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Evaluation of D-dimer Levels in COVID-19Patients in Tertiary Care Hospital, an Observational Study

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Abstract

Aim: *This study was aimed to measure and evaluate the D-dimer levels in diagnosed cases of COVID-19 Patients.*

Study design: *An observational study.*

Place and Duration of Study: *Department of Biochemistry, Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand, between 20th February 2021 and 20thApril 2021.*

Methodology: *We included 333 patients (216 men, 117 women; age range 18-99 years) with documented COVID-19. The patients were divided into two groups severe and non-severe COVID-19. The details were recorded on a pre-structured performa. Between groups, differences were tested using the Mann-Whitney's U-test. The receiver operating characteristic curve was plotted for D-dimer with severity. A binary logistic regression was used to identify variables independently associated with severity. The data was analyzed using Statistical Package for the Social Sciences (SPSS).*

Results: *Out of 333 patients, 230 patients were included in non-severe group and 103 patients in sever group. Patients with increased D-dimer levels were significantly higher (p=0.001) in severe cases [median 1.24 µg/mL, interquartile range (IQR)) 0.82-4.5] than in non-severepatients [median 0.42 µg/mL, interquartile range (IQR) 0.22-1.09]. Binary logistic regression showed D-dimer to be an independent predictor of all-cause severity supplemented with an AUC of 0.69 on ROC analysis.*

Conclusions*: D-dimer levels are an indicator of disease severity and prognosis of disease. Those patients who have higher D-dimer level have poor prognosis so D-dimer level must bemonitored during course of disease.*

Keywords: *[covid-19, D-dimer, severe, prognosis]*

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I. Introduction

The coronavirus disease-19 (COVID-19) is the disease caused by 2019-nCoV/SARS-CoV-2, a novel β corona virus of group 2B [1]. By March 30, 2021, 127,349,248 confirmed cases of COVID-19, including 2,787,593 deaths, were reported to the World Health Organization (WHO) [2]. Even though the rapidly evolving clinical course and presentation continue to amaze the medical fraternity, cases infected with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), often present with severe pneumonia and organ targeted injuries involving the liver, heart, and kidneys [3]. Coagulopathy was reported, and D-dimer elevations were seen in 3.75–68.0% of the COVID-19 patients [4]. With the surging devastating effects of the pandemic, the focus of scientific efforts was on developing optimal therapeutic regimens to combat the virus. Meanwhile, there wasalso a dire need for early risk stratification systems and biomarkers to predict disease progression, to identify high-risk patients at an early stage of the infection [5–6]. However, the role of D-dimer in COVID-19 patients has not been fully investigated. In this study, we showed D-dimer levels in patient groups stratified by clinical severities and assessed the role of D-dimeras a biomarker for disease severity and clinical outcome.

II. Material And Methods

2.1 Study Population

The observational study was carried out at Department of Biochemistry, Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand, from 20th February 2021 to 20thApril 2021. A total of 333 COVID-19 patients were enrolled from COVID ward of Sheikh Bhikhari Medical college and Hospital, Hazaribag, Jharkhand in this study and were divided into non-severe and severe groups. Non-sever group

included 230 patients and severe group included 103 patients. All patients with COVID-19 who enrolled in the recent study were diagnosed according to the WHO interim guidance for COVID-19 (6th edition) [7]. In other words, all patients with the physician and laboratory confirmed (positive nasopharyngeal/throat swab specimens by reverse transcription-polymerase chain reaction (RTPCR)) COVID-19 infection were included, while suspected cases with similar clinical symptoms were excluded. One of the following criteria was used to determine severe COVID-19 illness: respiratory rate >30 bpm, oxygen saturation <93% on room air, arterial oxygen partial pressure (PaO2)/ oxygen concentration (FiO2) ≤300 mm Hg, and intensive care unit (ICU) admission.

2.2Analysis of Plasma D-dimer

Plasma analysis for D-dimer was determined on specific protein analyser (Mispa i2) using Nephelometric immunoassay method. The blood sample was collected, as per the standard protocol. The concentrations of D-dimer were expressed in µg/mL.

2.3. Statistical Analysis

Statistical data were analyzed using SPSS version20.0. As the data that was skewed; median values were reported along with interquartile ranges (IQR) for continuous variables. Between group, median differences were tested using the Mann–Whitney's U-test and categorical variable were compared by chi-square test. The predictive value of the D-dimer was evaluated by measuring the area under the receiver operating characteristic curve (AUC). A "p value" below 0.05 was considered statistically significant and $p < 0.001$ considered statistically highly significant.

III. Results

A total of 333 inpatients were declared COVID-19 positive during the study duration. Out of these, 103 patients were included in the severe group, while 230 patients were included in the non-severe group. Median age of sever group was 59 (IQR: 52–70) years and median age of non-severe group was 50 (IQR: 45–65) years. The average age was higher in the severe group than in the non-severe group ($p = 0.06$) as shown in Table1. Out of 333 patients 216 patients were male and 117 patients were female. Out of 117 female, 28 female were included in sever group and 80 female in non-sever group. Out of 216 male, 75 male were included in severe group and 150 male were included in non- sever group as mentioned in table 2 and figure1. The severity ratio for males was higher as compared to females, but this difference was not significant ($p = 0.58$). Median D-dimer being

1.24 (IQR: 0.82–4.5) and 0.42 (IQR: 0.22-1.09) mg/L was found to be significantly higher in the severe groupcompared to the non-severe cases group respectively (p value = 0.001) as shown in table1and figure 3.

Table 1

Age and D-dimer levels in severe Vs Non-severe

Groups	**Age (median, IQR)(years)**	**D-dimer (median, IQR) (µg/mL)**
Severe case (n=103)	59 (52-70)	1.24(0.82-4.5)
Non-severe case (n=230)	50 (45-65)	0.42(0.22-1.09)
p value	0.06	0.001

$p < 0.05$ statistically significant and $p < 0.001$ highly significantIQR-Interquartile range

Table 2

Gender distribution in Groups

Groups	**Male(n=216)**	**Female(n=117)**
Severe	75	28
Non-severe	150	80

p value= 0.58

$p < 0.05$ statistically significant and $p < 0.001$ highly significant

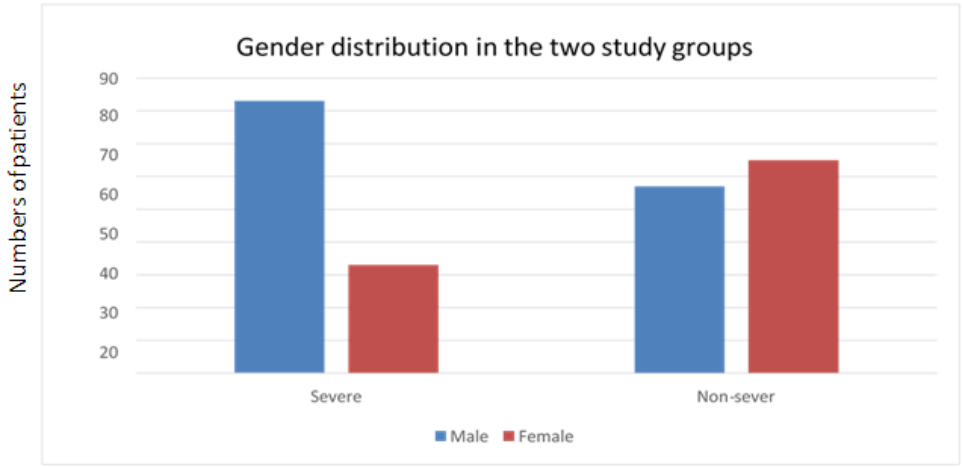
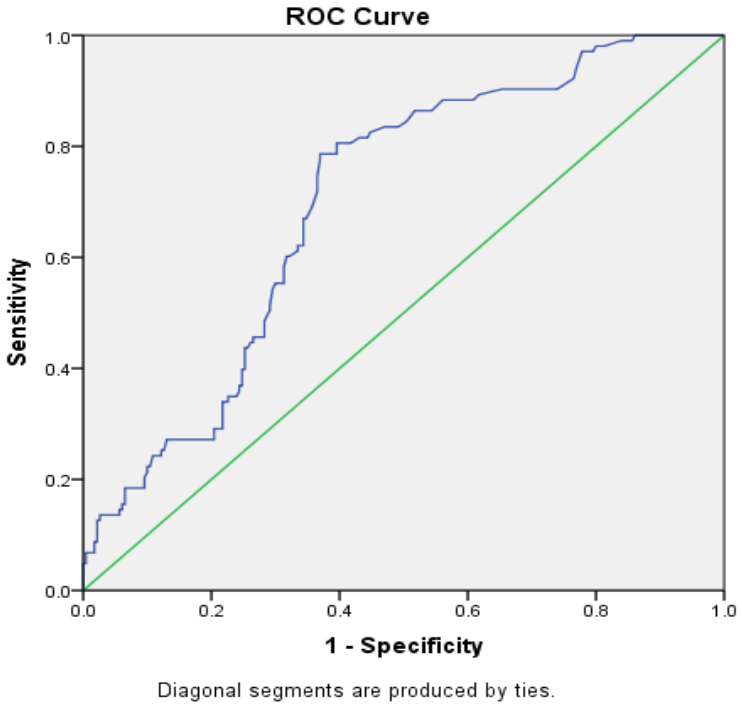


Figure 1. Gender distribution in two study group

ROC curve analysis was used to compare the performance of D-dimer as a predictor of severity with an AUC of
0.69 (95% CI: 0.57–0.74) as illustrated in Fig.2. The optimal cut-off for the prediction of severity was 1.2 µg/mL with a sensitivity of 78% at a compromised specificity i.e. 52%.



AUC-0.67

Figure 2*: Receiver operating characteristic (ROC) curves of D-dimer for predicting the disease severity in COVID- 19 patients*

Table 3: The area under the curve (AUC) and the optimal cutoff value of D-dimer

AUC	Optimal cutoff value (µg/mL)	Sensitivity (%)	Specificity (%)
0.69	1.2	78	52

AUC - area under the curve

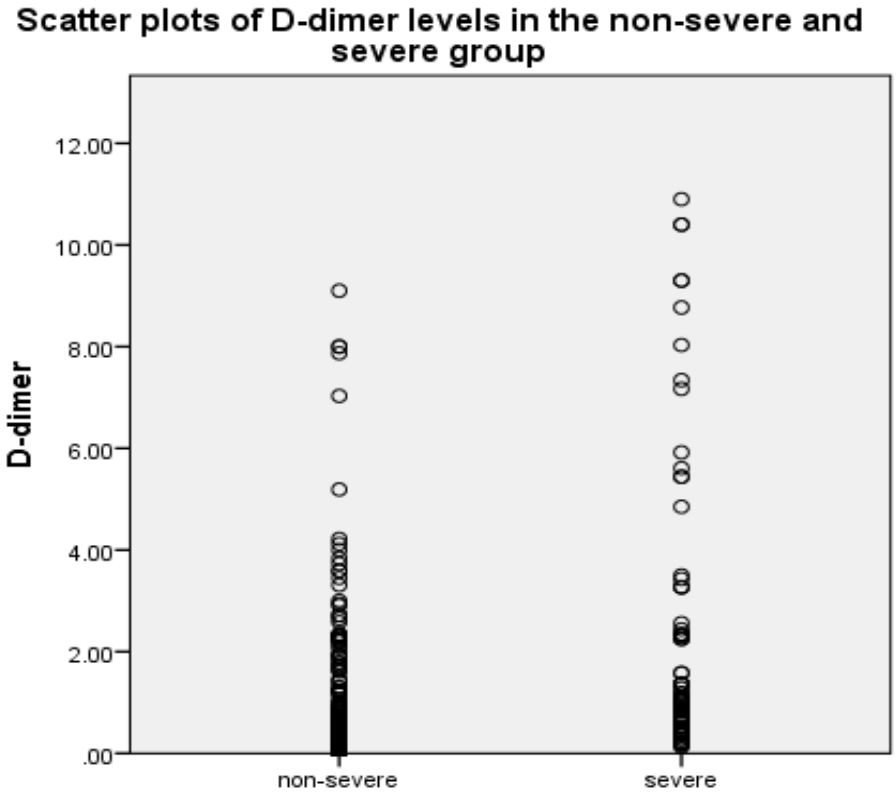


Figure 3. *Scatter plots of D-dimer (μg/mL) levels in the non-severe and severe group*

IV. Discussion

Abnormal coagulation function, including elevated D-dimer, has been demonstrated to be involved in the disease progression of COVID-19 [8, 9]. In this study, we evaluated the association between elevated D-dimer levels and the disease severity of COVID-19 based on the prospective observational study. In our study, the level of D-dimer was markedly increased in patients with severe COVID-19, D-dimer assays are commonly used in clinical practice to exclude a diagnosis of deep vein thrombosis or pulmonary embolism, and elevated D-dimer indicates increased risk of abnormal blood clotting. Elevated levels of D-dimer were also found to be related with higher mortality rate of community-acquired pneumonia [10]. Recent studies documenting the laboratory changes of patients with confirmed COVID-19 have noted that elevated D-dimer might be associated with the disease progression of COVID-19. The level of D-dimer in patients with COVID-19 admitted to the ICU was reported significantly increased [25]. Clinical attention to venous thromboembolism risk should particularly be paid to those patients with severe COVID-19, who were often bedridden and presented with abnormal coagulation function [11,12]. In addition to thrombosis and pulmonary embolism, D-dimer might be a manifestation of severe virus infection. A virus infection may develop into sepsis and induce coagulation dysfunction, which was common in serious disease progression. Moreover, the increase of D-dimer may be an indirect manifestation of inflammatory reaction, as inflammatory cytokines could cause the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system, and then increase the level of D-dimer [13,14]. And D-dimer greater than 1 μg/ml was found a risk factor of poor prognosis for patients with COVID-19 [15]. In the treatment of patients with COVID-19, the prevention and treatment of thrombus should be noted. It has been reported that reactive thrombocytosis occurred in 4% of patients, which may be related to the increased risk of thrombus [16]. In addition, considering that patients with COVID-19 might have increased blood viscosity due to high fever and excessive sweating, hypercoagulable state because of activation of coagulation system, together with the risk factors such as long-term bedridden, obesity and old age, the risk of thrombus is further increased [17]. D-dimers are one of the fragments produced when plasmin cleaves fibrin to break down clots. The assays are routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis. However, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels [18]. Examples include deep vein thrombosis/pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, and conditions such as pregnancy, inflammation, cancer, chronic liver diseases, post trauma and surgery status, and vasculitis. Among adults

admitted to the emergency room, infections, instead of VTE/PE, are the most common reason for D-dimer elevation [19]. We found that when using the cutoff value of 1.2 µg/mL, D-dimer levels upon admission for in-hospital severity has an AUC of 0.694. The sensitivity and specificity are 78% and 71.3%, respectively. The findings of this present study suggest that an elevated D-dimer level on admission (> 1.2µg/mL) may identify patients at higher risk for in-hospital severity and therefore inform physicians about suitable candidates for intensive care and early intervention. Yao et al found an AUC of 0.846 in ROC curve [20].

V. Conclusion

In conclusion, D-dimer levels are commonly elevated in patients infected with SARS-CoV-2. Significantly higher levels are found in those with critical illness and may be used as a prognostic marker for inhospital mortality.

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COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

" 'Hemanti designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of themanuscript. 'Rajiv kumar Mahli' managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript."

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