. The assessment of thrombotic risk during pregnancy by determining D-Dimers and fibrinogen concentrations is of limited value at present using ranges from the general population. This is due, as mentioned earlier, to the physiological and gradual increase in both D-Dimers and fibrinogen (Fb) that is observed in pregnant women. For this reason, during pregnancy, it is not possible to use the reference ranges of D-Dimers and fibrinogen concentrations determined for the general population (Prandoni et al., 2002).

D-Dimer in Cardiovascular Disease

Circulating D-dimer levels increase in patients with coronary artery disease, with the highest levels in patients with acute ischemic events, including myocardial infarction and unstable angina. In patients with chest pain, elevated D-dimer is an early marker of coronary ischemia and an independent prognostic factor for myocardial infarction. Only the D-dimer level significantly increased the model discrimination, and this factor was independent of other risk factors. More recently, plasma D-dimer levels in patients with coronary artery disease have been reported to independently predict no reflow after primary percutaneous coronary intervention (p-PCI) (Taylor et al., 2001, Danesh et al., 2001). The results of many studies have revealed elevated levels of D-dimer and other markers of coagulation activation in patients with atrial fibrillation. Also, a high D-dimer level was identified as a risk factor for subsequent thromboembolic and cardiovascular events (Lippi et al., 2008, Kuller et al., 2008). One study reported that a low D-dimer level was sufficient to exclude the presence of an atrial thrombus and to permit cardioversion to be performed without additional studies.

D-Dimer and Other Diseases

Elevated D-dimer levels have been reported in a wide variety of benign and malignant diseases characterized by infection, trauma, ischemia, bleeding, or thrombosis. In many of these diseases, investigators have attempted to use D-dimer levels for diagnosis, prognostication, or treatment. For example, D dimer levels have been investigated as an adverse prognostic and/or a risk factor for thrombosis in patients with malignant tumors, gastrointestinal bleeding and necrosis, intracerebral hemorrhage, sickle cell disease, migraine headaches, traumatic brain injury, tuberculosis, Cushing disease, asthma, membrane oxygenator failure, and many other diseases. Of these diseases, cancer has received the greatest interest. Overall, the risk of venous thrombosis in patients with cancer is as high as 7%, presumably due to the prothrombotic effect of malignant neoplasms and treatment-related risk factors such as immobilization, drugs, and surgical intervention (Hamlyn et al., 2015, Panting-Kemp et al., 2000). However, the common finding of elevated D-dimer levels in patients with cancer in the absence of thrombosis limits the diagnostic usefulness of these findings if used by themselves. However, age-adjusted cut-off values and risk-assessment models that combine the D-dimer with other biomarkers have been demonstrated to improve the diagnostic sensitivity of the D-dimer (Kline et al., 2005; Hijazi et al., 2017; Siegbahn, 2016, Ruff et al., 2016). Numerous studies have also shown the adverse prognostic significance of elevated plasma D-dimer levels in patients with cancer of the breast, colon, lung, gastric system, ovaries, prostate, and other organs.

Conclusion

As a marker of activation of coagulation and fibrinolysis, D-dimer levels provide a rapid assessment of thrombotic activity. The test has an established role in the diagnosis of VTE where it reduces the need for expensive imaging studies in the majority of patients with suspected DVT or PE. D-dimer is also used routinely for the diagnosis of DIC, and it may help to identify cancer and medically ill patients at high risk for VTE, who would benefit from extended thromboprophylaxis. D-dimer is of limited value in determining the optimal duration of anticoagulation in VTE patients and in ruling out

acute aortic dissection.

Standardization of D-dimer assays and further investigation of cut off adjustment by age or pre-test clinical probability would increase the effectiveness of the test for the diagnosis of VTE. Although D-dimer may be useful for risk assessment in other disorders, additional studies are needed to establish its role.

Elevated baseline D-dimer levels are associated with inflammation in COVID-19 patients and have limited predictive value for thrombosis. In the treatment of COVID-19 patients, the change of D-dimer levels should be observed dynamically. The abnormal changes of D-dimer and inflammatory factor suggest that anticoagulant therapy might be needed. Also, although the predictive value of VTE score need to be further studied in COVID-19 patients, it might be useful than baseline D-dimer levels for prophylaxis for venous thromboembolism in COVID-19 patients.

D-dimer test appropriately shows the presence of blood clot in the patient's body, even in lungs who have severe form of COVID-19, even this test is also beneficial in detecting other diseases like pulmonary embolism, in which there is decreased blood flow level downstream of the clot.

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