

D-Dimer Linked with Coagulopathies in Covid-19 Patients

Aishwarya Ujawane*, Shagun Kapoor, Himanshu Singh, Nihaal Singh

Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India

ABSTRACT

The devastating covid 19 has spread worldwide since December 2019 the initial stages of this disease can be linked with increased d dimer, prolonged PT and high levels of fibrinogen indicating the links between coagulation, thrombosis and covid 19 pandemic. In these review article we analysis different patient with different d dimer levels in SARS COV-2. D dimer levels are a potent marker of patient suffering or having complication related to thrombosis and coagulation. Studies have reported 3 to 4 folds increased in d dimer levels have been indicated with worst prognosis. Measuring coagulation parameters and d dimer levels in the early stages of the disease can help in controlling and proper management of covid 19 diseases. Hematological abnormalities like lymphopenia, thrombocytopenia, elevated d dimer levels, elevated cytokines, FDP's, interleukin 6 (IL6) appear as important predictors of the adverse effect of covid 19. covid 19 has a major risk factor for elderly patient when suffering as a complication of increased d dimer levels linked with coagulopathies or also associated with high death rate. In the severity of covid 19 infection fibrinolytic events and thromboembolic event correlates with each other. Reduced circulatory d dimer levels indicate any thrombotic events occurring also having high concentration of cardiac enzymes indicating emerging ventricular tension caused due to high increased pulmonary pressure leading to hypertension. In patient suffering from covid infection ROTEM pattern indicates hypercoagulability and reduce fibrinolysis without disturbing elevated d dimer levels. We conclude that the pulmonary organ that is the lung is the main source of d dimer in covid 19 patient.

Key words: Covid 19, SARS-Co-2, D- dimer, Thrombosis, Coagulopathy

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Corresponding author: Aishwarya Ujawane

e-mail ✉: ujawaneaishwarya@gmail.com

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INTRODUCTION

The outbreak in HUBEI located in central China gave the birth to beginning of new disease called corona virus or SCAR COV -2 which causes lung related disease. The mucosal barrier is the primary site for entry of this covid infection. In the recent cases or new cases showing biopsy a modified covid 19 transplantation has also been shown on internal and skin image but not the virus itself [1].

Introduction to D-Dimer

Covid 19 diseases has been associated with stimulation or induction of coagulation cascade pathway which leads to coagulation and thrombotic events and also associated with increased level of d dimer elevated prothrombin

time (PT) and also increased level of fibrinogen. Studies have reported 3 to 4 folds increased in d dimer levels have been indicated with worst prognosis. In the manifestation such as diabetes, cancer, stroke and pregnancy can cause elevated d dimer level in patient suffering from covid 19. For controlling and preventing covid 19 we can estimate d dimer level and coagulation parameter in early stages which can be helpful to cure the diseases. The d dimer consists of 2 fragments of fibrin formed by the action on the fragment by the enzyme plasmin. Which indicates presence of fibrinogen degradation product (FDP'S) in the blood? Elevated d dimer level closely link with hypercoagulability and fibrinolysis. The d-dimer score or value can be detected by trade kits available which are based on monoclonal antibody [2].

Normal levels of d dimer

With normal d dimer level of 327 ng /ml considered within the normal local range however quarter of the patient have d dimer levels higher than 500ng per ml upto 4 months after diagnosis [3].

D dimer link with coagulopathy in covid19 patient

From studies wherein hematologic parameters have been investigated in intense suffering with COVID-19, there have been modifications in the specific coagulation index, i.e., higher D-dimer level, longer prothrombin length and calculation of lower platelet thrombocyte count. These mutations reflect a hypercoagulable circumstance present in severe sufferers with COVID-19, which may additionally create micro thrombosis within the lungs and different organs [4]. In the case of pulmonary micro thrombosis, endothelial cell damage leads to over expression, accumulation of platelet thrombocyte count and thrombus formation at the damage site lead to platelet thrombolytic count and depletion of megakaryocytic leading to reduced platelet production and increase in usage. The growing body of evidence that identifies PLTs as progenitor cells involved in prodrotic and prothrombotic responses in many viral diseases. Increase coagulability is also a major sign of inflammation and other chemical cytokines and such as interleukin (IL), can affect all forms of thrombus formation. Therefore, inhibition of PLTs overuse and compounding can reduce inflammation and the seriousness of respiratory distress [5]. The presence of thrombotic property of virus indicates the thrombus formation detected in pulmonary bronchial and lung autopsies.

Objective

In this article the main objective is to compile different research article based on D-dimer linked with coagulopathies in covid 19 patient.

Laboratory findings

On admission, typical tests included a complete blood count, coagulation profile, renal and hepatic function, creatine kinase, electrolytes, myocardial enzymes, CD4 and CD8 cell counts, C-reactive protein, and procalcitonin. The level of D-dimer is measured by an immunoturbidimetric assay with a reference range of 0–0.50 mg/l. Any patients with a strong clinical suspicion of pulmonary embolism/deep vein thrombosis (PE/DVT) underwent Doppler ultrasonography and CT pulmonary angiography. All patients have received a chest CT scan [6]. All medical data is collected in a clinical laboratory, including the number of leukocytes, lymphocytes, and eosinophil's; lymphocyte and eosinophil percentages; D-dimer, high-sensitivity protein C (hsCRP), procalcitonin (PCT), and serum creatine kinase concentrations; and D-dimer, high-sensitivity protein C (hsCRP), procalcitonin (PCT), and serum creatinine [7].

Diagnosis

D-dimer levels were found to be elevated in nearly half of the patients, and aberrant D-dimer levels are linked to a bad prognosis. As a result, in some stable individuals who die suddenly, acute organ failure, embolism, and infarction should be considered. Although the incidence of thrombosis in COVID-19 patients has not been identified, deep vein thrombosis (DVT) and pulmonary

embolism (PE) were found to be 20.5 percent and 11.4 percent in SARS cases, respectively. In addition, pathologic studies based on autopsies or biopsies revealed the formation of thromboembolisms, which closely resembled the symptoms of SARS and MERS corona virus contamination [8].

We tested the connection among D-dimer levels with patients experiencing the ISTH technique of intravascular coagulopathy (DIC). The D-dimer levels of COVID-19 patients with DIC who met the ISTH diagnostic technique have been better than the ones without DIC at baseline and final checks, and the distinction changed into vast [9,10].

The fibrinolytic breakdown of fibrin which is known as d dimer when it is increase in the blood it causes hypercoagulability and secondary fibrinolysis in body this is very helpful in finding out diseases related to clot formation. Patient suffering from covid 19 disease having noninvasive condition and 71 % of patient killed by SCAR COV 2 have been related to disseminated intravascular coagulation level. The covid 19 patient surviving rate was 0.6%. Furthermore, 25% of patients with severe COVID-19 had venous thromboembolism (VTE), while the 30% of patient suffering from covid 19 were also diagnosed with thromboembolic event occurring in lung, the patient also suffer from ischemic stroke have found to have raised d dimer levels [11,12].

Treatment

As the patient suffering from covid 19, this viral infection created a pandemic worldwide which leads to complication such as thrombo-embolism events occurring various organs such as in lungs, peripheral veins etc. Anticoagulant is the primary therapy for curing this embolism. VTE like complication in covid 19 is best treated by heparin therapy as it has major benefits over other drugs as it does not interfere in metabolism of other drug and its duration of action is also short. Regular drug monitoring is required like activated partial thromboplastin time along with aXa test is used [13].

Therapy including low molecular weight heparin may also be used as an alternative to heparin therapy. It has advantages over heparin is that the regular drug monitoring is not required if taken successfully.

Anticoagulant drugs administered by oral routes such as warfarin, rivaroxaban powder, edoxaban, apixaban, factor Xa inhibitor are used for the treatment in covid 19 patient [14]. Heparin therapy is one of the best treatments in covid 19 due to having better outcome in treatment disease.

More findings that can be done are the discovery of a laboratory feature of CAC indicates a thrombotic state with a high fibrin benefit [15]. However, some of the symptoms of intravascular coagulation distribution remain unchanged. Prothrombin time and duration of prescribed thromboplastin are slightly extended, in that case, and platelet counts are usually normal or slightly

lower. Prothrombin time, thromboplastin time activated. Doctors did not report D-dimer levels, but experienced coagulopathy (e.g., prothrombin duration of more than 3 seconds or active thromboplastin duration more than 5 seconds) to be at risk independent thrombosis [16].

Pathophysiology

Corona virus causes pneumonia that progressively increases cytokines level in severity. There is the extensive inflammatory condition in lungs of patient [17]. This disease causes many deformities in other systems like in hemostatic system. The inflammatory reaction in lung causes damages to the lung vascular system which lead to coagulation in lung at the initial stage of the disease. There is increase in frequency of thrombosis in veins and also the frequency of thrombotic increases the is 16 to 69 % [18]. The pathology behind the covid 19 complication related to thromboembolism is related to complex interaction between release of cytokines, platelet hyper activation and damage to the endothelium of blood vasculature.. The viral infection also induces inflammatory reactions by stimulating proinflammatory cytokines and also inflammation within the reproductive system. There is functional impairment of endothelial which the major factor for formation of clot in covid 19 [19].

Severe infections with sepsis and acute respiratory distress syndrome, disseminated intravascular coagulopathy develops with interactions between cells and plasmatic cells within thrombosis and the production of thrombin, is together associated with inflammatory as well as thrombotic condition. There are 4 proteins involve spike (S), membrane (M), envelope (E), and nucleocapsid (N). An additional layer of s protein has associated with binding of ACE 2 receptor [20]. Various other mechanism which causes complication are increased secretion of von-Willebrand factor (vWF) from injury to endothelium, production of toll like receptor and complementary activity has been additional related with covid 19 induce clot formation [21]. CAM, TAT, thrombolytic activator factor are important indicators for precisely assessing thrombosis related pathology in covid 19 [20-22].

Complications

The complication in covid 19 patient is related to thromboembolic events and autoimmune disorders. The risk of formation of clot in vein is an emerging problem. Past history of this complication and hereditary thrombophilia may elevate greater risk of thromboembolism with patient in hospital. It has been found that compliance with disseminated intravascular coagulopathy and microangiopathy of lung thrombi lead to suppression of immune system in severe cases of covid 19 in the body. Damage to the vascular endothelium of blood vessel stimulate intravascular, coagulopathies may lead to multifailures. Apart from d dimer count it is uncommon to detect various other products of fibrin degradation (d dimer – E complex) in human plasma.

Decrease in platelets count less than 1,50,000 and

elevated d dimer level more the 2500ng per ml is the initial finding which also associate with bleeding problems during admission of patient to the hospital leading to serious illness and death as well as different coagulation infirmities. Symptoms of inflammation, including c reactive protein and erythrocyte sedimentation rate, were also associated with thrombosis high thresholds and symptoms of inflammation are associated with serious illness and death. Increase in the inflammatory markers as well as thrombotic markers also leads to serious illness and mortality [23].

Examined the incidence of venous and arterial thrombotic events, including deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, myocardial infarction and systemic arterial events in 184 patients with Covid-19 pneumonia allowed in the critical care facility.

D dimer measurement laboratory test required is the initial investigation of patient in this disease. Because there is the major complication of thromboembolic events occurring in multiple organs with further immune system failure in covid 19 patient. Checking or monitoring d dimer levels is the important means for the treatment. In patient the ROTEM pattern shows increase in coagulation which reduces thrombolytic potency inspire a disturbing elevation in d dimer level. It is concluded that in covid positive patient the pulmonary organ that is the lung is the main source of d dimer.

Elevation d dimer level s and associated with disseminated intravascular coagulopathy may the major cause of deaths in hospitals. There is increase in risk with the patient already suffering from major CVS or CNS diseases. Elevation in d dimer levels are consistent with seriousness of the disease and is accurate indicator of increased mortality rates in the hospitals in patients of corona virus disease. Elevated d-dimer level have found to be directly associated with magnitude of pulmonary embolism and leads to adverse effect which are detect by various clinical parameters. Therefore d dimer test is mandatory in covid patient. If the reports indicates high d dimer levels it means that there are abundance of blood cloths present in the patient's body which further indicates that higher the d dimer levels more is the requirement of the oxygen in covid 19 patients because of increase blood cloths and less supply of blood to the organs. Related studies were reported [24-27].

The antigen of d dimer is formed by the combination of fibrinolysis and fibrin process. The enzyme involved in formation of these antigen are plasmin, factor 12a etc. the molecules of fibrin which contain d antigen is formed during repairing of tissues, stoppage of bleeding, formation of cloth. The d dimer antigen is an important factor which shows indication in when there is formation of cloth in the veins it also shows the risk of the particular disease. The antigen of the d dimer is not recognized until by the action of plasmin which results in release of fibrin which is cross linked to each other which

is under action of important enzyme that is plasmin enzyme. So the d dimer antigen plays a major important role in disease identification. One the FDP that is the d dimer assays helps measure an epitope on degradation product of factor 13 a fibrin which is crosslink by various methods. All the assays used monoclonal antibodies to detect an epitope. It is very specific antigen detection test as each monoclonal antibody has its own specificity. The level of d dimer especially below 250 ng per ml after removal of oral anticoagulant drugs has lesser risk of relapse of venous thromboembolism. The risk of development of disease is small during intake of oral contraceptives but the risk increases as on stoppage of anticoagulant because the coagulation again comes back to normal and formation of clot can occurs. D-dimer measurement is important in determining not only the performance of fibrinolysis but also the magnitude of the unaffected state. D-dimer measurements such as high-density fragments may be helpful in determining whether patients will continue fibrin degradation.

Preexisting any CVS and CNS disease carries high risk of covid 19 to complications, this is concluded by any hypothesis or requires any clinical investigation in order diagnose it. As there is increase of level of d dimer this may be indication of any heart damage of heart related disease in the patient which may lead to serious complication. The anticoagulants which are given for controlling the level of d dimer are safe for the patient suffering from covid 19. Covid related coagulopathies used for explaining thrombogenic changes in the patient suffering from covid patient. The patient related with increased level of d dimer along with the heart damage leads to serious side effect in hospitals. D dimer is the potent marker for accessing patient for detecting thromboembolism which is the major complication or problem of covid 19. Lower level of d dimer exclude thrombus formation in veins and have a low clinical probability. Elevated d dimer level is not the only investigation done for detecting formation of thrombus in vein there are other criteria for diagnosis of formation of thrombus in vein. The increase level of prothrombin markers can be indicative of synthesis of thrombus formation or increased fibrinolysis.

CONCLUSION

By seeing or estimating the level of d dimer we can say that if there is increase level means there are many clots present in the body. D dimer level increased in patient of covid 19 indicates that intensive care should be taken because there may be formation of cloth and the patient may die due to infarction of various organs. D dimer is formed from fibrin which is cross linked to each other its increase levels does not mainly indicates patient suffering from formation of thrombus in vein unless signs and clinical features are present related to the disease. Hence we conclude that different coagulation disorders and its complication is linked with increase d-dimer count.

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