How to Cite:
Purohit, A., Purohit, A., Shah, L., & Gami, S. (2022). Evaluation of D-dimer as a prognostic indicator in patients with severe COVID-19 disease. *International Journal of Health Sciences*, *6*(S4), 10715–10725. https://doi.org/10.53730/ijhs.v6nS4.10892

Evaluation of D-dimer as a prognostic indicator in patients with severe COVID-19 disease

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***Abstract*---**Background – COVID-19 has been a global pandemic since its inception more than two years ago due to rapid transmission in humans. It can cause severe respiratory illness which may lead to death. As it is a novel disease, there are many speculations regarding its diagnosis and management. Thus, this study was planned with an aim to evaluate the role of D-dimer as a marker in predicting poor prognosis in COVID-19 patients. Materials and methods – This was a prospective, observational study carried out for a duration of three months in Unique hospital. The patients of 18 years and above diagnosed with severe COVID-19 disease diagnosed by clinical and radiological picture by pulmonologist were included in the study. Their demographic details were recorded and blood samples were taken once on the day of admission and second time on 5th day. Routine laboratory tests along with D-dimer were performed. The data was statistically analyzed using receiver operating curves to evaluate cut-off values of D-dimer. The patients were divided into two groups based on cut-off values of D-dimer on day of admission and day 5 post admission. Kaplan Meier survival analysis was used to determine the prognostic importance of D-dimer values in predicting mortality. Results – The data was evaluated for a total of 84 patients. The mean age of patients was 54 years and majority of the patients were male

(71.04%). The cut-off value for D-dimer on the day of admission was 310 ng/ml and on day 5 was 864 ng/ml. There was statistically significant difference between D-dimer levels on admission and on 5th day of admission (P <0.01). D-dimer levels on day 5 had significant positive correlation with the length of hospital stay (r = 0.286, P = 0.006). There was a statistically significant increase in in-hospital mortality in the patients with D-dimer levels > 846 ng/ml compared to those with ≤ 846 ng/ml on day 5 (P = 0.04). Conclusion – D-dimer can help in predicting in-hospital mortality in COVID-19 patients. The values above 846 ng/ml on day five can help in early recognition of patients with poor prognosis.

***Keywords*---**COVID-19 pandemic, D-dimer, prognosis.

Introduction

The first case of coronavirus disease-2019 (COVID-2019) was reported in December 2019 from Wuhan, the capital city of Hubei province in China.[1] The World Health Organization (WHO) declared it a global pandemic on March 11, 2020.[2] It was a novel disease which spread throughout the world at an alarming rate and increasing severity; little was known about its diagnosis, management and prognosis. COVID-19 primarily is a respiratory illness affecting lungs and resulting in a pneumonia. But, the spectrum of disease is not limited and in a variety of cases it was shown to affect multiple organ systems especially cardiac, renal, gastrointestinal, hepatic and cerebral.[1, 3] There were various complications following COVID-19 in many patients including coagulopathies such as disseminated intravascular coagulation. This activation of coagulation cascade could likely be due to viremia or a superinfection leading to organ dysfunction.[4] D-dimer is a fibrin degradation product which is commonly used to test hypercoagulable states and coagulopathies. The normal cut-off value for D-dimer is less than 0.5 μg/ml. The level of D-dimer increases with increasing age and in pregnancy.[5] Initially, there is an elevation of D-dimer and fibrinogen in COVID-19 patients.[4] Thus, D-dimer has been under evaluation as the potential prognostic indicator in COVID-19 patients. Recent studies have identified elevated levels of D-dimer in COVID-19 non-survivors suggesting a role of hypercoagulable state in the poor prognosis of these patients.[6, 7] For successful management of COVID-19, availability of an accurate and easily accessible prognostic biomarker plays a crucial role. Also, the cut-off values of D-dimer to predict the severity in COVID-19 are not well defined yet. Hence, this study was carried out to evaluate the possible use of D-dimer as a prognostic marker by comparing the values of D-dimer on admission with that of subsequent therapy and its correlation with the final prognosis of the COVID-19 patients.

Materials and Methods

This was a prospective, observational study carried out for a duration of 3 months during the second wave of COVID-19 from 1st April 2021 to 30th June 2021. The study was carried out at Unique hospital after approval from the ethics committee. The patients were enrolled based on the following inclusion criteria:

1. Patients aged 18 years and above of both genders.
2. Patients diagnosed with COVID-19 and admitted to the hospital
3. Patients willing to give written informed consent.

Thus, all patients above 18 years of age, suffering from COVID-19 and eligible for hospital admission were included in the study. Patients at the extremes of age as well as those not willing to give consent were excluded from the study. Diagnosis of COVID-19 was made by the attending physician and a pulmonologist based on WHO guidelines and was confirmed by quantitative reverse transcription-polymerase chain reaction (RT-PCR) using throat-swabs. Patients suffering from pneumonia as defined by clinical symptoms and lung imaging findings compatible with COVID-19 pneumonia were eligible for hospital admission. Following criteria were set to define severe pneumonia:[8]

- Respiratory rate >30 breaths/minute or lung infiltrates >50%
- SpO_2 <94% at room air or severe respiratory distress

The patient's data was collected in a pre-validated, pre-approved patient data sheet. Demographic details of the patient such as age, gender were collected. Also, details regarding any co-morbid underlying conditions were also recorded. On admission, patient's blood sample was collected within 24 hours and sent for routine blood tests such as complete blood count, coagulation profile, renal function tests and liver function tests. In addition to that, samples were also collected for testing C-reactive protein and D-dimer on the day of admission. Another sample was collected in patients on 5^{th} day for D-dimer evaluation. The tests were run within 2 hours of sample collection. D-dimer was measured using enzyme linked immunosorbent assay principle using D-dimer test kits. The reference range was 0-500 ng/ml. The results were expressed in ng/ml fibrinogen equivalent unit (FEU). Outcome following the treatment was noted. Patients were discharged based on the following criteria: improvement in respiratory symptoms clinically, absence of fever for minimum 3 days, lung imaging tests show remission and two consecutive negative RT-PCR for SARS-CoV-2 RNA. The patients were divided into two groups based on their D-dimer levels on admission and on day 5. The length of hospital stay and in-hospital mortality between the two groups was assessed.

Data analysis

The data was analyzed using SPSS v 19.0. Descriptive statistics of mean, percentage, median and interquartile range was used to describe categorical and continuous variables. Chi-square test and Mann-Whitney U test were used to compare the differences between both groups. Receiver operating characteristic (ROC) curve was used to calculate the mortality discrimination for D-dimer levels. The optimal D-dimer cut off points for the day of admission and day 5 were evaluated. Also, C-statistic for routine laboratory investigations was done. Spearman correlation was used to assess the correlation between D-dimer levels and length of hospital stay. Kaplan-Meier survival analysis and log rank test was used to evaluate the prognostic value of D-dimer levels. $P<0.05$ was considered statistically significant.

Results

A total of 108 patients were admitted in Unique hospital during the study duration. Out of 108 patients, some patients had mild disease and some took discharge against medical advice before completing 5 days of admission. Thus, after excluding such patients, the data was analyzed for 84 patients in total.

Baseline characteristics

Table 1 gives the baseline characteristics of the study participants. The average age of the patients was 54 years (IQR 45 - 62.75 years) of age, ranging from 24 years to 82 years. More than half of the patients were male (71.4%, n = 60). 44.05% study participants suffered from comorbidities. The most common comorbidity was hypertension (16.7%) followed by diabetes (14.3%). The other comorbidities were chronic kidney disease and coronary heart disease. The most common symptoms encountered were cough and fever, followed by fatigue and dyspnea.

Table 1: Baseline Characteristic of COVID 19 patients (n = 84)

COVID-19 Patients Parameters	Total Patients (N=84)	D-dimer on admission ≤ 310 (n = 40)	D-dimer on admission > 310 (n = 44)	P - Value	D-dimer on 5th day ≤ 846 (n = 52)	D-dimer on5th day > 846 (n = 32)	P - Value
Age (years) (median ,IQR)	54 (45 - 62.75)	51.5 (44.25 - 61.0)	54.5 (45.25 - 63.75)	0.45	52 (44.0 - 63.75)	55 (47.25 - 63.75)	0.19
Age above 65 Years, N(%)	12 (14.3 %)	4 (33.3 %)	8 (66.7 %)	0.73	5 (41.7 %)	7 (58.3 %)	0.99
Male N(%)	60 (71.4%)	31 (51.7%)	29 (48.3%)		37 (61.7%)	23 (38.3%)	0.63
Female , N (%)	24 (28.6%)	9 (37.5%)	15(62.5%)		15(62.5%)	9 (37.5%)	0.23
Hypertension , N(%)	14 (16.7%)	3 (21.4%)	11 (78.6%)		3 (21.4%)	11 (78.6%)	0.3
Diabetes , N(%)	12 (14.3%)	5 (41.7%)	7 (58.3%)		4 (33.3%)	8 (66.7%)	0.68
Chronic Kidney Disease, N (%)	6 (7.2%)	4 (66.7%)	2 (33.3%)		3 (50%)	3 (50%)	0.08
Heart Disease , N(%)	5 (5.9%)	2 (40%)	3 (60%)		1 (20%)	4 (80%)	0.17
WBC, (median ,IQR)	1440 (400 - 4395)	655 (403 - 895)	740 (520 - 1287)	0.04	675 (734 - 800)	805 (540 - 1345)	0.16
Haemoglobin, (median ,	13.35 (12.2 -	13.65 (12.28 -	13.25 (11.65 -	0.23	13.5 (12.8 -	13 (11.6 -	0.42

IQR)	14.5)	14.6)	14.3)		14.6)	14.35)	
Platelet , (median, IQR)	19500 (14450 - 26125)	19150 (14025 - 24650)	19900 (15250 - 27425)	0.46	20500 (14450 - 29750)	18800 (14975 - 23425)	0.81
CRP, (median ,IQR)	47.9 (10.0 - 87.0)	28.35 (7.67 - 56.93)	66.9 (12.15 - 90.0)	0.02	22.35 (8.04 - 69.45)	56.45 (11.0 - 92.0)	0.1
Creatinine , (median, IQR)	0.8 (0.70 - 1.00)	0.8 (0.70 - 1.00)	0.80 (0.70 - 1.10)	0.16	0.8 (0.70 - 0.90)	0.90 (0.72 - 1.30)	0.05
Survivors COVID-19 Patients, N(%)	69 (82.1%)	34 (49.3%)	35 (50.7)		48 (69.7%)	21 (30.3%)	0.21
Non - Survivors COVID-19 Patients, N(%)	15 (17.9%)	6 (40%)	9 (60%)		4 (26.7%)	11 (73.3%)	0.04
Hospital Stay Days, (median ,IQR)	6 (5.0 - 9.75)	6 (5.0 - 9.7)	6 (5 - 9.8)	0.60	6 (5.0 - 6.75)	9 (5.0 - 12.0)	0.01

C-statistic (area under ROC curve) was calculated for routine laboratory tests. It is presented in Table 2. D-dimer levels on 5th day had the highest C-index to predict mortality in the COVID-19 patients. ROC curve for the same is given in figure 1.

Table 2. C-statistic of laboratory tests to predict mortality in patients with COVID-19 Patients (n = 84)

Laboratory Tests of COVID-19 Patients	C-Index	95 % Confidence Interval
White Blood Cells	0.411	0.245 - 0.577
Haemoglobin	0.377	0.211 - 0.543
Platelet	0.478	0.317 - 0.640
C-Reactive Protein	0.557	0.395 - 0.719
Creatinine	0.600	0.426 - 0.773
D - dimer on Admission	0.680	0.498 - 0.861
D - dimer on 5th day	0.761	0.632 - 0.890

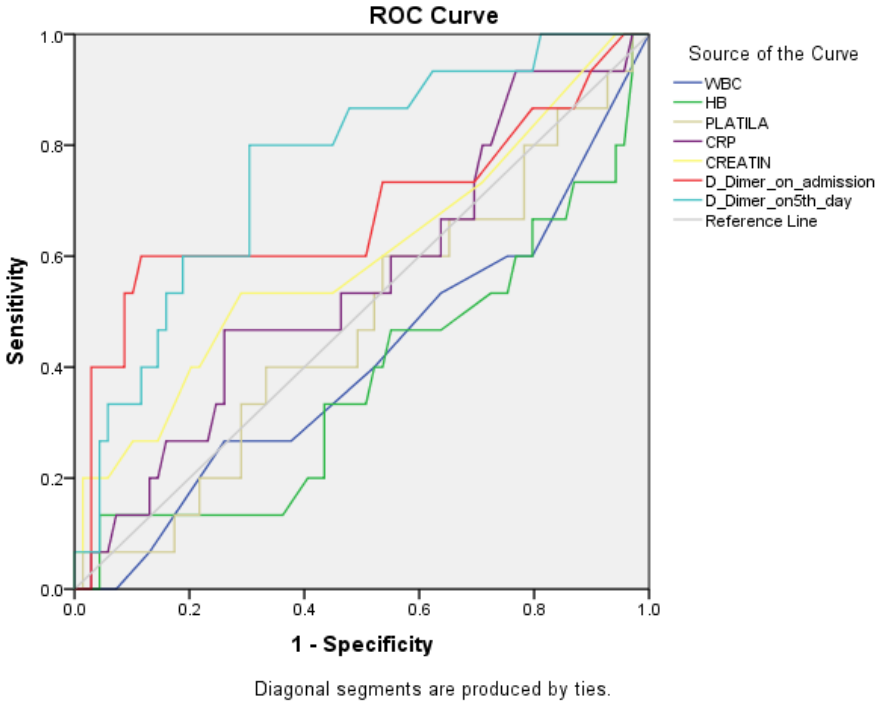

Figure 1. Receiver operating characteristic curve for laboratory investigations.

D-dimer levels for predicting prognosis

As shown in Figure 2, the best cut off points using D-dimer levels on admission to predict mortality in COVID-19 was 310 ng/ml with ROC curve area 0.680 and P value of 0.03 (sensitivity 73.3%, specificity 53.6%). Also, the same for D-dimer levels on day 5 was 846 ng/ml with ROC curve area 0.761 and P value of 0.002(sensitivity 80.0%, specificity 30.4%). There was statistically significant difference between D-dimer levels on admission and on 5th day of admission in terms of ROC curve area (P <0.01).

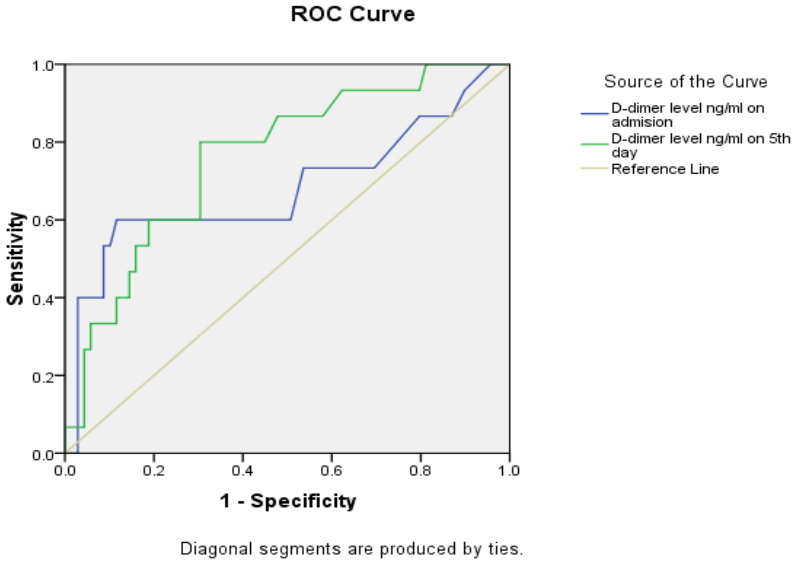

Figure 2.Receiver operating characteristic curve for D-dimer levels in predicting prognosis of COVID-19 patients (n=84)

Based on the cut off value for D-dimer on admission (310 ng/ml), 40 (47.67%) patients had values below 310 ng/ml and 44 (52.33%) patients had values above it. Same way, 52 (61.90%) patients had values below the cut off value of 846 ng/ml for D-dimer levels on 5th day of admission and 32 (38.10%) patients had values above the cut off. There was a significant correlation between D-dimer levels on admission and D-dimer levels on day 5 ($r = 0.45$, $P < 0.001$). The D-dimer levels on admission had no significant correlation with length of hospital stay in COVID-19 patients ($r = 0.08$, $P = 0.94$). On the other hand, D-dimer levels on day 5 had significant positive correlation with the length of hospital stay ($r = 0.286$, $P = 0.006$). The number of days of hospitalization were increased with increased levels of D-dimer on day 5 of admission.

Total 15 in-hospital deaths were reported during hospitalization. 9 out of 15 deaths occurred in patients with D-dimer levels > 310 ng/ml on admission and 4 occurred in patients with D-dimer levels ≤ 310 ng/ml (9/40 vs 6/44). In the second group with D-dimer values on day 5 of admission, there were 4 deaths in patients with D-dimer levels ≤ 846 ng/ml, but 11 deaths in patients with D-dimer levels > 846 ng/ml on 5th day of admission (4/52 vs 11/32). As shown in Figure 3, Survival analysis using Kaplan-Meier curves and log rank test revealed a statistically significant difference in the survival function i.e. higher incidence of in-hospital mortality between the patients with D-dimer levels ≤ 846 ng/ml and > 846 ng/ml on 5th day of admission ($P = 0.04$). There was no such statistical significance in survival function and D-dimer levels on admission.

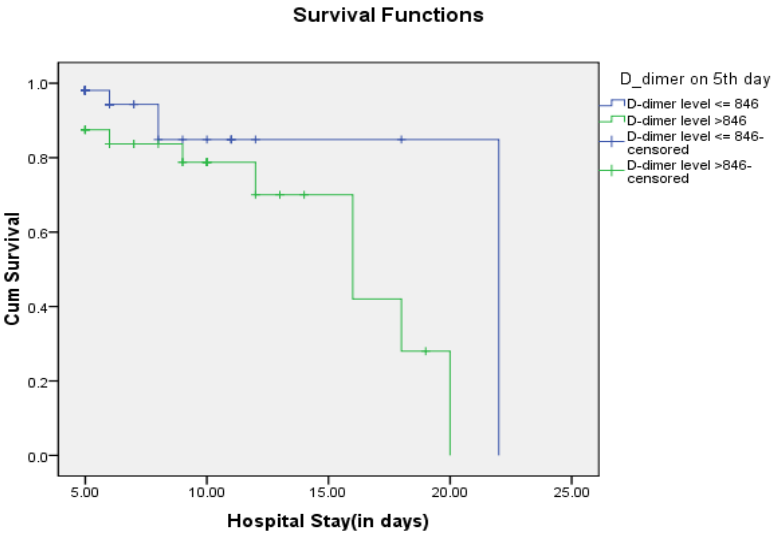

Figure 3. Kaplan-Meier survival analysis curves for patients with D-dimer levels > 846 ng/ml on Day 5 (P = 0.04)

Discussion

The emergence of COVID-19 and fast spread of this infectious disease have been a unique challenge faced by mankind in 21st century. Due to the pandemic, lots of research was done to gain insight for diagnosis and management of this novel viral disease for which nothing was known to world. One such marker was evaluated in this study. Due to the knowledge gained by various signs and symptoms regarding COVID-19, it was observed that it leads to coagulopathy in patients. D-dimer is a fibrin degradation product, which serves as a marker to predict coagulopathy. Hence, it was suggested as a predictor for assessing the prognosis of COVID-19 patients. Thus, this study aimed at finding the prognostic value of D-dimer in the hospitalized COVID-19 patients.

The average age of patients was 54 years and the IQR was 45 to 62.75 years. There were more number of male patients hospitalized 71.4% as compared to female patients (28.6%). This shows that disease was more severe requiring hospitalization in older age groups and in male gender. This was similar to findings obtained in a recently published study where COVID-19 was more prevalent in older age groups and more severe in male gender.[9]

It was observed that there was a significant elevation in the D-dimer levels on day 5 post admission as compared to D-dimer levels on the day of admission. There have been similar findings in other studies where there was an increase in D-dimer levels in COVID-19 patients which was more in severe disease as compared to milder forms. A descriptive study by Chen et al. in Wuhan detected increased D-dimer in 36% of patients.[10] Another study by Huang et al. conducted in Wuhan in small number of COVID-19 patients reported a five times higher D-dimer values in patients with severe disease as compared to patients with mild

disease.[11] Similar findings were reported by Wang et al. by a study in 138 patients where in an increase of 2.5 fold was reported in D-dimer in patients with severe disease.[12] In a study by Poudel et al. elevated D-dimer levels on admission was significant predictor of mortality among the COVID-19 patients.[13] A recently published systematic review also reported poor prognosis in patients with higher D-dimer levels as compared to people with lower ones.[14]

The study identified a cut off value for D-dimer on the day of admission as well as on day 5 post admission to predict mortality in COVID-19 patients. The cut off value on 5th day after admission was found to be 846 ng/ml. There was a significant increase in length of hospital stay as well as in-hospital mortality in the patients with D-dimer values on day 5 of admission above 846 ng/ml. This was similar to the findings observed by a multicenter retrospective study carried out in China by Zhou et al. in the beginning of pandemic. The study included 560 COVID-19 patients and defined a cut off value of D-dimer at 500 ng/ml. The patients with severe disease frequently had D-dimer levels above 500 ng/ml.[15] Another study in Wuhan by Zhang et al which retrospectively evaluated data of 343 patients identified a cut off value of 2000 ng/ml for D-dimer. The patients with values more than 2000 ng/ml had a higher incidence of mortality compared to those with D-dimer levels below 2000 ng/ml.[16] A similar study carried out in Morocco reported increased mortality in patients with higher D-dimer levels with cut off value of 1360 ng/ml on day 5 of admission.[17] The increase in D-dimer levels points towards existence of hypercoagulable state in a COVID-19 patient.[18] This could be due to many reasons, such as, a direct myocardial injury by the SARS-CoV-2 virus as the virus infects cardiomyocytes through ACE2 receptors.[19] Inflammation can cause indirect injury through inflammatory mediators by causing endothelial cell dysfunction and excess thrombin generation.[20] The resulting hypercoagulability of blood increases the chances of thrombus formation and embolization. This may lead to ischemia which can result in disease progression and ultimately death. Thus, it is clear from the findings of the study that measurement of D-dimer levels is important predictor of mortality in COVID-19 patients.

Our study had certain limitations. Firstly, the sample size of the study is small and so the findings cannot be generalized to the population at a large. Secondly, some patients were admitted very late in the disease course with significant disease progression. This may have affected the results. Thirdly, the patients who were still in the hospital after the duration of study were excluded, so it is possible that case fatality ratio in the study may not reflect the true mortality of COVID-19.

Conclusion

In conclusion, it can be said that D-dimer levels are usually elevated in patients with COVID-19. There is a significant correlation between D-dimer levels on admission and D-dimer levels after 5 days of admission. There was a significant increase in the length of hospital stay and in-hospital mortality in patients with increased levels of D-dimer above the cut off value of 1360 ng/ml. Thus, monitoring and serial measurement of D-dimer levels in COVID-19 patients would help in early recognition of COVID-19 patients who may have poor prognosis. This

would help the pulmonologists and physicians to individualize the treatment approach and provide prompt intensive care to patients in need.

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