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Study on the assessment of disease severity in COVID-19 patients from D-dimer estimation in a tertiary care level hospital, in West Bengal

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a RNA virus which infects both human beings and animals. COVID-19 infection is presently a very important, global health related problem. It is contagious. The COVID-19 or severe acute respiratory syndrome (SARS)-CoV-2 virus affects the lungs very commonly through the angiotensin converting enzyme 2 receptor which is present in abundance on the surface of type II alveolar cells. It leads to SARS. The severely ill COVID-19 patients suffer from massive intra vascular clot formation. Therefore, coagulation tests are very useful to assess the severity of the cases. **Aims and Objectives:** The aim of our study is to assess, that whether by examining the blood of a COVID-19 patient for D-Dimer, the treating physician can judge the severity of the case and come to a conclusion regarding the line of management. **Materials and Methods:** This is a retrospective study conducted in the departments of Pathology and Radiology of RG Kar Medical College. Records of the patients who were admitted for COVID-19, from September 2020 to September 2021, have been studied for their D dimer levels. The computed tomography (CT) scan findings of the respective patients have also been studied from the departmental records. **Results:** In our study, the median value of D-Dimers of 80 samples came out to be 1.4. (1) CT scores, (2) presence or absence of crazy paving sign, and (3) perilobular fibrosis in CT scan have been studied and compared with the median D Dimer values. It has been seen from our study that out of 54 cases whose D-Dimers were <1.4, 41 cases had moderate CT score, and 13 had CT score in the severe range, 26 cases had crazy paving sign in their CT findings, and 28 cases did not show crazy paving sign in their CT findings, and 22 cases had perilobular fibrosis in their CT reports, and 32 cases did not have perilobular fibrosis. The P-values came out to be <0.05 for all the three parameters. **Conclusion:** We concluded from the study that D-Dimer levels can reflect the severity of lung parenchymal injury and can be used to judge the severity and to plan the line of management of COVID cases.

Key words: COVID-19; Coagulation parameters; Coagulopathy

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome (SARS)-CoV-2, a virus that causes illness in humans and animals. The outbreak of the disease was first noticed in a seafood market in Wuhan city in Hubei Province of China in mid-December 2019 and has now spread worldwide. WHO has declared COVID-19 a pandemic on March 11, 2020.

COVID-19 is a RNA virus related to the SARS virus. The virus uses the angiotensin-converting enzyme 2 receptor for entry into cell.

Persons who are infected by the virus are the main source of infection. Droplets from infected persons serve as main source of infection. Droplets which have landed on surfaces may also serve as source of infection on touching, as the virus remains viable. The incubation period ranges

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from 2 to 14 days. Period of infectivity starts 2 days before onset of symptoms and lasts up to 8 days.

Common symptoms of COVID-19 include fever, cough, and fatigue, shortness of breath, expectoration, myalgia, rhinorrhea, sore throat, diarrhea, anosmia, and loss of taste.

Patients of COVID-19 may suffer from serious respiratory distress, disorders of blood coagulation, renal, neurological, and cardiological complications. Elderly persons and persons with existing illnesses such as hypertension, cardiovascular disorders, chronic renal disorders, disorders of respiratory system, and those with immunodeficiency are at higher risk of severe COVID infection.[1]

Severe COVID-19 can be complicated with coagulopathy, that is, disseminated intravascular coagulation (DIC). It has a prothrombotic character with high risk of venous thromboembolism. The incidence of venous thromboembolism among COVID-19 patients in intensive care units appears to be somewhat higher compared to those patients with coagulopathy from other diseases and reported in other studies. D-dimer level estimation might help in early recognition of such high-risk patients. D-dimer level estimation can also predict outcome of the patient. Data show that in patients with severe COVID-19 infection who meet the criteria of sepsis-induced coagulopathy or have markedly elevated d-dimer, anticoagulant therapy appears to be associated with lower mortality in such patients. Recent recommendations suggest that all hospitalized COVID-19 patients if indicated should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation.[2]

Pattern recognition receptors which are present in plasma membrane and endosomal vesicles, in response to viral infection, recognize different molecular structures of the invading virus (pathogen associated molecular pattern). Binding of the two results in activation of several signaling pathways causes some gene expression. Such genes are responsible for production of cytokines such as IL-1, TNF, and IL-6, adhesion molecules and anti-viral cytokines. Cytokines are produced by macrophages, endothelial cells, epithelial cells, connective tissue cells, and activated lymphocytes.

Cytokines cause endothelial cell activation in blood vessels. This activation leads to expression of endothelial adhesion molecules such as E selectin, P selectin, and ligands for leukocyte integrins and increased procoagulant activity of endothelium. Cytokines mediate and regulate immune and inflammatory reactions. Thus COVID-19 can lead to a cytokine storm as the immune system gets activated and the uncontrolled release of cytokines that may ultimately result in multi-organ failure. SARS-CoV-2 mainly targets the lung epithelial cells, lymphocytes, and the vascular endothelial cells. In the lung alveoli, there is infiltration of neutrophils, and thrombus formation in the lung microvasculature. This leads to injury to lung alveoli, interstitial edema, and increased vascular damage.

Patients suffering from severe COVID infection have been found to be associated with CT chest abnormalities, diminished platelet (PLT) count, prolonged prothrombin time (PT), and increase of blood D-Dimer level. The former changes in severe COVID infection are related with the process of DIC.[3]
D-dimer is a fibrin degradation product (FDP). D-dimer value <0.5 μg/mL is usually considered normal. It is widely used as a biomarker for thrombotic disorders.

Most of the current studies only use D-Dimer as an indicator of disease progression.[4-6] The coagulation profile of critically ill and dead patients was worse than that of lightly infected patients, which includes increased D-Dimer, decreased PLT, and prolonged PT. Therefore, COVID-19 patients should be given special attention in relation to anticoagulation therapy.[3]

Another research showed that 71.4% of patients who died of coronavirus met the criteria of DIC given by the International Society of Thrombosis and Hemostasis (ISTH).[3] One study on COVID-19 suggested that the characteristics of COVID associated coagulopathy (CAC) are different from clotting disorders caused by bacterial infections and other diseases. CAC usually presents in case of COVID-19 infection, D-dimer (D-D), and fibrinogen (FIB) levels are elevated, but there are few abnormalities in the PT and PLT count during the initial course of the disease.[3]

The ISTH has recommended routine testing and monitoring of blood for the hemostatic markers in all COVID-19 cases and released the guidance for the management of coagulopathy.[7]

Routine testing of blood of COVID patient for the parameters of hemostasis has been recommended by the ISTH.[7]

Thrombocytopenia is considered as a sensitive indicator of coagulopathy induced by sepsis. However, in case of COVID 19 infection thrombocytopenia is not very common.[8]

It has been seen that patients who are suffering from moderately severe COVID infection are showing higher PLT counts in their blood. Patients with very high PLT

counts and with diminished lymphocyte count in their blood have been reported longer period of hospitalization.[9]

COVID-19 cases have some typical coagulation disorders. Blood coagulation parameters show predominant increase of D-dimer and FDP over PT prolongation and thrombocytopenia. Among the cases who did not survive from COVID-19 infection, the maximum score in the DIC parameter was in the D-dimer measurements (85.7% compared with 23.8% in PLT count, 28.6% in FIB, and 47.6% in PT).[10]

Blood level of D-dimer serves as a marker of inflammation.[11]

CT scan of chest is the parameter by which the extent of lung parenchymal involvement and severity of inflammation can be visualized.[12] CT assessment provides a direct visualization of the anatomic injury of lung parenchyma as compared to non-specific inflammatory biomarkers. Total percentage of involvement of the 5 lobes of right and left lungs by ground glass opacity is given as a score out of 25, which is called Modified CT Severity Index.

In this study, we have taken the help of CT scan parameters to assess the severity of the disease.

Aims and objectives

To determine whether higher blood levels of the coagulation parameter D-Dimer are associated with greater disease severity. Disease severity is assessed from the chest CT scan findings of the respective patient. Thus from the study we want to assess that, whether the level of blood D Dimer can be used as a parameter to judge the severity of COVID related lung injury, which can guide the clinician to decide the line of management.

MATERIALS AND METHODS

Our inclusion criteria are (1) adult patients who were laboratory-confirmed as infected with COVID-19 and were admitted in the hospital and (2) Patients who also had report of CT scan of chest with CT severity index.

Study type and design

The study is a retrospective study.

Place of study

The study has been performed in the Department of Pathology and Department of Radiology of RG Kar Medical College and Hospital.

Study period

The study has been started after the approval of the ethical committee. Records of patients who were admitted for COVID-19, from September 2020 to September 2021, have been studied for their D dimer levels in the department of Pathology. The CT scan findings of the respective patients have also been studied from the departmental records of radiology department.

Study population

The study was conducted on the D Dimer reports of 80 hematological samples and Chest CT reports of the respective COVID-19 patients who were hospitalized during the period between September 2020 and September 2021.

Study sample size

80 case reports were studied. Sample size has been derived using the statistical formula for estimating proportions, $n=z^2 pq/d^2$ (z=confidence coefficient, p=proportion from previous study, $q=100-p$).

Tools and technique

Blood samples of patients admitted for COVID-19 are tested in the pathology department for complete blood count, D-Dimer level, PT, and activated partial thromboplastin time (APTT). Many of them with respiratory symptoms are also advised CT scan of thorax.

This study has been performed on 80 such reports of blood D-Dimer levels and also their respective Chest CT reports.

D Dimer has been estimated by an immunoturbidimetric assay method using venous plasma of COVID 19 patients in 3.2% sodium citrate anticoagulant, using STA-Liatest D-Di Plus kit.

Plasmin is the fibrinolytic enzyme derived from the inactive plasminogen. Plasminogen is converted into plasmin by plasminogen activators such as tissue plasminogen activator and urokinase. Plasmin degrades fibrin into FDPs among which D-Dimer is the terminal product. Thus presence of D-Dimer in blood reflects activation of coagulation system.

Suspension of latex microparticles coated by monoclonal antibodies specific for D-Dimer is mixed with the test plasma. Antigen antibody reaction takes place leading to an agglutination of the latex microparticles which results in increase in turbidity. This increase in turbidity is reflected by an increase in absorbance measured photometrically.

The D-Dimer levels of 80 COVID patients and their respective CT findings were gathered, tabulated and finally analyzed statistically. The CT features which are considered in our study are (1) CT scores; (2) crazy paving sign; and

(3) perilobular fibrosis. CT scores were graded by the Radiologists as mild, moderate, and severe according to their values.

Statistical analysis

Significance levels were calculated using social science statistics Chi-square calculator indexed in February 2013.

RESULTS

The median value of D-Dimers of 80 samples came out to be 1.4. Out of 54 cases whose D-Dimers were <1.4, 41 cases had moderate CT score and 13 had CT score in the severe range, out of 26 cases with D-Dimer>1.4, 9 cases had moderate CT score and 17 had CT score in the severe range (Table 1).

Out of 54 cases whose D-Dimers were <1.4, 26 cases had crazy paving sign in their CT findings and 28 cases did not show crazy paving sign in their CT findings. Out of 26 cases with D-Dimer>1.4, 23 cases had crazy paving sign and 3 did not show crazy paving sign (Table 2).

Out of 54 cases whose D-Dimers were <1.4, 22 cases had perilobular fibrosis in their CT reports and 32 cases did not have perilobular fibrosis. Out of 26 cases with D-Dimer >1.4, 10 had perilobular fibrosis and 16 cases did not have it (Table 3).

The CT Score – 16/25, consolidation, crazy paving, lobar pneumonia, perilobular fibrosis, and traction bronchitis are present with D Dimer values-1.86 (Figure 1).

The CT Score-9/25, consolidation, and crazy paving are present with D Dimer -0.95 (Figure 2).

The CT Score -9/25, consolidation, and crazy paving are present with D Dimer – 1.34 (Figure 3).

DISCUSSION

In our study, the median value of D-Dimers came out to be 1.4. (1) CT scores, (2) presence or absence of crazy paving sign and (3) perilobular fibrosis in CT scan have been studied and compared with the median D Dimer values.

It has been seen from our study that out of 54 cases whose D-Dimers were <1.4, 41 cases had moderate CT score and 13 had CT score in the severe range.

Out of 26 samples that had D-Dimers more than 1.4, 9 cases showed moderate CT scores and 17 cases showed severe CT scores. The P value came out to be <0.05, that is, statistically significant.

Table 1: Distribution of patients according to CT score and D-Dimer (n=80)

CT score	D-Dimer ≤1.4	D-Dimer >1.4	Total
	No (%)	No (%)	No (%)
Moderate	41 (51.2)	9 (11.2)	50 (62)
Severe	13 (16.2)	17 (21.2)	30 (37.5)
Total	54 (67)	26 (32.5)	80 (100)

The P<0.05

Table 2: Distribution of patients according to crazy paving and D-Dimer (n=80)

Crazy paving	D-Dimer ≤1.4	D-Dimer >1.4	Total
	No (%)	No (%)	No (%)
Present	26 (32.5)	23 (28.75)	49 (61.25)
Absent	28 (35)	3 (3.75)	31 (38.75)
Total	54 (67.5)	26 (32.5)	80 (100)

The P<0.05

Table 3: Distribution of patients according to Peri-lobular fibrosis and D-Dimer (n=80)

Peri-lobular fibrosis	D-Dimer ≤1.4	D-Dimer ›1.4	Total
	No (%)	No (%)	No (%)
Present	22 (27.5)	10 (12.5)	32 (40)
Absent	32 (40)	16 (20)	48 (60)
Total	54 (67.5)	26 (32.5)	80 (100)

The P<0.05

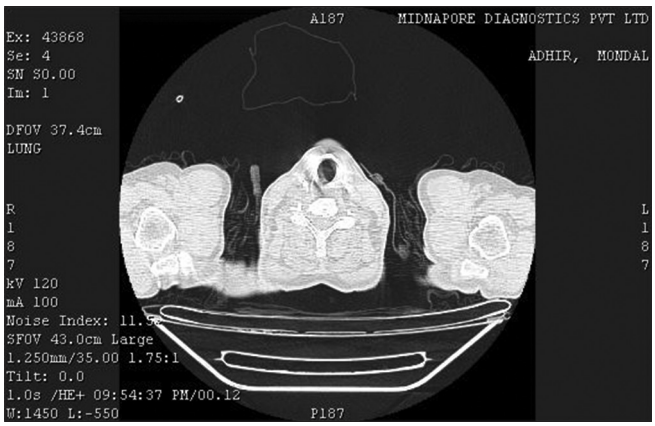

Figure 1: CT findings with D-Dimer >1.4

Next out of 54 cases whose D-Dimers were <1.4, 26 cases had crazy paving sign in their CT findings and 28 cases did not show crazy paving sign in their CT findings.

Out of 26 samples that had D-Dimers more than 1.4, 23 cases had crazy paving sign in their CT findings and 3 cases did not show any crazy paving sign in their CT findings. And the P value came out to be <0.05, i.e. statistically significant.

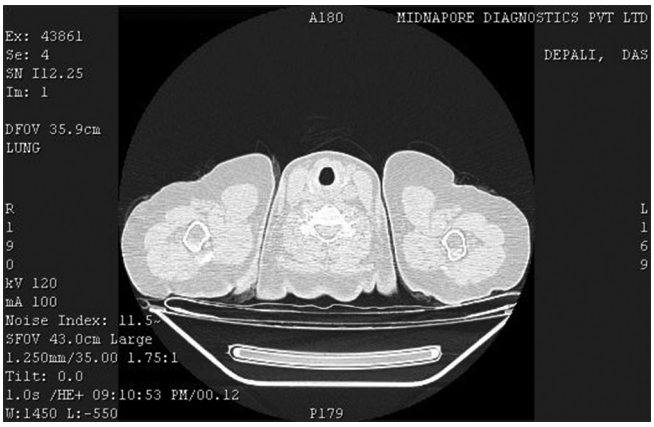

Figure 2: CT findings with D-Dimer <1.4

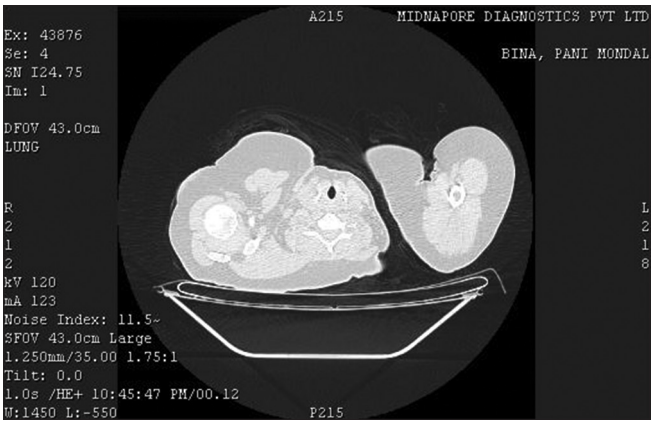

Figure 3: CT findings with D-Dimer <1.4

Finally out of 54 cases whose D-Dimers were <1.4, 22 cases had perilobular fibrosis in their CT reports and 32 cases did not have perilobular fibrosis.

Out of 26 samples that had D-Dimers more than 1.4, 10 cases had perilobular fibrosis in their CT reports and 16 cases did not have perilobular fibrosis. And the P value came out to be <0.05, that is, statistically significant.

A meta-analysis on similar topic that was published in 2020, studied (1) the association between coagulation parameters and severity of COVID-19, (2) association between coagulation parameters of intensive care unit (ICU) and non-ICU patients, and (3) association between coagulation parameters of survivors and non-survivors.

The results showed that PT, D-Dimer, and FIB of mild cases were all lower than those of severe cases, *P*<0.05; P<0.05; and P<0.01; respectively.

The results also showed that PLT count, APTT, and D-Dimer between ICU and non-ICU patients had no statistical difference, P>0.05; P>0.05; and P>0.05; respectively. The PT of ICU patients was higher than that of non-ICU patients P<0.05.

The results also showed that the PLT level of survivors was higher than that of non-survivors P<0.001. PT and D-Dimer of survivors were both lower than those of non-survivors P<0.001; P<0.001; respectively.

Another similar study was conducted in Tongji Hospital of Huazhong University of Science and Technology in Wuhan in 2020 on 183 patients suffering from Novel COVID Pneumonia. The results of the study showed that D-dimer (μg/mL) in 162 survivors was 0.61 (0.35–1.29) and in the non –survivors was 2.12 (0.77–5.27), P<0.001 and the normal value of D Dimer are <0.50.

A study conducted in 4 hospitals in Kathmandu on 182 patients showed the mean D-Dimer among patients who survived was1.067 μg/ml and in non-survivors was 3.208 μg/ml.[13]

Limitations of the study

The study is record based involving two departments. So the sample size could not be increased.

CONCLUSION

Our study shows that D-Dimer level in COVID-19 cases can be considered as a risk factor for assessing the disease severity. This may help clinicians to identify the patients who may have poor outcomes and may require intensive therapy. The definite diagnosis for COVID infection depends on real-time reverse-transcriptase-polymerase chain reaction. However, chest CT is a reliable method to assess the extent of lung parenchymal involvement.

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REFERENCES

1. Clincical Management Protocol: Covid-19. Government of India Ministry of Health and Family Welfare Version 5,03.07.20. New Delhi: Directorate General of Health Services (emr Division).
2. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS and Syrigos S. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: Emerging evidence and call for action. Br J Haematol. 2020;189(5):846-847. https://doi.org/10.1111/bjh.16727
3. Zhang A, Leng Y, Zhang Y, Wu K, Ji Y, Lei S, et al. Meta-analysis

of coagulation parameters associated with disease severity and poor prognosis of COVID-19. Int J Infect Dis. 2020;100:441-448.
https://doi.org/10.1016/j.ijid.2020.09.021

4. Tang N, Li D, Wang X and Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020a;18(4):844-847.
https://doi.org/10.1111/jth.14768
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
https://doi.org/10.1016/S0140-6736(20)30566-3
6. Pryzdial EL, Sutherland MR, Lin BH and Horwitz M. Antiviral anticoagulation. Res Pract Thromb Haemost. 2020;4(5):774-788.
https://doi.org/10.1002/rth2.12406
7. Thachil J, Thang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026.
https://doi.org/10.1111/jth.14810
8. Iba T, Levy JH, Levi M and Thachil J. Coagulopathy in COVID-19. J Thromb Haemost. 2020;18(9):2103-2109.
https://doi.org/10.1111/jth.14975
9. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with corona virus disease-19. J Med Virol. 2020;92(9):1533-1541.
https://doi.org/10.1002/jmv.25767
10. Tang N, Li D, Wang X and Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
https://doi.org/10.1111/jth.14768
11. Agapakis DI, Tsanilas D, Psarris P, Massa EV, Kotsaftis P, Tziomalos K, et al. Coagulation and infammation biomarkers may help predict the severity of community-acquired pneumonia. Respirology. 2010;15(5):796-803.
https://doi.org/10.1111/j.1440-1843.2010.01773.x
12. Scherer PM and Chen DL. Imaging pulmonary infammation. J Nucl Med. 2016;57(11):1764-1770.
https://doi.org/10.2967/jnumed.115.157438
13. Poudel A, Poudel Y, Adhikary A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS One. 2021;16(8):e0256744
https://doi.org/10.1371/journal.pone.0256744

Authors' Contributions:
NBB- Concept and design of study, prepaired manuscript, interpreted results, reviewed literature, and statistical analysis; **JB-** Radiological interpretations and revision of the manuscript.

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