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"D-DIMER LEVEL AS PREDICTIVE BIOMARKER FOR COVID-19 DISEASE SEVERITY: AN ANALYSIS"

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ABSTRACT

Objectives- COVID-19 is now a global pandemic and it was first reported in Wuhan, China, in December 2019. In is observed in few critically ill patients that that he course of disease is rapid and with in short period of time the clinical condition may worsen. Deranged coagulation profile, including elevation of D-dimer level are identified during course of COVID-19 infection. Raised serum level of D dimer is associated with increased mortality in COVID-19 Patients. **Methods-** The data of 128 COVID 19 patients was retrospectively collected and analyzed. After categorization of patients into two groups the optimal cutoff value of D-dimer on admission was evaluated by receiver operator characteristic (ROC) curve. **Result-** Out of total 128 enrolled in the study, 81(63.28%) patients were in non severe group and 47(36.72%) patients in severe group and mean value of D-dimer in non severe group and severe group was 2.17 (2.78)mg/L, and 11.26 (7.56)mg/L respectively. The area under the curve (AUC) of ROC curve was 0.886 (95% CI 0.818-0.954; p value<0.0001) with optimal threshold value was 2.345 mg/L. **Conclusion-** In COVID-19 patients D-dimer value ≥ 2.345 mg/L can be used to effectively predict the severity of disease. A significant association has been found in raised D-dimer level and disease severity.

KEYWORDS : D-dimer, COVID-19 infection, Predictive biomarker, ROC curve

INTRODUCTION

Since December 2019, in Wuhan, China, a novel member of human corona virus was newly identified and officially named by International Committee on Taxonomy of Viruses, ICTV as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).[1-3] It has not been previously identified in humans as it is a new strain of RNA viruses which belongs to the beta-corona virus 2b lineage in the phylogenetic tree. [4] Later this disease has been officially named "COVID-19" by the World Health Organization (WHO).[5,6] The disease is rapidly progressive in nature, and with in short period of time severely ill patients can develop acute respiratory distress syndrome, sepsis, and multiple organ dysfunction syndromes.[7]

Early diagnosis, strict clinicopathological monitoring and appropriate treatment protocol are the key for improvement of patient outcome. Chest CT scan has an important role in assessing the disease severity.[8] However the limited availability of Chest CT scan and being expensive diagnostic modality it is not readily reached by common people. So we have to consider some laboratory markers must be inexpensive, within reach for all persons and simultaneously specific and sensitive. D dimer is one of them and with the help of this marker clinician can assess the severity of COVID-19 disease.

In the end of coagulation cascade activated factor XIII cross-linked the fibrin monomers. These fibrins are hydrolysed by plasmin and D dimer is produced. D dimer is a specific marker of fibrinolysis process. [9] COVID 19 infection is associated with deranged coagulation profile, including elevation of D-dimer level. Elevated D dimer level is associated with increased mortality in COVID 19 Patients. [10,11] Due to increased risk of bleeding in patients with COVID-19,conventional anticoagulation may need to be considered carefully [12].D-dimer highlights its role as a potentially helpful biomarker as it helps in clinical decision for ruling out pulmonary embolism. [13] Our study objective was to reinforce the fact that elevated D dimer level is associated with severe disease in COVID-19 patients, to determine optimal cutoff value of D dimer level and its predictive ability to assess the severity of disease which is helpful in crucial therapeutic decision making.

MATERIALS AND METHODS

This was a retrospective observational study conducted at our tertiary care hospital. Total 128 confirmed COVID 19 patients from April mid to May 2021were included in the study. Patients with a positive RT- PCR as per ICMR guidelines were considered as confirmed COVID 19 cases.[14] The information of patients such as demographic details, laboratory and clinical details were collected retrospectively from hospital records system and analyzed.

Patients were categorized as mild, moderate and severe; clinically according to ICMR guidelines. [14] We then re-categorized the patient into two groups non-severe and severe for our study purpose. Patients who had mild and moderate symptoms, like fever, upper respiratory tract symptoms without breathlessness, SPO2 90 to 93% at room air were grouped into non severe group and severe group had those Patients who had severe symptoms like breathlessness and SPO2 <90 on room air. D-dimer values within 24 hour of admission were collected for all the patients enrolled in the study.

Statistical Analysis

SPSS (*Statistical Package for Social Sciences*, version 16.0.1 of IBM, USA) and Excel were adopted for data analysis. All study variables depending on the data type were summarized using appropriate measures of central tendency (mean, median) and dispersion - standard deviation (SD) or interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Receiver operation curve (ROC) was used, computation of areas under curve (AUCs; with 95% confidence intervals) and cut off value of D-dimer was done. AUC >0.70 was considered to be clinically significant or relevant for good predictive score. For optimal cut off value sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. *P value* ≤ 0.05 were considered statistically

significant along with the 95% confidence interval for the test statistic computed.

RESULT

The data of 128 patients above 18 year of age and a confirmed diagnosis of COVID-19 were included and analyzed in our study. Patients were divided into two comparison groups according to their clinical profile. In non-severe group 81(63.28%) patient were included and 47(36.72%) patient were in severe group. Majority of the patients were male 68(53.12%) as compared to female patients 60(46.87%) in our study. **(Figure 1)** As per laboratory findings mean D dimer of non severe group and severe group was 2.17 (2.78) mg/L, and 11.26 (7.56) mg/L.**(Table-1)**

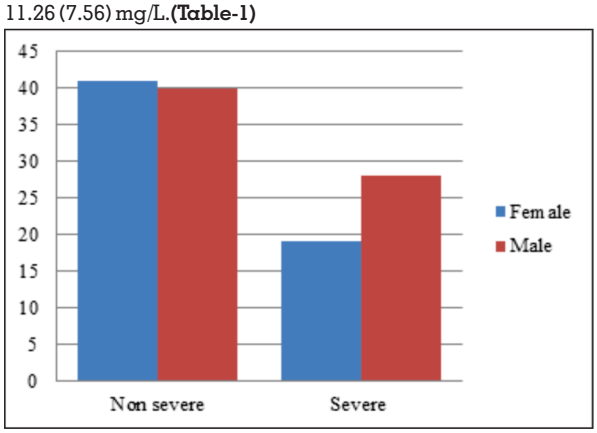
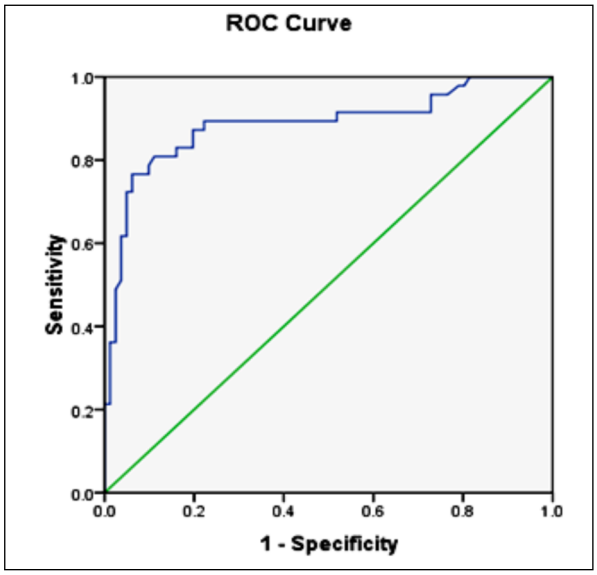


Figure-1: Gender Wise Distribution Of Severe And Non-Severe Cases

Table1: Baseline characteristics of COVID-19 patients

		Age(Years)	D-dimer(mg/L)
Non-Severe Patients(81)	Male (40)	54.72 (14.01)	1.63 (1.95)
	Female (41)	47.22(15.09)	2.69 (3.35)
	Total (81)	50.92 (14.96)	2.17 (2.78)
Severe Patients(47)	Male (28)	61.93(14.18)	10.29 (7.61)
	Female (19)	50.79(12.34)	12.68(7.46)
	Total (47)	57.42 (14.43)	11.26 (7.56)
p value		<0.0178	<0.0001

ROC curve analysis indicated moderate accuracy, with an area under the curve (AUC) of 0.886 (95% CI 0.818-0.954; p value<0.0001) .**(Figure 2)** The optimal cut off or threshold value for D-dimer for prediction of disease severity using ROC curve analysis was 2.345 mg/L. The highest value for sensitivity and specificity this cutoff were 89.36% and 77.78% respectively. **(Table-2)**



AUC	SE	95% CI
0.886	0.035	0.818-0.954

Figure2: Receiver Operating Characteristic (ROC) Curve Of D- Dimer For Diagnosis Of Severe COVID-19 Patients

Table 2: Indices Of Performances Of D-dimer

		95% CI
Sensitivity	89.36%	76.90%-96.45%
Specificity	77.78%	67.17%-86.27%
Positive Predictive Value	70.00%	60.54%-78.01%
Negative Predictive Value	92.65%	84.51%-96.68%

Correlation analysis showed that in the severe group of patients D-dimer had a significant correlation with severe COVID-19 pneumonia ($P < 0.05$). D-dimer showed high negative predictive value with severe COVID-19 pneumonia in the severe group of patients.

DISCUSSION

COVID 19 infection is transmitted through respiratory droplets and entry of SARS-CoV-2 virus target cells is facilitated by angiotensin-converting enzyme2 (ACE2) receptor. [15,16] In incubation period of 2-14 days patients remain asymptomatic after that a symptomatic phase may manifest, which ranges from mild symptoms like fever, and coughing to severe clinical presentations like pneumonia, severe respiratory dysfunction, sepsis and global deterioration. [17] Multiple procoagulants are activated during sepsis. Cellular damage by pathogen and immune response mediated activation of pathogen-associated molecular patterns (PAMPs). PAMPs promote the inflammation and coagulation by releasing the DNA from damaged cells, histones and pattern- recognizing receptors. [18,19] Neutrophils are activated by different pathogens like viruses and molecules like endothelial P selectin. After that a special type of apoptosis NETosis is initiated which results in the production of extracellular proteins, histones and DNA-intertwined compounds. These compounds act as a scaffold for thrombus formation resulting in hypercoagulative states. [19]

The COVID 19 patients are presented with variety of symptoms and imaging findings, and the varying degree of disease progression which complicate the clinical condition and prognosis of these patients. [20] Assessment of severity of disease and monitoring of clinical condition is performed by using different serological test and chest computed tomography (CT) scans. More than 75% of cases are observed with bilateral abnormalities like ground-glass opacities, interstitial involvement, and crazy paving in chest CT scans [17]. Severe disease is associated with abnormal laboratory findings like leucopenia, thrombocytopenia and hypercoagulative state with elevated D-dimer level. [21] Findings of autopsy and histopathological examination have revealed thrombus or micro thrombus in the lungs, heart and liver. [22,23]

Our study suggests that level of D dimer is significantly raised in severe patients of COVID 19. In a study of ZHANG et al also observed similar findings. [24] TANG et al. observed in their study that mean D-dimer levels in non-survivors were significantly higher compared to survivors. [25] A meta-analysis conducted by Runzhen Zhao et al reported weighted mean difference of D-dimer was 0.97 μg/mL (95% CI 0.65, 1.29) between mild and severe groups. Their findings also support that elevated D-dimer level is an independent predictor for both mortality and complications in COVID-19 patients.[26] Jeffrey S. Berger et al in their study for determining prevalence and outcome in patients of COVID 19 in hospital settings found elevated D-dimer at the time of admission and was associated with higher incidence of critical illness, thrombotic events, acute kidney injury, and death.[27] A similar study from South India suggest from their findings that D-dimer

value ≥ 2.01 μg/mL can effectively predict in-hospital mortality in patients with COVID-19. [28]

There are few limitations present in our study. First, study was conducted on small sample size from single clinical research center. Secondly, we classified patients into two groups on the basis of clinical findings. It would have been better that we could have included some other parameters like CT score. Lastly patients in nonsevere group who developed severe illness during hospital stay were not followed up.

CONCLUSION

Level of D-dimer can be used as predictive biomarker to assess the severity of COVID-19 disease. D-dimer value ≥ 2.345 mg/L can be used to effectively predict the severity of disease. A significant association has been found in raised D-dimer level and disease severity but further studies are needed to see how useful they are in determining prognosis.

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