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Original Research Article

D Dimer – Prognostic indicator for disease severity in patients hospitalised with COVID 19

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ABSTRACT

Introduction: Patients of Covid 19 infections present with different severity. Levels of D Dimer in these patients can be correlated with disease severity for management and prognosis.
Aims and Objectives: To evaluate the usefulness of D-Dimer levels in blood to correlate with disease severity in COVID 19 patients.
Materials and Methods: Retrospective study was done in Department of Pathology of Secondary Care hospital that became designated covid hospital from May 2021 to June 2021 on 60 COVID 19 positive admitted patients. D dimer levels were analysed and correlated with clinical severity of disease.
Results: Out of total 60 patients, 33 were in mild, 23 in moderate and 4 were in severe category. In mild cases D Dimer varies from 43 ng/ml to 183 ng/ml. In moderate cases D Dimer varies from 270 ng/ml to 991 ng/ml. In severe cases D Dimer varies from 1043 ng/ml to 2463 ng/ml. The study suggests cut off levels for D Dimer as up to 200 ng/ml for mild, 200-1000 ng/ml for moderate and more than 1000 ng/ml for severe category in COVID 19 patients.
Conclusion: D dimer helps in identifying severe disease and can be used as an essential biomarker in developing the management protocol for COVID 19 patients.

1. Introduction

December 2019 witnessed the inexplicable outbreak of pneumonia cases in Wuhan, China. On January 9^{th}, 2020 a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as the culprit for the outbreak and the infection was later named as coronavirus disease 2019 (COVID-19) by the World Health Organisation.[1] The number of COVID-19 patients spread globally, grew exponentially and thus COVID-19 was declared as a pandemic state on 11^{th} March 2020.[2]

SARS-CoV-2 is transmitted by respiratory droplets which enters the target cell through the ACE 2 receptor.[3] The disease has incubation period of 2–14 days followed by a symptomatic phase which may manifest, with fever, dyspnoea and cough, may progress to pneumonia, severe respiratory distress or multi system involvement. In few studies, the signs and symptoms of the disease were observed to be of mild type while the cases which were severe on admission had a higher mortality rate.[4] Therefore, it is essential to identify the cases early, evaluate the possible prognosis for the clinical diagnosis and treatment of the COVID-19 patients.

Earlier researches carried out for community-acquired pneumonia & chronic obstructive pulmonary disease have suggested the utility of D-dimer as a prognostic biomarker.[5,6] It was also documented that D-dimer > 1000 ng/ml is a risk factor for mortality in COVID-19.[7] In this study, we evaluated the epidemiological and clinical characteristics of COVID -19 patients and correlated it with

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the D-dimer values. This can potentially assess the role of D-dimer as a biomarker for stratifying disease severity.

2. Aims and Objectives

The present study was undertaken to evaluate the usefulness of D-Dimer levels in blood to correlate with disease severity in COVID 19 patients.

3. Materials and Methods

The present retrospective study includes 60 patients hospitalised for COVID-19 during a period from May 2021 to June 2021 at Acharyashree Bhikshu Government Hospital, Delhi. The laboratory confirmation for COVID-19 was carried out by RT – PCR or Rapid Antigen test as per ICMR criteria. The epidemiological data, comorbidities and clinical condition of the patients were obtained from the medical records department. Blood sample was collected during the hospital stay for testing D-dimer. D-dimer evaluation was performed using an immunoturbidimetric assay on Erba Mannheim ECL 105 machine. Sample was collected in citrate vial. D-dimer levels were evaluated along the clinical course of the disease and values were compared for those having severe versus non-severe disease.

4. Observations and Results

The study was conducted on 60 COVID 19 positive patients admitted to the hospital. Of the total patients, 39 (65%) were male and 21 (35%) were female. There was no significant difference in the severity of the disease between the two. (Table 1). Maximum cases (65%) belong to the age range of 31-60 years. The severity of the disease was directly proportional to the patient age. All the patients below 30 years were mild (Figure 1).

The most common clinical symptoms at the time of admission was high grade fever, cough and hypoxia. Few of the patients had complaints of dyspnoea, chest tightness and gastrointestinal discomfort. Nearly one-third of the cases had comorbidities like hypertension, diabetes mellitus, COPD and cardiovascular disorders; hypertension being the most common associated underlying disease followed by diabetes mellitus.

All the cases were divided in mild, moderate and severe as per Clinical guidelines for covid management by ICMR National Task Force, May 2021. Out of total 60 patients, 33 were in mild, 23 in moderate and 4 were in severe category.(Figure 2) In mild cases D Dimer varies from 43 ng/ml to 183 ng/ml with mean 97.4 and median 99. In moderate cases D Dimer varies from 270 ng/ml to 991 ng/ml with mean 641.1 and median 720. In severe cases D Dimer varies from 1043 ng/ml to 2463 ng/ml with mean 1609.5 and median 1466 (Table 2).

At the time of admission 35 cases (58.3%) showed D-dimer levels < 200 ng/ml in which only one case progressed to severe category with D-dimer levels > 1000 ng/ml. One case progressed to moderate category with D-dimer levels 200- 1000ng/ml. 22 cases were admitted with D-dimer levels 200-1000 ng/ml but post active intervention all the cases gradually improved and were eventually discharged except one that had a poor prognosis. Patients with D-dimer >1000 ng/ml at the time of admission were at greater risk of mortality. Out of the 4 severe cases admitted, two had poor outcome and one had to be referred to the higher centre. The study suggests cut off levels for d dimer as upto 200 ng/ml for mild, 200-1000 ng/ml for moderate and more than1000 ng/ml for severe category of clinical severity in COVID 19 patients.

As per linear regression model the coefficients of severity of illness of COVID 19 with d dimer levels in blood for moderate and severe category are statistically significant at 99.9% wit p value less than 0.001.(Table 3).

D-dimer progression observed in our study correlated well with the clinical course of the disease. Advancing age with associated underlying disease can be seen to influence the levels of D-dimer which can affect the progression of the disease clinically. So D-dimer can also be used as a tool for early identification of disease severity so that prompt active intervention can be administered.

Table 1: Gender distribution of COVID 19 patients

Gender	Total	Mild	Moderate	Severe
Male	39	19	17	3
Female	21	14	6	1

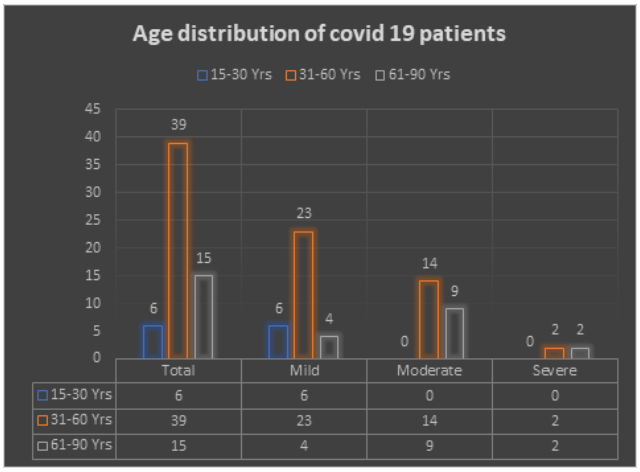

Fig. 1: Gender distribution of COVID 19 patients

5. Discussion

SARS-CoV-2 is amongst the three coronaviruses discovered in the past two decades after SARS-CoV-1 as well as Middle East respiratory syndrome (MERS)-CoV.[8] SARS-CoV-1 infected around 9000 cases with a mortality of 774 people

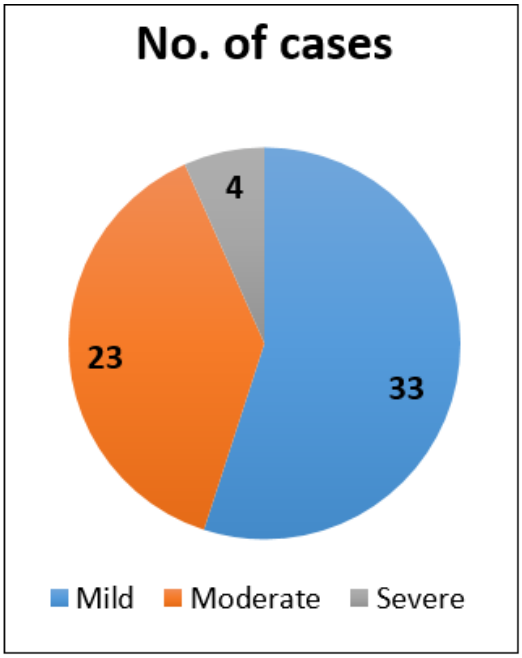

Fig. 2: Clinical distribution of COVID 19 patients

Table 2: D Dimer levels in patients as per severity of COVID 19

D Dimer level (ng/ml)	Mild	Moderate	Severe
Minimum	43	270	1043
Maximum	183	991	2463
Mean value	97.4	641.1	1609.5
Median value	99	720	1466

Table 3: Statistical significance of D dimer levels as per severity of COVID 19

Clinical Types	Estimate	Std. Error	t value	Pr(>ItI)
Mild	97.42	39.02	2.497	0.0154
Moderate	543.71	60.88	8.931	2e-12
Severe	1512.08	118.66	12.743	<2e-16

Residual Standard Error:224.1 on 57 degree of freedom
Multiple R squared: 0.7809
Adjusted R squared: 0.7732
Statistics: 101 6 on 2 and 57 D F
Value <2 2e-16

in the year 2002–2003. MERS-COV was responsible for an epidemic in the Middle East in 2012 with a fatality rate of 38%.[9] SARS-CoV-2 involves binding of glycoprotein envelope of virus to ACE2 receptor which is present on the cells of numerous tissues such as alveoli, intestinal epithelial and others.[10] The innate tropism of endothelial cells and activation of inflammatory response along with the coagulation pathways, leads to pro-coagulative state.[11] Abnormal coagulation profile which includes D-dimer elevation is observed in COVID-19 as the disease becomes severe.[12] This predisposes to micro-thrombotic alterations thus leading to multi-organ failure, DIC and ARDS in severe COVID-19 patients.

D-dimer assays are routinely used in clinical setting for diagnosing Deep vein thrombosis and pulmonary embolism. Rise in D-dimer level indicates abnormal clotting of blood. D-dimer containing moieties are formed by plasmin degradation of factor XIIIa cross-linked fibrin. Elevated levels indicate a hyper coagulable state and fibrinolysis.[13] Previous research works consider COVID-19 to be associated with haemostatic deviation which indicates that D-dimer values are elevated in non-survivors.[12]

In the present study, we observed an association between D-dimer and disease severity. It was noted that most patients who were hospitalised for COVID-19 initially had a D-dimer value within normal range. Few cases had drastically elevated D-dimer levels indicative of increased disease severity; for which they had to undergo active intervention. Similarly, Chen et al. found elevated levels of D-dimer in non survivors in comparison to the survivors.[14] Huang et al., described that D-dimer levels on hospitalisation can be used for triage cases. D-dimer levels were more in ICU patients in comparison to ward patients (2.4 mg/L versus 0.5 mg/L).[1]

Zhou et al. did a retrospective cohort study on 191 patients, of which 137 were discharged while 54 died. In-hospital deaths were seen more in patients with older age and D dimer >1 μg/ml on admission. These risk factors help the clinicians to identify those patients with poor prognosis at an early stage.[7] This similar observation was made in our study as well as a study done by Yao et al.[15]

In studies performed by Richardson et al[16] and Zhou et al[7] the most common comorbidity was hypertension followed by obesity, and diabetes[16] which is in concurrence with our study.

The demographic profile in our study supports the data reported by numerous authors stating that advancing age is a predisposing factor for COVID-19 and leads to severe disease and even death. For instance, Zhou et al. opined that age more than 50 years was strongly associated with the disease while age around 65 years increases chances of mortality.[7] The basis for this might be impaired cellular immunity superimposed with longer duration of inflammation in adults.

In a study, conducted by Chen et al,[17] male sex was reported as a factor influencing the COVID-19 severity. In our study as well as a study conducted in Iran it was observed that there was no sex predilection.[18]

6. Conclusion

The aim of this study was to evaluate usefulness of D dimer in covid patients as prognostic marker for disease severity. The study concludes that D dimer levels are elevated in moderate and severe COVID 19 patients and its level can be used as prognostic marker for disease severity. It helps in identifying the high risk group and providing

early management to prevent mortality. Thus, D dimer can be used as an essential biomarker in developing the management protocol for COVID 19 patients.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare no conflict of interest.

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