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Original Research Article

Among COVID-19 Hospitalized Patients Does D-Dimer Value at the Time of Admission Predict Future Outcome

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Abstract

Background: COVID-19 is still going on with lots of uncertainties. There is a need for early and effective marker for prognostication of COVID-19 patients. Coagulation dysfunction and increased D-dimer levels are seen in this disease. Thus, present study was aimed to compare D-dimer value in relation to disease severity and disease mortality, and to evaluate prognostic significance of D-dimer.

Method: All symptomatic SARS-CoV-2 RT-PCR confirmed COVID-19 patients admitted in Hospital from March 31, 2021, to May 31, 2021 were evaluated and clinical, demographical and laboratory findings were collected and analysed. According to disease severity patients were grouped and death events and D-dimer value were assessed. Optimal D-dimer cut off point in all groups were evaluated.

Results: 388 patients were included in the study out of which 142 (36.5%) died during hospital stay. Mean D-dimer value in mild disease was 1.17±0.21, moderate disease was 1.47±0.17 and in severe disease was 2.92±0.23 FEUμg/ml. Mean D-dimer value in non-survivors were significantly (P<0.001) different and higher (59.3%) as compared to survivors. ROC curve analysis showed a prognostic value of D-dimer in mild (AUC=0.755, Z=3.30, P=0.001), moderate (AUC=0.762, Z=4.65, P<0.001) and severe (AUC=0.694, Z=5.08, P<0.001) patients. Optimal cut off of D-dimer between survivor and non survivors was >0.78 in mild cases, >1.05 in moderate patients and >2.11 in severe cases.

Conclusion: Mean D-dimer value showing increasing trend with increase disease severity and prognostic significance was found highest in moderate patients followed by mild patients and least in severe patients in terms of mortality.

Introduction

Corona virus disease 2019 (COVID-19), still a ongoing pandemic disease caused by severe respiratory corona virus 2, first identified in Wuhan, China, in December 2019. More than 44 million confirmed cases are from India with number of death approximately 0.53 million so far. [1] The second wave of COVID-19 was devastating in India and highlighted the various

potholes in India's healthcare eco system. It was the worst humanitarian and public health crisis the country has witnessed since independence and healthcare system was overstretched and almost at the brink of collapse. Thus, for future control strategy potential biomarkers for prediction of disease severity, clinical outcome and risk stratification are utmost urgently needed.

Viremia and cytokine storm in the COVID-19 leads to coagulation dysfunction and D-dimer has been identified as a marker for disease progression and severity. [2] D-dimer is the fibrin degradation product of cross-linked fibrin. In normal healthy individuals the value is < 0.5 µg FEU/ml. Increased value reflects the ongoing activation of homeostatic system as seen in deep vein thrombosis (DVT) and disseminated intravascular coagulation (DIC) and pulmonary embolism (PE). Increased levels are also found during pregnancy and with increasing severity of community-based pneumonia. [3]

Thus, a retrospective study was carried out to know the role of D-dimer at the time of admission in prediction of disease severity and hospital mortality in patients with COVID-19.

Materials and Methods

This diagnostic study was approved by Hospital ethics committee (Ref No.: SH/IEC/NEW/INST/5589/01). The committee waived the informed consent to the participants in view of retrospective nature of study with review of records only.

Study Design: Retrospective Cohort Study

Study Population: All the symptomatic COVID-19 patients confirmed with SARS-Cov-2 RT-PCR, qualifying specific criteria for admission admitted in the Hospital, tertiary care hospital (Lucknow, India) from March 31,2021 to May 31, 2021.

Exclusion Criteria: Cases without definite outcome-loss of follow up, LAMA (left against medical advice) & DOPR (discharge on personal request) patients.

Cases without recorded D-dimer value at the time of admission.

Cases already on anticoagulant therapy.

Patients with Deep vein thrombosis/ Pulmonary embolism.

Data Collection:

All demographic, clinical, and disease outcome data was obtained from patient's hospital record (file) and laboratory data retrieved from hospital information system.

The severity of the disease is being followed as defined by WHO.

Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but who do not have shortness of breath, dyspnoea or abnormal chest imaging.

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have oxygen saturation (SpO_2) between 90-94% on room air at sea level.

Severe Illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate > 30 breaths/min or lung infiltrates >50%.

Critical Illness: Individuals who have respiratory failure, septic shock and/or multiple organ dysfunction.

All the patients were treated as per standard treatment protocol (Clinical management protocol for COVID-19, by Government of India, Ministry of health and family welfare, version 4, dated 27.06.20). [4]

Patient with RT-PCR negative and asymptomatic and SpO2 ≥94 will be considered as cured and mortality due to any cause was considered as disease mortality.

Data was captured on data abstraction form, entered and analyzed on SPSS

statistical software (Windows version 22.0).

Laboratory Assay and Intervention:

Blood samples of all the admitted patients were collected within 24 hours, such as complete blood count, coagulation profile, liver function test and kidney function test along with D-dimer estimation. All the D-dimer tests were performed on same instrument (Cobas integra 400 plus) using Tina- quant D-Dimer kit by immunoturbidimetric method. Measuring range of the test is 0.1- 9.0 µg FEU/ml. Results were reported as fibrinogen equivalent units/ml (µg FEU/ml) and accepted values is <0.5 µg FEU/ml. All the tests were performed within 1 hour of sample collection.

Statistical Analysis

The continuous data were summarised in Mean ± SE (standard error of the mean) whereas discrete (categorical) in number (n) and percentage (%). Continuous two independent groups were compared by Student's t test. More than two independent groups were compared by one way analysis of variance (ANOVA) and the significance of mean difference between groups were done by Student Newman-Keuls test after ascertaining normality by Shapiro-Wilk's test and homogeneity of variance between groups by Levene's test. The categorical groups were compared by chi-square (χ^2) test. The diagnostic and prognostic accuracy (sensitivity and specificity) of D-dimer value were assessed using receiver operating characteristic (ROC) curve analysis. A two-tailed (α=2) $P < 0.05$ was considered statistically significant. Analyses were performed on SPSS software (Windows version 22.0).

Results

The present study assesses diagnostic and prognostic significance of D-dimer value in COVID-19 hospitalized patients. A total of 388 patients (mild=74, moderate=128 and severe=186) of both the sex (male=264 and female=124) age between 21-92 yrs were recruited and evaluated. The outcome measure of the study was D-dimer assessed using Tina-quant D-dimer kit on Cobas integra 400 plus instrument (Roche Diagnostic) and measured in µg FEU/ml.

Basic Characteristics

The basic characteristics of three groups of COVID-19 patients (mild, moderate and severe) is summarised in Table 1. The patients of three groups were age and sex matched as these did not differ (P>0.05) among the three groups.

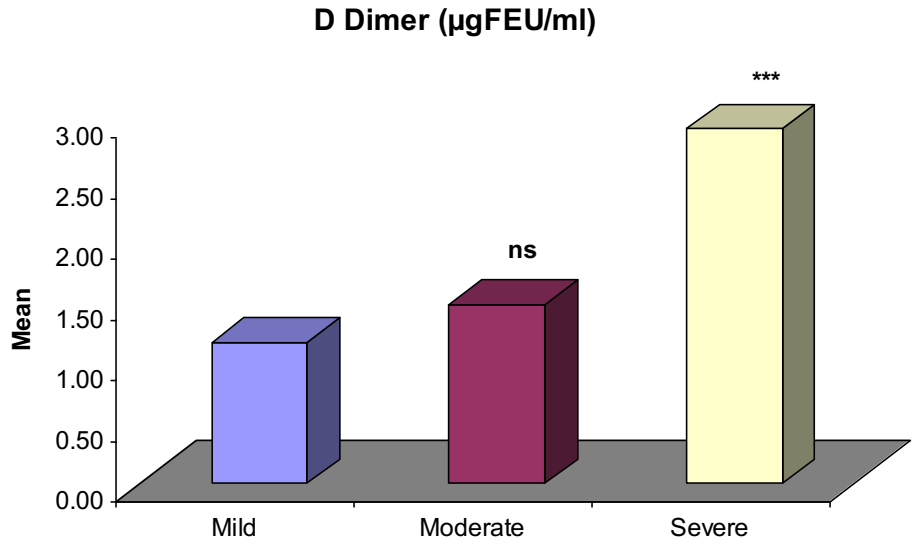
However, the mean D-dimer values show increasing trend with increase in disease severity. Comparing the mean D-dimer values of three groups of patients, ANOVA showed significantly different D-dimer values among the groups (F=18.05, P<0.001) (Table 1). Further, comparing the mean D-dimer values between three groups, Newman-Keuls test showed significantly (P<0.001) different and higher D-dimer value in severe group (60.1 and 49.7%, respectively) as compared to both mild and moderate groups but did not differ (P>0.05) between mild and moderate groups though it was 20.7% higher in moderate group as compared to mild group (Table 1 and Fig. 1).

Like, D-dimer values, the mortality in patients also increase with increase in disease severity. Comparing the status (survived/non survived) of the three groups of patients, the χ^2 test showed significantly different status among the groups (χ^2=42.62, P<0.001). The frequency (%) of deaths was significantly higher in severe group as compared to both mild and moderate group but did differ (P>0.05) between mild and moderate groups.

Table 1: Basic characteristics of three groups of COVID-19 patients

Variable	Mild (n=74) (%)	Moderate (n=128) (%)	Severe (n=186) (%)	F/χ^2 value	*P* value
Age (yrs)	56.38 ± 2.04	54.09 ± 1.35	57.19 ± 1.09	1.55	0.215
Sex:					
Female	22 (29.7)	39 (30.5)	63 (33.9)	0.61	0.736
Male	52 (70.3)	89 (69.5)	123 (66.1)		
D-dimer (µgFEU/ml)	1.17 ± 0.21	1.47 ± 0.17	2.92 ± 0.23	18.05	<0.001
Status:					
Survived	59 (79.7)	100 (78.1)	87 (46.8)	42.62	<0.001
Non survived	15 (20.3)	28 (21.9)	99 (53.2)		

The age and D-dimer value of three groups were summarised in Mean ± SE and compared by ANOVA (F value) whereas discrete sex and status were summarised in number (n) and percentage (%) and compared by χ^2 test (χ^2 value).



$^{ns}P > 0.05$ or $^{***}P < 0.001$- as compared to mild

Figure 1: Mean D-dimer values of three groups of COVID-19 patients.

D Dimer value- Survived and non-survived patients

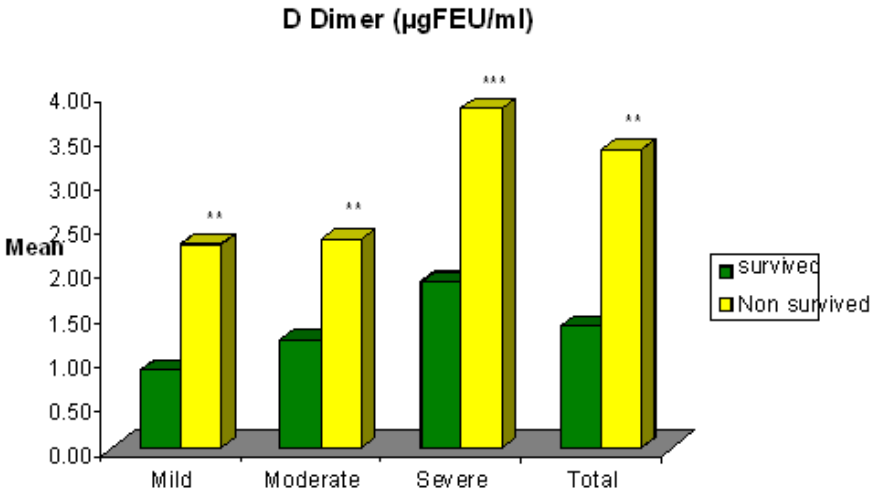
The D-dimer value of three groups of survived/ non survived patients is summarised in Table 2 and depicted in Fig. 2. In all three groups, the mean D-dimer values in non-survived patients were comparatively higher as compared to survived patients. Comparing the mean D-dimer values between survived and non-survived patients of each of the three groups, Student's t test showed significantly ($P < 0.01$ or $P < 0.001$) different and higher (61.9, 48.0 and 50.8%, respectively) D-dimer value in non-survived mild, moderate and severe patients as compared to respective survived patients.

Moreover, mean D-dimer value of total (mild+moderate+severe) non survived patients was also found to be significantly ($P < 0.001$) different and higher (59.3%) as compared to survived patients.

Table 2: Distribution of D-dimer (µgFEU/ml) values in three groups of Survived and Non survived COVID-19 patients

Group	Survived		Non survived		Mean difference	t value	*P* value
	n	Mean ± SE	n	Mean ± SE			
Mild	59	0.88 ± 0.18	15	2.30 ± 0.67	1.43 ± 0.49	2.92	0.005
Moderate	100	1.22 ± 0.17	28	2.35 ± 0.45	1.13 ± 0.39	2.88	0.005
Severe	87	1.89 ± 0.26	99	3.83 ± 0.35	1.95 ± 0.45	4.35	<0.001
Total	246	1.37 ± 0.12	142	3.38 ± 0.28	2.01 ± 0.27	7.56	<0.001

The D-dimer values of survived and non-survived patients were summarised in Mean ± SE and compared by Student's t test (t value).



$^{**}P < 0.01$ or $^{***}P < 0.001$- as compared to live

Figure 2: Mean D-dimer values in three groups of survived and non-survived COVID-19 patients.

Prognostic significance of D-dimer values: To assess whether D-dimer values have prognostic significance, ROC curve analysis was subjected in all three groups of survived and non-survived patients and summarised in Table 3 and shown in Fig. 3-5, respectively. The ROC curve analysis showed significant prognostic of D-dimer value in mild (AUC=0.755, Z=3.30, $P = 0.001$), moderate (AUC=0.762, Z=4.65, $P < 0.001$) and severe (AUC=0.694, Z=5.08, $P < 0.001$) patients. Further, the D-dimer value at cut-off value of >0.78 discriminating the survived and non-survived mild patients with 73.33% sensitivity (95% CI: 44.0-92.0) and 77.97% specificity (95% CI: 65.3-87.7) and with 45.8% positive predictive value and 92.0% negative predictive value.

Similarly, in moderate patients, the D-dimer value at cut-off value of >1.05 also discriminating the survived and non-survived patients with 71.43% sensitivity (95% CI: 51.3-86.7) and 77% specificity (95% CI: 67.5-84.8) and with 46.5% positive predictive value and 90.6% negative predictive value.

Similarly, in severe patients, the D-dimer value at cut-off value of >2.11 also discriminating the survived and non-survived patients with 49.49% sensitivity (95% CI: 39.3-59.7) and 82.76% specificity (95% CI: 73.2-90.0) and with 76.6%

positive predictive value and 59.0% negative predictive value.

Moreover, the D-dimer value at cut-off value of >0.73 also discriminating the total (mild+moderate+severe) survived and non-survived patients with 84.51% sensitivity (95% CI: 77.5-90.0) and 56.10% specificity (95% CI: 49.7-62.4) and with 52.6% positive predictive value and 86.3% negative predictive value (Table 3 and Fig. 6).

Among three groups of patients, the prognostic significance of D-dimer value was found highest in moderate patients followed by mild patients and least in severe patients.

Table 3: Prognostic significance of D Dimer (µgFEU/ml) values in discrimination of three groups of survived and non-survived COVID-19 patients using ROC curve analysis

Group	Cut off value	Sensitivity (95% CI)	Specificity (95% CI)	+PV	-PV
Mild	>0.78	73.33 (44.9-92.0)	77.97 (65.3-87.7)	45.8	92.0
Moderate	>1.05	71.43 (51.3-86.7)	77.00 (67.5-84.8)	46.5	90.6
Severe	>2.11	49.49 (39.3-59.7)	82.76 (73.2-90.0)	76.6	59.0
Total	>0.73	84.51 (77.5-90.0)	56.10 (49.7-62.4)	52.6	86.3

CI: confidence interval, **+PV:** positive predictive value, **-PV:** negative predictive value

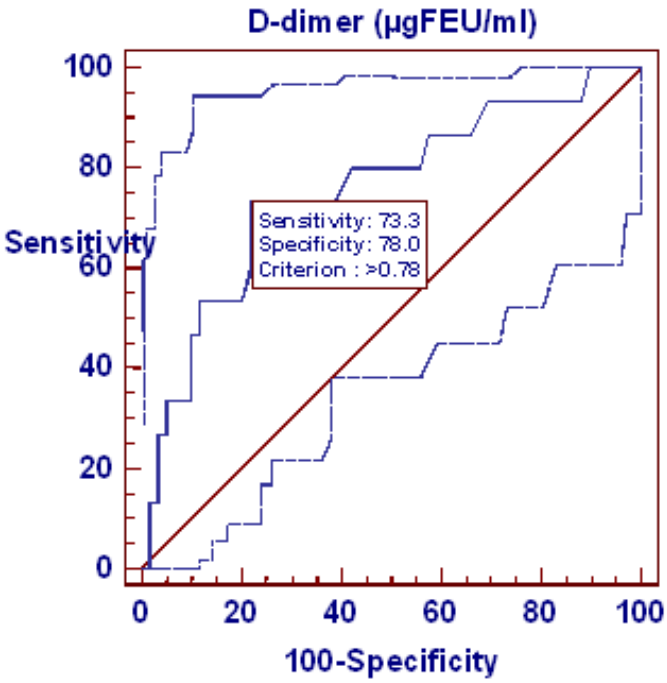


Figure 3: Prognostic significance of D Dimer values in discrimination of survived and non-survived mild COVID-19 patients using ROC curve analysis.

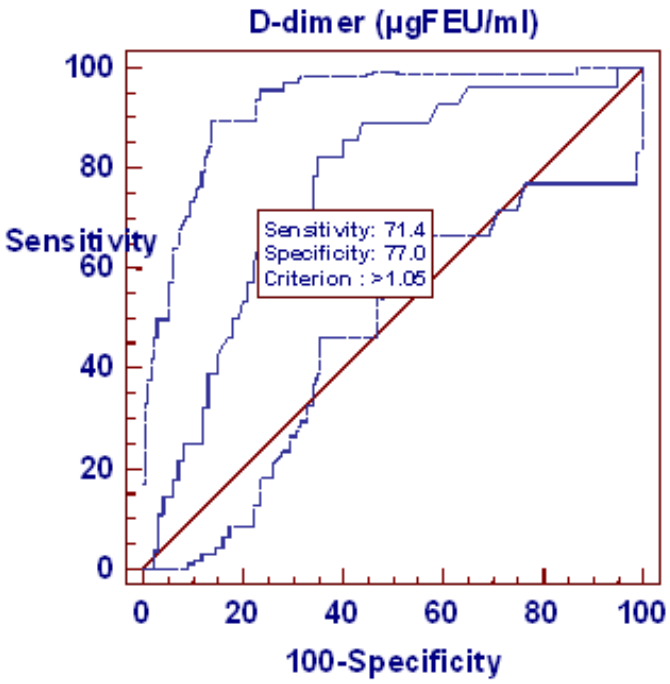


Figure 4: Prognostic significance of D Dimer values in discrimination of survived and non-survived moderate COVID-19 patients using ROC curve analysis.

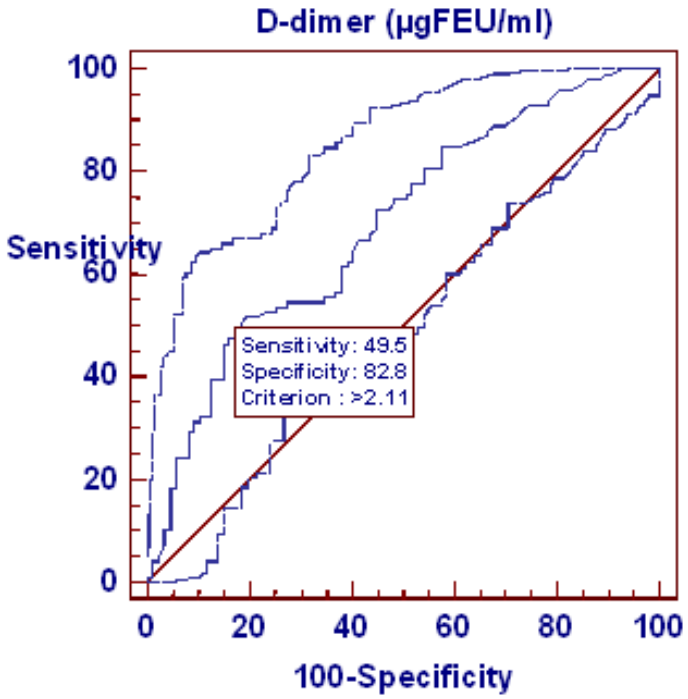


Figure 5: Prognostic significance of D Dimer values in discrimination of survived and non-survived severe COVID-19 patients using ROC curve analysis.

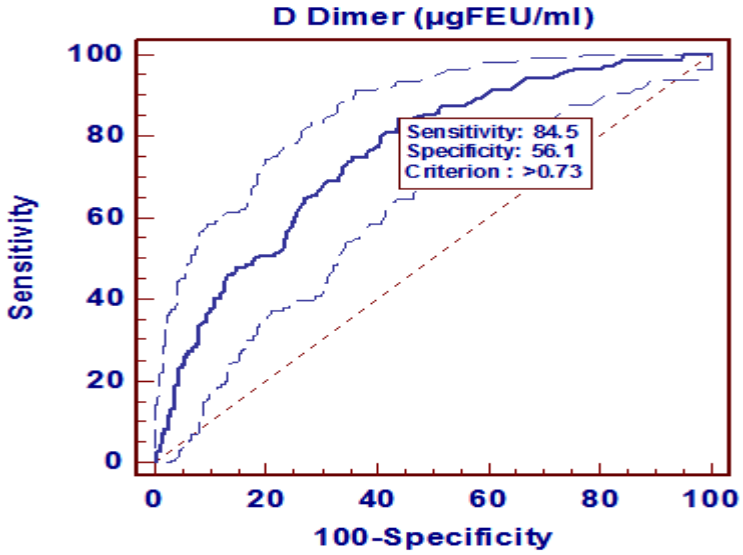


Figure 6: Prognostic significance of D Dimer values in discrimination of total survived and non-survived COVID-19 patients using ROC curve analysis.

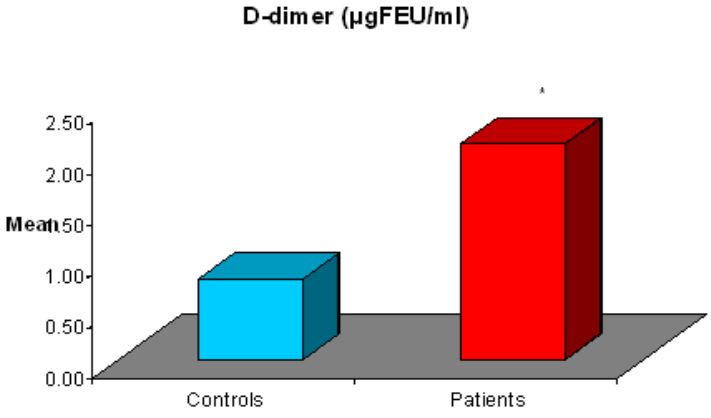
Diagnostic significance of D-dimer values

To know diagnostic significance of D-dimer value, the D-dimer values of 24 age and gender matched normal healthy controls (i.e. without COVID-19) were also estimated and compared with D-dimer values of total COVID-19 patients (Table 4 and Fig. 7). The mean D-dimer value was comparatively higher in patients as compared to controls. Comparing the mean D-dimer values of two groups, Student's t test showed significantly ($P < 0.05$) different and higher (62.6%) D-dimer values in patients as compared to controls suggesting its diagnostic significance between two groups.

Table 4: D-dimer (µgFEU/ml) values of controls and total COVID-19 patients

Controls (n=24)	Patients (n=388)	Mean difference	t value	*P value*
0.79 ± 0.16	2.11 ± 0.14	1.32 ± 0.55	2.39	0.017

The D-dimer values of two groups were summarised in Mean ± SE and compared by Student's t test (t value).



*$P < 0.05$- as compared to controls

Figure 7: Mean D-dimer values of controls and total COVID-19 patients

To assess whether D Dimer values have diagnostic significance, ROC curve analysis was subjected between controls and total patients and summarised in Table 5 and shown in Fig. 8. Like prognostic significance, the ROC curve analysis also showed diagnostic of D Dimer value (AUC=0.717, Z=4.74, $P < 0.001$) and at cut-off value of >0.55 it discriminating the controls and patients with 74.23% high sensitivity (95% CI: 69.6-78.5) and 66.67% high specificity (95% CI: 44.7-84.3) and with 97.3% positive predictive value and 13.8% negative predictive value.

Table 5: Diagnostic significance of D Dimer (µgFEU/ml) values in discrimination of controls and COVID-19 patients using ROC curve analysis

Cut off value	Sensitivity (95% CI)	Specificity (95% CI)	+PV	-PV
>0.55	74.23 (69.6-78.5)	66.67 (44.7-84.3)	97.3	13.8

CI: confidence interval, **+PV:** positive predictive value, **-PV:** negative predictive value.

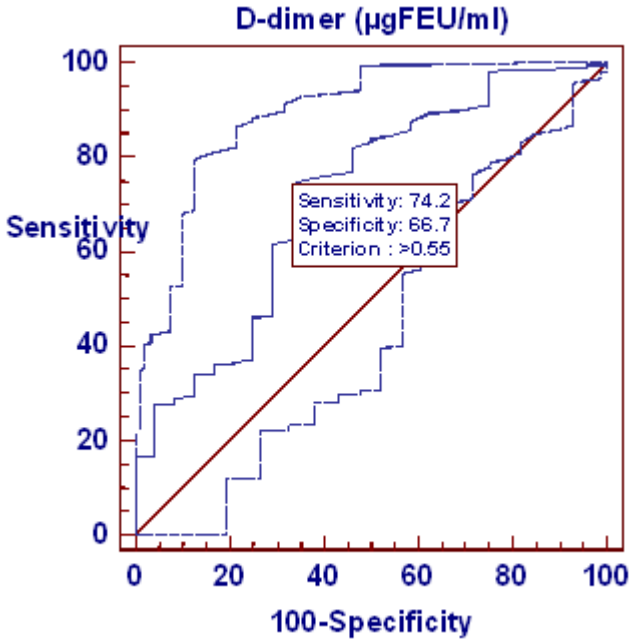


Figure 8: Diagnostic significance of D-dimer (µgFEU/ml) values in discrimination of controls and COVID-19 patients using ROC curve analysis.

Discussion

Second wave of COVID-19 was devastating in India and was started in March 2021 followed by a steady increase and exponential surge in April 2021 which gradually declined in May 2021. [5] The sharp surge in cases across country overwhelmed the healthcare system. Various double and triple mutant strains of SARS-CoV-2 were identified which were more pathogenic and lethal. [6]

There are various risk factors like age, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, stroke, cancer etc which have been associated with disease severity and mortality in Covid 19. [7] Among all the risk factors the most consistent factor for disease severity in COVID-19 is uncontrolled Diabetes mellitus which is responsible for imbalance between clotting factors and fibrinolysis. [8,9]

Cycle of COVID-19 is vicious. Viral infection leads to pro inflammatory

response and inadequate control of anti-inflammatory response, hypoxemia, increased blood viscosity, vascular occlusion, endothelial dysfunction, inflammation coupled with co-morbidities leads no escape situation. Co-morbidities itself leads to hypercoagulable state and thromobsis. [10,11]

Thus, for future control strategies potential biomarkers for prediction of disease severity are utmost needed.

Role of elevated D-dimer and various thrombotic complications were well reported during the first wave in year 2020 as a single institutional study and in large meta- analysis, While the data and studies during the second wave of COVID-19 in India and especially from the northern region of the country are not much published.

In our study mortality is reported as 36.5% and 47.9% of our patients are having severe disease at the time of admission which is far more than previous studies. [11-14].

The mean D-dimer level in mild disease group is 1.17±0.21, moderate disease group is 1.47±0.17 and severe disease group is 2.92±0.23 in our study, while a single tertiary care hospital in Mumbai from May 2020 to September 2020 comprising of 497 patients revealed mean D-dimer level of 2.64 in severe disease group while in mild to moderate group it was 1.05. [15]

In a meta- analysis involving nine studies with 2574 patients showed mean D-dimer value for patients with severe disease was 0.89 (standard deviation 0.34) while with non-severe disease it was 0.30 (standard deviation 0.12) clearly suggesting that D-dimer is positively associated with severity of disease. [16]

In our study mean D-dimer level in survived group is 1.37±0.12 while in non-survived group is 3.38±0.28 which is again slightly different from previous studies.

In study of Tang et al mean D-dimer in non-survived group was 2.12 (0.77—5.27) while in survivor group it was 0.61 (0.35-1.29), and p value<0.01. Here Mortality was 11.4%. [12]

In one Indian study from single tertiary care hospital in Chennai from April 2020 to July 2020 analysing data of 483 patients found significant difference of median D-dimer level among survivors and non-survivors (6.34 µg/ml Vs 0.94 µg/ml). Thus, higher values were observed in Cases with fatal outcome. [14]

Two large systematic reviews; one involving 71 and another 100 studies respectively from various countries again concluded that higher D-dimer value is associated with overall risk of disease progression and mortality. [17,18]

One study from Nepal from March 1,2020 to December 31, 2020 revealed overall mortality of 18.7% with mean D-dimer value among survivors was 1.067 µg/ml (±1.705 µg/ml) and non survivors 3.208 µg/ml (±2.613 µg/ml) [19]

A large systematic review comprising of 18 studies (16 retrospective and 2 prospective) all from China showed pool weighted mean (WMD) in non-survived group of 6.13mg/L; 95% confidence interval 4.16-8.11, p<0.001. Study also revealed 4-fold increase of mortality with increased D-dimer level. [20]

Predictive value of D-dimer for disease mortality was also studied previously. [21,22] However in our study ROC curve analysis was done in all three disease groups. In mild disease group cut off value of D-dimer is >0.78 µgFEU/ml (AUC=0.755), while in moderate group it is >1.05 µgFEU/ml (AUC=0.762), and in severe group it is >2.11 µgFEU/ml (AUC=0.694). [23]

Previous studies from India showed cut off of >1.44 and >2.16 with area under curve was 0.683 and 0.883 respectively. [14,15]

Zhang et al in his study reported cut off of >2µg/ml on admission to predict hospital mortality. [11]

In our study prognostic significance of D-dimer is found highest in moderate group followed by mild group and least in severe group patients.

In our study we also compare D-dimer value in Covid patients with normal healthy controls and found statistically significant ($P<0.05$) and higher value in patients compare to control.

This study will have several limitations.

1. Selection bias: As this is the single institutional retrospective study the study population will represent certain demographic area. Findings might not be generalizable to target population and need to be corroborated with multicentric meta-analysis.
2. Information bias: Length of onset of illness till admission in the hospital was not significantly captured on the patient's record which might influence the level of D-dimer value at the time of admission.
3. Confounding: As most of the patients were having co-morbidities especially in severe disease group which were poorly documented. This might influence the relationship of D-dimer and mortality in COVID-19.

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