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Original Research Article

Role of D-Dimer Values for Predicting Disease Severity and Mortality in Covid-19 Patients – A Hospital Based Observational Study

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Abstract

Introduction: Corona virus disease 2019 (COVID-19) was identified as an outbreak in December 2019 in Wuhan, China and declared global pandemic by WHO on March 11, 2020. The disease has a wide spectrum of symptomatology and out of which coagulopathy is a common manifestation amongst critically ill patients. We aimed to explore risk factors associated with mortality in COVID-19 patients and association of D-Dimer values for predicting disease severity and mortality.

Methods: In this observational study, 260 COVID RT-PCR positive patients admitted from September 2020 to March 2021 in covid dedicated wing, were recruited and stratified on the basis of their clinical characteristics into mild and moderate and severe illness groups on the day of admission and recategorized similarly on day 5 on the basis of MoHFW guidelines of India. D-Dimer levels were obtained on the day of admission and on the day 5 of admission. Association of D-Dimer values on the day of admission and on day 5 of admission with increasing or decreasing severity of disease, recovery and in-hospital mortality were analysed. Receiver operating characteristic curve was used to determine the optimal cut off level for D-dimer.

Results: The optimal cut off of D-dimer for predicting the severity and mortality of disease on Day of admission and Day 5 were 1106ng/ml FEU (AUC 0.699) and 1795ng/ml FEU (AUC 0.787) with sensitivity of 74% and specificity of 65.71% (p value<0.0001) on the day of admission and also on the Day 5 with a sensitivity of 80.43% and specificity of 71.02% (p value<0.0001). Out of 150 patients below cut off on the Day 1, 13(8.6%) patients died and 137(91.33%) patients were discharged from hospital. Out of 110 patients above cut off, 37(33.63%) patients died and 73(66.36%) patients were discharged from hospital. Out of 133 patients below cut off on the Day 5, 9(6.7%) patients died and 124(93.23%) patients were discharged from hospital. Out of 89 patients above cut off, 36(40.44%) patients died and 53(59.55%%) patients were discharged from hospital. The patients with D-dimer level less than cut off showed better recovery, less in-hospital mortality and majority of patients from this group were discharged satisfactorily as compared to the group of patients with D-dimer level above cut off. The patients with D-dimer values more than cut off were sick and high in-hospital mortality was noted.

Conclusion: The mean D-Dimer values are found to be elevated on Day 1 and Day 5 as 1374.5 and 2000.5 respectively. The serial D-Dimer levels are higher in the non-survivors than the survivor's i.e. Those patients, who were recategorized in moderate and severe illness groups on day 5 of admission, were showed rising titres of D-Dimer.

Keywords: COVID-19; COVID RT-PCR; D-Dimer.

Introduction

COVID-19, an infectious disease caused by the SARS-CoV-2 virus, was classified as a global health emergency by the WHO on January 30, 2020, and as a pandemic on March 11, 2020 [1]. In COVID-19, thrombotic consequences and coagulopathies, such as disseminated intravascular coagulopathy, are frequent. This is probably due to activation of coagulation cascade by viremia or a cytokine storm, or it could also be because of superinfection and organ failure [2].

Biomarkers are quantitative measurements that reflect the pathophysiology of a disease and help doctors identify the severity of a medical condition. They also help in the development of medical care management algorithms that can improve patient outcomes [3]. High levels of fibrinogen, increased D-dimer level, prolonged pro-thrombin time, thrombocytopenia, lymphopenia, leukocytopenia, increased concentration of interleukin-6 and ferritin are observed in most COVID-19 patients. The degree of increase in these changes correlates with severity of the inflammatory process and serves as a prognostically unfavourable sign [4].

COVID-related mortality is mainly associated with increased risk of hypercoagulability and venous thromboembolism, which in severe cases causes a thromboinflammatory process [5]. Coagulation biomarkers may therefore indicate disease severity and mortality and guide patient triage, treatment strategies, and prognostic monitoring. D-dimer, which is a degradation product of cross-linked fibrin reflects ongoing activation of the coagulation cascade and has been linked with coagulopathy in COVID-19 infection [6]. Some previous studies have shown correlation between elevated D-dimer (prevalence up to 46.4%) & increased severity and adverse outcomes of COVID-19. [7-9]

Some previous studies on community-acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) patients have shown that D-dimer level is higher in severe cases and may be used as a prognostic biomarker. D-dimer > 1 µg/ml is one of the risk factors for mortality in adult inpatients with COVID-19 [10]. Patients with D-dimer levels above 1000 ng/mL have a 20-fold increased risk of death compared to those with low D-dimer levels [8,11].

So, in the above context present study was done with the following objectives:

1. To determine the sensitivity and specificity of D-dimer for predicting disease severity and mortality.
2. To determine the mean D-dimer levels in COVID-19 patients.

Methodology

The present study was conducted in the department of Medicine, Dr. S.N. Medical College, Jodhpur. This was a hospital based ambispective observational study. This study was carried over a period of September 2020 to March 2021. Consecutive sampling method was used to recruit study subjects. Consecutive COVID-19 patient was defined as a patient with positive reverse transcriptase polymerase chain reaction (RT-PCR) in a diagnostic specimen, admitted during the study period. COVID-19 positive male and

female patients aged 18 to 80 years were included in this study.

Following patients were excluded from study:

- Patients with recent myocardial infarction, stroke.
- Patients with evidence of trauma/ post operative patients.
- Patients having valvular heart disease or artificial valve or on warfarin.
- Patients with any malignancy.
- Patients with chronic liver disease.
- Patients with deep vein thrombosis (ruled out clinically)

Data related to the demography, comorbidities and laboratory parameters were noted from the medical records of the patients.

Assessment of clinical severity was done a per MoHFW guidelines:

- Mild – without evidence of hypoxia or breathlessness (normal saturation on room air).
- Moderate – with clinical features of dyspnoea and hypoxia, fever, cough including SpO2 range 90 to 94% on room air, respiratory rate or equal 24/minute.
- Severe – with clinical signs of pneumonia plus one of the following; respiratory rate >30/min, severe respiratory distress, SpO2 < 90% on room air.

Method of estimation of serum D-Dimer: Serum D-Dimer estimation test is performed in biochemistry lab on point of care testing (POCT) equipment F-200 standard by fluorescent immune assay system.

Method of estimation of serum Ferritin: Serum ferritin estimation test was performed on chemiluminescence Immuno Assay ACCESS-– II (Beckmann Coulter).

Statistical analysis

Data were collected as per the pre-defined proforma and entered into excel sheet using Microsoft Excel version 2007. The data was arranged in tabular form, expressed in the form of self-explanatory tables and figures. Results on continuous measurements were presented in the form of mean ± SD and results on categorical measurements were presented in the form of numbers and percentage (%).

The data were further analysed statistically using IBM SPSS software of statistics version 22, by applying appropriate tests of significance. Student's t-test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square test was used to find the significance of study parameters on categorical scale between two groups. Significance was assessed at 5% level of significance, i.e., p value of less than 0.05 was considered as significant.

Results

The mean age of 260 patients included under the present study was calculated to be 55.78±15.55 year, with maximum number of patients of 61-70 years as shown in table 1. It was observed that, number of males 181 (69.62%) were more than females 79 (30.38%) as shown in table 2. Among the total 260 patients, 203 patients had co-morbidities as shown in table 3. Baseline clinical features are shown in table 4. It was observed that 157 (60.38%) patients had cough, followed by shortness of breath 153 (58.85%), 145 had fever (55.77%) and 139 had fatigue (53.46%).

To evaluate the disease severity, patients were categorized into three groups as mild, moderate and severe and compared on day 1 and day 5 of the clinical onset. Case severity on day 1 and day 5 is shown in table 5. Table 6 analyses the cases on day 0 and day 5 based on severity of disease. Out of total 260 cases, on day 0, 144 cases had mild disease, out of which 24 got discharged, 108 remained mild, 10 progressed to moderate disease and 2 cases progressed to severe disease, over next 5

days. No death was reported among the cases who had mild disease on day 0. 97 cases had moderate disease on day 0, out of which 19 remained moderate, 40 improved to mild disease and 10 got discharged, over the next 5 days, while 24 cases progressed to severe disease and 4 deaths were reported among these cases. 19 cases were admitted with severe disease on day 0, out of which 11 remained severe, 7 improved to moderate and 1 case improved to mild disease. No cases from those severe cases could be discharged. Deaths reported from this group were zero.

Mean D-dimer levels estimated on day 0 and day 5 are shown in table 7. Compared with day 0, on day 5 the patients had elevated levels of D-dimer in all the three categories of mild, moderate and severe. More D-dimer levels were found on day 5 in patients complaining severe condition than other categories. Table 8 compares the conditions of the cases of various levels of severity on Day 0 with their outcome before and after day 5. Average duration of hospital stay has also been depicted in the table 8.

Out of the 144 cases, who had mild disease on Day 0, 24 got discharged; no deaths or LAMA cases were reported before day 5. After day 5, 109 got discharged and 11 were declared dead. Out of the 97 cases, who had moderate disease on day 0, 10 got discharged and 4 led to death before 5 days. After 5 days, 50 got discharged, 27 were dead and 6 got LAMA. Out of the 19 cases, who were admitted with severe disease on day 0, no cases could be discharged before day 5. 10 cases could be discharged after day 5, 8 led to death and one cases was reported to get LAMA.

CRP levels were also estimated in this study which are shown in table 9. IL-6 levels are shown in table 10. Blood pressure findings on day 0 and 5 is shown in table 11. Mean systolic BP was observed to be 120.77±12.290 and 122.33±11.023 mm of Hg on day 0 and day 5 respectively. And mean diastolic BP was observed to be 80.30±7.366 and 80.53±5.60 mm of Hg on day 0 and day 5 respectively. Statistically no significant difference was observed between the BP of day 0 and day 5. On day 0, 116 (44.61%) patients required oxygen, which decreased on day 5 and only 73 patients (33.18%) showed requirement of oxygen as shown in table 12. On systemic examination, 151 (58.08%) patients showed to have respiratory findings (crepitations on auscultation), followed by 4 (1.54%) cases with CNS findings (altered sensorium), 3 (1.15%) patients with CVS findings (had murmur or additional heart sounds) and 3 (1.15%) abdominal findings (generalized pain or tenderness in abdomen). Mean D-dimer levels in COVID-19 patients on the day of admission were found to be 1374.5 and on Day 5 , 2000.5 as shown in table 13.

The area under the curve for receiver operating characteristic curve (ROC) for D-dimer values on Day 1 and outcome was plotted as shown in the figure 1. The area under the curve at the time of admission was 0.699(95% CI 0.639-O.754 P <0.0001) as shown in table 14. The optimal cut off value was ≥1106ng/ml with sensitivity of 74 % and specificity of 65.71% with a positive predictive value of 33.90 and negative predictive value of 91.40) as shown in table 15. Out of 150 patients below cut off, 13(8.6%) patients died and 137(91.33%) patients were discharged from hospital. Out of 110 patients above cut off, 37(33.63%) patients died and 73(66.36%) patients were discharged from hospital.

The area under the curve for receiver operating characteristic curve (ROC) for D-dimer values on Day 5 and patient's outcome was plotted as shown in the figure 2. The area under the curve at the time of admission was 0.787(95% CI 0.727-O.839, P <0.0001) as shown in table 16. The optimal cut off value was ≥1795ng/ml with sensitivity of 80.43% and specificity of 71.02% (PPV=42, NPV= 93.30) as shown in table 17. Out of 133 patients below cut off, 9(6.7%) patients

died and 124(93.23%) patients were discharged from hospital. Out of 89 patients above cut off, 36(40.44%) patients died and 53(59.55%%) patients were discharged from hospital. Mean values of various pathological parameters were computed, as summarized in the table 18.

Table 1: Age-wise distribution

Age groups	Frequency	Percentage
18-20 years	5	1.92%
21-30 years	22	8.46%
31-40 years	23	8.85%
41-50 years	36	13.85%
51-60 years	56	21.54%
61-70 years	76	29.23%
71-80 years	42	16.15%
Total	260	100%

Table 2: Gender wise distribution of COVID patients

Gender	Frequency	Percentage
Male	181	69.62%
Female	79	30.38%
Total	260	100%

Table 3: Co-morbidity wise distribution

Co-morbidity	Frequency	Percentage
Diabetes mellitus	44	16.92%
Hypertension	47	18.08%
IHD	24	9.23%
Thyroid disorders	3	1.15%
COPD	2	0.77%
Tuberculosis	9	3.46%
Surgical history	10	3.85%
Substance Abuse	64	24.62%

Table 4: Baseline clinical features

Clinical Features	Frequency	Percentage
Asymptomatic	16	6.15%
Fever	145	55.77%
Fatigue	139	53.46%
Sore throat	110	42.31%
Shortness of breath	153	58.85%
Chest pain	91	35%
Cough	157	60.38%
Abdominal Pain	33	12.69%
Weight loss	59	22.69%
Altered sensorium	6	2.31%
Loss of smell and taste	115	44.23%

Table 5: Severity of Disease

Severity of disease	Day 1	Day5
Mild	144(55.38%)	149(67.12%)
Moderate	97(37.31%)	36(16.22%)
Severe	19(7.31%)	37(16.67%)
Total	260(100%)	222(100%)

Table 6: Analysis of cases on Day 0 to Day 5, depending on severity

Severity on Day 0	Total number of cases on Day 0	On or before Day 5				
		Mild	Moderate	Severe	Death	Discharge
Mild cases	144	108	10	2	0	24
Moderate cases	97	40	19	24	4	10
Severe cases	19	1	7	11	0	0
Total	260	149	36	37	4	34

Table 7: Mean D- dimer levels on Day 0 and Day 5 in Mild / Moderate and Severe Cases

Severity	Mild	Moderate	Severe
Day 0	1095.95 ng/ml	1699.14 ng/ml	1828.36 ng/ml
Day 5	1489.76 ng/ml	2409.26 ng/ml	3657.22 ng/ml

Table 8: Conditions of the cases of various levels of severity on Day0, compared with their outcomes before and after Day 5

Severity on Day 0	Total no. of cases on Day 0	Before Day 5			After Day 5		
		Discharge	Death	LAMA	Discharge	Death	LAMA
Mild cases	144	24	0	0	109	11	0
Average stay in days	Mean± SD	3.17± 0.8681	-	-	8.32± 4.851	13.0± 6.410	-
Moderate cases	97	10	4	0	50	27	6
Average stay in days	Mean± SD	3.5± 0.7071	3.5± 0.5774	-	8.84± 4.032	10.9± 4.816	7.83± 2.787
Severe cases	19	0	0	0	10	8	1
Average stay in days	Mean± SD	-	-	-	16± 8.498	12.1± 4.257	11±0

Table 9: CRP levels

CRP Levels	Number of Patients(n=163)	Frequency
<10	54	33.13%
11-20	37	22.70%
21-30	21	12.89%
31-40	16	9.82%
41-50	11	6.75%
51-60	8	4.91%
61-70	4	2.45%
71-80	1	0.61%
81-90	3	1.84%
91-100	0	0
>100	8	4.91%

Table 10: IL-6 levels:

IL6 Levels	Number of Patients	Frequency (n=197)
<6	48	24.36%
6-10	19	9.64%
10-20	26	13.19%
20-30	16	8.12%
30-40	11	5.58%
40-50	13	6.59%
50-60	5	2.53%
60-70	5	2.53%
70-80	5	2.53%

80-90	6	3.04%
90-100	1	0.5%
>100	42	21.31%

Table 11: Mean Blood Pressure on Day 0 and Day 5:

Day	Systolic				Diastolic			
	Mean	Std Deviation	P value	T value	Mean	Std deviation	P value	T value
Day 0	120.77 (260)	12.290	0.1720	1.368	80.30 (260)	7.366	0.7039	0.3802
Day5	122.33 (222)	11.023			80.53 (222)	5.60		

Table 12: Oxygen Requirement on day 0 and Day5:

Day	Required	Not Required
Day 0 (n=260)	116(44.61%)	144(55.38%)
Day 5 (n=222)	73(33.18%)	149(67.72%)

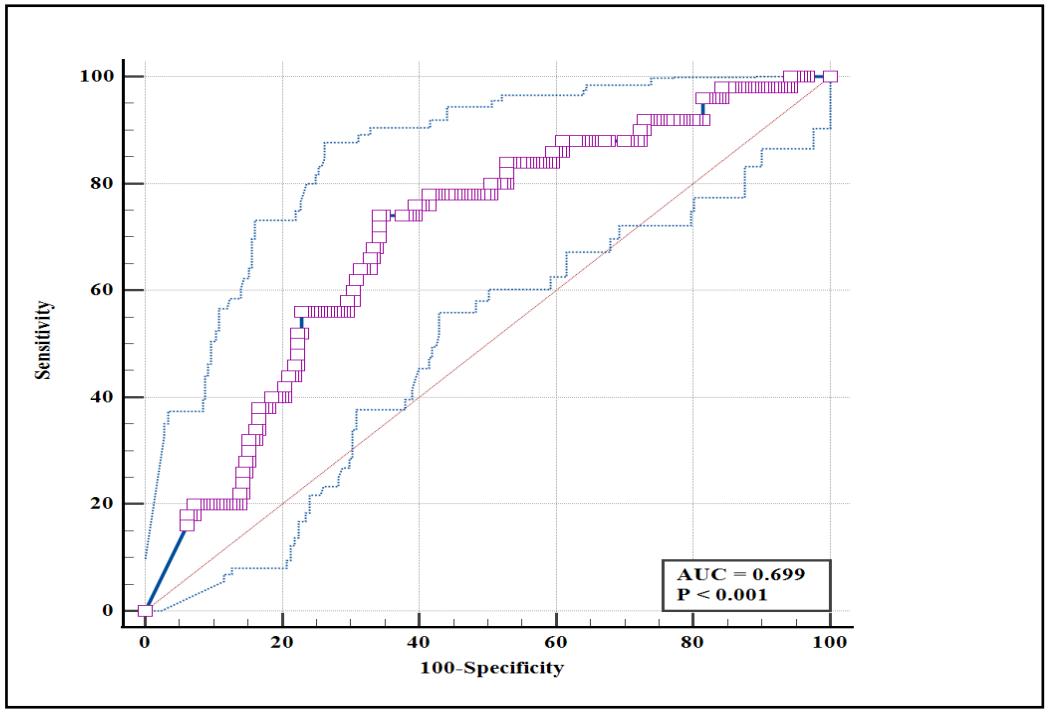

Figure 1: Receiver operating characteristics (ROC) between outcomes with D-Dimer on day 1 at admission in patients of COVID-19 -ROC curve

Table 13: Mean D-dimer values on Day 1 and Day 5

	N	Minimum	Maximum	Mean	Median	Variance	SD
D Dimer on day 1	260	25.00	5000.00	1374.511	903.00	1922246.43	1386.45
D Dimer on day 5	222	25.00	5000.00	2000.518	1343.50	2640674.51	1625.01

Table 14: Area under the ROC curve (AUC) on day 1

Area under the ROC curve (AUC)	0.699
Standard Error	0.0396
95% Confidence interval	0.639 to 0.754
Significance level P (Area=0.5)	<0.0001

Table 15: Youden index on day 1

Youden index J	0.3971
95% Confidence interval [a]	0.2514 to 0.5101
Associated criterion **[Cut-off value]**	>1106
95% Confidence interval [a]	>1004 to >1812
Sensitivity	74.00
Specificity	65.71
PPV	33.90
NPV	91.40

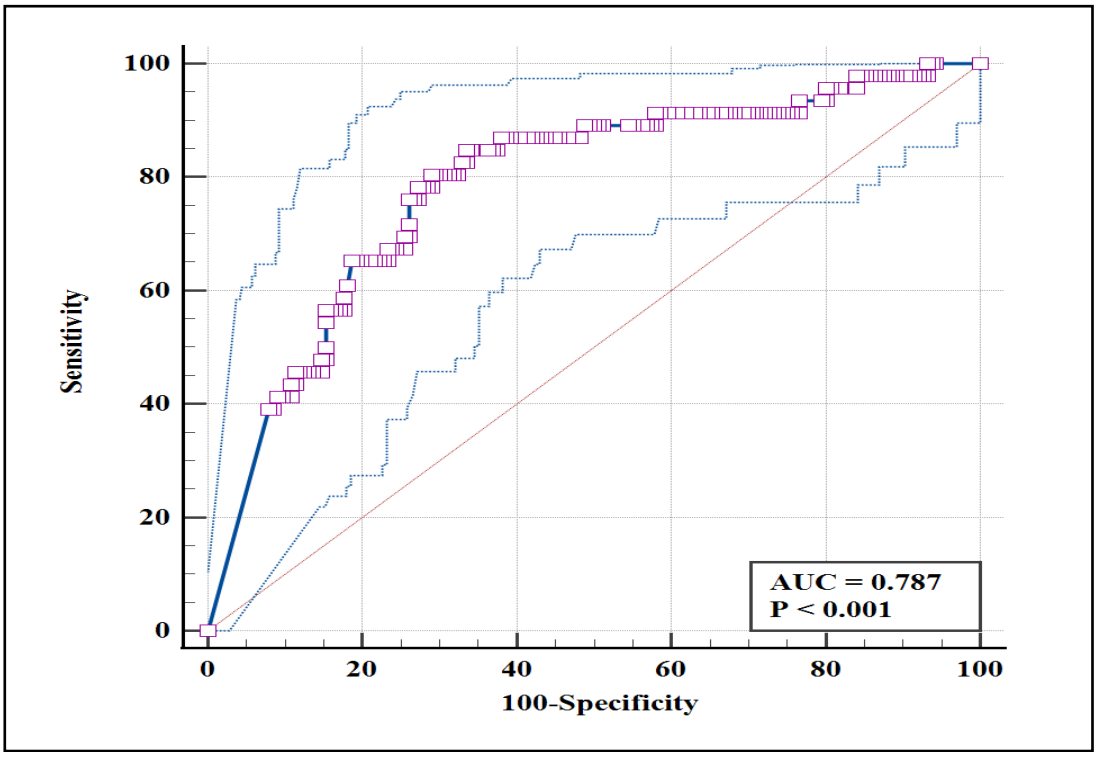

Figure 2: Receiver operating characteristics (ROC) between outcomes with D-Dimer on day 5 in patients of COVID-19 -ROC curve

Table 16: Area under the ROC curve (AUC) on day 5

Area under the ROC curve (AUC)	0.787
Standard Error	0.0385
95% Confidence interval	0.727 to 0.839
Significance level P (Area=0.5)	<0.0001

Table 17: Youden index on day 5

Youden index J	0.5146
95% Confidence interval [a]	0.3602 to 0.6041
Associated criterion [Cut-off value]	>1795
Sensitivity	80.43
Specificity	71.02
PPV	42.00
NPV	93.30

Table 18: Biochemical Parameters

Parameters	N	Mean	Standard deviation
Haemoglobin	260	10.86	2.467
RBC count	260	4.69	0.639
WBC Count	260	10.77	4.68
Platelet count	260	231.45	126.63
MPV	260	9.427	1.208
MCV	260	85.00	10.97
MCH	260	29.55	3.491
MCHC	260	31.28	3.073
RBS	260	162.20	82.561
Serum Bilirubin	260	1.11	0.8619
SGOT	260	72.41	51.969
SGPT	260	62.10	59.327
Albumin	260	2.97	0.5422
Total Protein	260	6.06	0.8012
Serum Creatinine	260	1.28	0.6436
Blood Urea	260	56.51	32.673
CT Severity Score	224	12.54	12.723
Sr. Ferritin	220	433.58	55.45
CRP	163	35.06	104.20
IL-6	197	116.09	286.04

Discussion

In the present study, we found that maximum patients were of 61- 70 years age group with a mean age of 55.78±15.55 years. In accordance with our study, a study from Bulgaria concluded that the older age groups had higher odds ratio of getting COVID with the highest number of patients in age group of 60-79 years [12]. Although all age groups are at increased risk of contracting COVID-19, we found that elderly people are affected more, this could be due to physiological changes that come with aging and underlying health conditions or could be due to socio-cultural issues, demographic characteristics, reduced immunity which need further evaluation. In the present analysis, gender wise distribution showed that male patients outnumber the female patients as out of total patients. Similar findings have been observed in some previous studies [13-15]. In the co-morbidity wise distribution, substance abuse was seen in 24.62% of patients whereas hypertension and diabetes were reported in 18.08% and 16.92% of the study population respectively. A study done by Guan WJ *et al* [16], has also reported hypertension and diabetes as prevailing co-morbidities in COVID-19 patients. Another study by Bandari S *et al* [17], reported that the most prevalent comorbidity was hypertension followed by diabetes mellitus, bronchial asthma/COPD, coronary artery disease, chronic renal disease, and valvular heart disease. It was found in baseline clinical features that 157 (60.38%) patients had cough, followed by shortness of breath 153 (58.85%), 145 had fever (55.77%) and 139 had fatigue (53.46%). Similar findings were seen in a study by Tanaka *et al* [18]. In our study, it is observed that overall mild cases were more than moderate and severely ill patients on day 1 and day 5.

Overall mild cases were common and outnumbering the moderate and severely diseased patients, which could be due to the high attack rate and infectivity of the disease and also the public awareness. On following up the patients we also found that number of severely ill patients

increased on day 5, which could be due to early discharge of mild cases, disease progression due to complete invasion of virus, high virulence and poor immune system to defend and slow recovery. Mean D-dimer levels estimated on day 1 and day 5 were analysed in all the three category patients.

Compared with day 1, on day 5 the patients had elevated levels of D-dimer in all the three categories of mild, moderate and severe. More D-dimer levels were found on day 5 in patients complaining severe conditions than other categories. This indicates that as the days progresses the biochemical levels increases with viral invasion, hence showed more elevated levels of D-dimer on day 5. In accordance with our study, a study by Zou *et al* [19] demonstrated the link between high D-dimer levels and disease severity in 129 COVID-19 patients admitted in Shanghai, China.

Islam Eljilany *et al* [20] and Huang *et al* [21], reported that D-dimer values were higher in those with severe disease than in mild disease. Our study is also supported by meta-analysis done in Turkey which revealed that the D-dimer concentrations were significantly higher in patients with more severe COVID-19 ($p<0.001$) [22].

The patients with D-dimer level less than cut off showed better recovery, less in-hospital mortality and majority of patients from this group were discharged satisfactorily as compared to the group of patients with D-dimer level above cut off.

The patients with D-dimer values more than cut off were sick and high in-hospital mortality was noted. The mean D-dimer on day of admission and Day 5 were found to be 1374.5 and 2000.5 respectively. Also, the D-dimer values changes in accordance with clinical status of the patients because on following up the patients on Day 5 of their hospitalization it was observed that as the severity of disease increases the D-dimer levels also rises and the level of D-dimer found lower in patients showing recovery pattern.

A study performed in India by Shah S *et al* [23], considered that, the d-dimer levels were higher in patients with severe COVID-19 infection and those who succumbed to death, compared with non-severe disease and those who survived, and observed that patients with elevated d-dimer levels were at an increased risk of developing severe COVID-19 infection and increased all-cause mortality compared with those with normal d-dimer levels.

In present study, CRP levels which is an acute phase reactant is found to be >10mg/L in 109 patients out of 163 patients. IL-6 appears as a potential predictor for the development of the severe Covid-19 and might serve for early identification of patients in need of hospitalization. In present study, IL-6 levels are also found to be elevated i.e. >6pg/ml in 149 patients out of 197 patients.

According to known evidence, IL-6, CRP and other markers of inflammation in predicting respiratory failure in Covid-19 [24-25]. The application of CRP in COVID-19 as a diagnostic biomarker is supported by multiple studies [26-28] done in Wuhan, China where the majority of patients in the severe cohort showed significantly higher levels compared to the non-severe cohort.

In present study, mean serum ferritin levels were found to be 433.58ng/ml (n=220). Ferritin is key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm [29]. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome [21].

Our study had a few limitations, such that we did not follow up of patients after discharge, so trend of D-dimer could not be studied later on. We lacked to study

radio-interventional investigations such as pulmonary angiography, colour doppler to rule out evidence of pulmonary embolism and deep vein thrombosis because of highly infectious nature, containment of these patients and severity of illness.

Conclusion

Our study concluded that the COVID-19 positive patients were having high D-dimer levels on Day 1 as well as day 5. The patients in clinical category of mild illness were outnumbering moderate and severe disease on Day 1 and Day 5.

The levels of D-dimer were lower in the mild cases as comparison to moderate and severe cases on Day 1 and Day 5. Likewise, moderate and severe illness patients were found to have high D-dimer levels on Day 1 and Day5. We concluded that role of D-dimer for predicting disease severity and mortality in COVID-19 patients is significant with a sensitivity of 74% and specificity of 65.71% (p value<0.0001) on the day of admission and also on the Day 5 with a sensitivity of 80.43% and specificity of 71.02% (p value<0.0001).

The patients with D-dimer level less than cut off showed better recovery, less in-hospital mortality and majority of patients from this group were discharged satisfactorily as compared to the group of patients with D-dimer level above cut off. The patients with D-dimer values more than cut off were sick and high in-hospital mortality was noted. Finally, we conclude our study findings stating that the D-dimer levels are sensitive for early detection, triaging the patients and also an important tool for monitoring the progression of disease.

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