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Significance of D-dimer in Assessment of Severity and Mortality of COVID-19 Patients A Tertiary Care Hospital Study

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Abstract: The outbreak of COVID-19 has brought public health emergency worldwide and has been the biggest challenge to date. This study aims to study the correlation between D-dimer levels with severity and mortality in COVID-19 patients. This study will help us understand the disease's progression and monitor the disease severity and mortality in Covid-19 patients. This retrospective descriptive study was conducted over four months from April 2021- to June 2021 in a tertiary care hospital in Central Karnataka. Demographic details and clinical and laboratory parameters were obtained from electronic hospital records. Inclusion criteria are Patients who were RT-PCR confirmed positive cases were only included in this study. Exclusion criteria are Patients who had cancer, hematologic malignancies, and acute coronary syndrome were all excluded. Results of the research are A total of 75 cases were evaluated and analyzed in this study. Patients were categorized based on severity as mild to moderate and severe. Out of which 50 patients had recovered from the illness, and 25 patients have succumbed to death. Our study revealed that elevated D-dimer levels were significant ($p<0.02$) with the outcome of the disease, and with the mean level of 929.27 in severe patients and 466.47 in mild-moderate patients, elevated D-dimer were highly significant ($p<0.001$) with the severity of the disease. Conclusion research detailed investigations of 75 COVID-19 patients suggests that a significant increase in D-dimer levels was associated with mortality and severity of the disease. Therefore, we strongly recommend that the D-dimer be used to screen patients with COVID-19 to evaluate the severity and predict the prognosis and mortality in hospitalized COVID-19 patients during admission and follow-up throughout hospitalization.
Keywords: COVID-19; D-dimer; prognostic marker

INTRODUCTION

The highly contagious Coronavirus disease (COVID-19) was first reported in Wuhan, China, in December 2019. It has spread throughout the world and created a great threat to global health. The causative agent was a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 belongs to a class of single-stranded RNA viruses, beta coronaviruses of the family Coronaviridae, and has a long incubation period with human-to-human transmission (Ghaith M et al.,2021). Though the symptoms were usually mild to moderate, in the early stages, patients developed acute respiratory symptoms, and few developed acute respiratory failure and other serious complications (Zheng J et al., 2020)

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In the case of mild to moderate cases symptomatic treatment and isolation are required, but in severe patients, Intensive Care Unit (ICU) admission is required. Thus, early assessment of risk factors for critical illness has to be assessed to reduce the mortality of COVID-19 patients (Liu. J et al.,2020).

D-dimer is a biomarker of fibrin formation and degradation. If D-dimer is within normal limits, it is used to rule out the diagnosis of deep venous thrombosis and pulmonary embolism. An elevated D-dimer is independently associated with an increased risk of Venous Thromboembolism (VTE), recurrent VTE, and mortality (Halaby R et al., 2015). The levels of D-dimer, an important prognostic factor, were found to be higher in patients with a clinically severe case of SARS-CoV-2 than in non-severe cases (Mattiuzzi C et al.,2020). And the outbreak of the COVID-19 pandemic, D-dimer, has been identified as a potential indicator for its prognosis in COVID-19 patients. In other studies, admission day D-dimer has shown promise for predicting the disease severity in multiple studies (Zohu F et al.,2020, Yao Y et al.,2020, Zhang L et al.,2020, Soni M et al.,2020).

Compared to other studies done around the world, our study has categorized the cases based on severity and survivors and nonsurvivors. Therefore, this study will help us understand the correlation between D-dimer levels, severity, and mortality of the disease and know the disease's progression with risk stratification of patients for Intensive Care Unit (ICU) admission.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at a tertiary care center in JJM Medical College, Davangere, Karnataka, India. We commenced the study after approval from Institutional Ethical Committee- J.J.M.Medical College, Davangere, Karnataka (IEC Registration No- ECR/731/Inst/KA/2015/RR-18 issued under rule 122DD of the Drug & Cosmetics Rules 1945. Ref No:- JJMMC/IEC-05-2022). Our study selected 75 in-patient COVID-19 cases who were RT-PCR positive. The clinical details and laboratory parameters in these 75 patients with COVID-19 from April 2021 to July 2021 were retrospectively analyzed from medical records. Automated latex enhanced immunoassay was used to quantitatively determine D-dimer in human citrated plasma in ACL-ELITE PRO. Inclusion criteria are Patients who were RT-PCR confirmed positive cases were only included in this study. Exclusion criteria are Patients who had cancer, hematologic malignancies, and the acute coronary syndrome were all excluded.

All Categorical variables will be expressed as percentages. To study the association between variables Chi-square test or the Fisher's exact test (if the cell value was small) will be used. Continuous variables will be expressed as the mean and standard deviations for normally distributed variables. The student t-test unpaired will be used to compare normally distributed variables, and the Mann–Whitney U test to compare non-normally distributed variables. IBM SPSS version 21 for Windows will perform all statistical analyses. A value of $P<0.05$ will be considered significant.

RESULTS AND DISCUSSION

The study population included a total of 75 hospitalized Covid-19 patients. Among them, 25 cases (33.3%) were non-survivors, and 50 (66.7%) were survivors, among which 45 cases (60%) were mild-moderate cases, and 30 cases (40%) were severe cases. Among the 45 mild-moderate cases, 7 cases (15.6%) have succumbed to death, and among 30 severe cases, 18 cases (60%) have succumbed to death. The

p<0.001 value of severity of the disease was highly significant with the outcome of the disease (Table 1).

Table 1. Comparison of Severity of the Disease with Outcome.

Severity	Outcome of the Disease		Total
	Survivors	Non-Survivors	
Mild-Moderate	38 (84.4%)	7 (15.6%)	45(60%)
Severe	12 (40%)	18 (60%)	30 (40%)
Total	50 (66.7%)	25 (33.3%)	75 (100%)

Chi-square Test p<0.001, Highly Significant

Association with Data Variables and Outcome of the Disease.

There was a significant positive association (p<0.05) between age and outcome of the disease, with the mean age in recovered being 51.10 and in dead being 58.76. Still, there was no statistical significance seen between sex and outcome of the disease. Among the total number of cases, 45 cases (60%) had associated comorbidities most common comorbidities being DM (29 CASES) and HTN (29 cases), and other comorbidities were COPD, Asthma, TB, IHD, CKD, and one case of Thrombolytic disorder. Still, there is no statistical significance (p>0.05 value) between the comorbidity and outcome of the disease (Table 2).

Laboratory Analysis of D-dimer in Relation to Severity and Outcome of the Disease.

Laboratory findings of D-dimer on admission in COVID-19 patients revealed that among the 75 patients, D-dimer was elevated in 35 cases (40%) out of which 18 cases (51%) succumbed to death and 17 cases (48%) recovered from the disease. In contrast, D-dimer was normal in 40 cases (60%), out of which only 7 (17.5%) patients succumbed to death, and 33 (82.5%) of them recovered from the disease. Therefore, with the p-value <0.02, elevated D-dimer levels are highly significant for the outcome of the disease. Our analysis also showed that the mean of D-dimer in mild to moderate cases was 466.47, and in severe cases, the mean was 929.27. With the p-value <0.001, the D-dimer levels were highly significant with the severity of the disease (Table 2&3).

SARS-COV caused a rapid epidemic worldwide in no period. Even though most of the patients suffered mild symptoms like fever, cough, and anosmia without pneumonia, there was also a larger proportion of patients who had breathlessness or other complications such as pulmonary embolism, deep vein thrombosis, and even death. Therefore, we must evaluate, and this biomarker will help us predict the prognosis and severity of the disease and help the clinician better manage the patients.

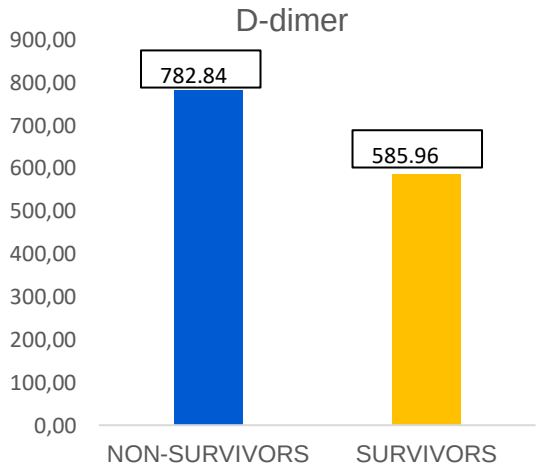
D-dimer is a useful tool for diagnosing and predicting the recurrence of VTE. It is also a sensitive early marker of DIC but with low specificity. A higher D-dimer level is frequently encountered in critically ill patients compared to milder cases and inversely correlates with survival (Hadid T et al., 2021). The mechanisms for increased D-dimer levels in patients with COVID-19 include pulmonary endothelial injury with inflammation-associated deposits of intra-alveolar fibrin, systemic endothelial injury with diffuse thrombosis of smaller or larger veins, and coagulopathy (Valerio L, et al.,2021).

Table 2. Comparison of Social Demographics, D-dimer Levels in Survivors and Non-Survivors.

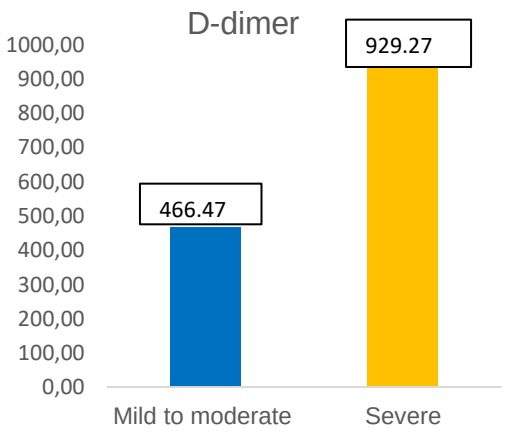
Demographics		Outcome		Total	P-Value (Chi-square Test)	Statistical Significance
		Survivors	Non-Survivors			
Age	≤50	29 (80.5%)	7 (14.5%)	36 (48%)	<0.05	Significant
	≥50	21 (53.8%)	18 (46.2%)	39 (52%)		
Sex	Male	28 (62.2%)	17 (37.8%)	45 (60%)	>0.05	Not Significant
	Female	22 (73.3%)	8 (26.7%)	30 (40%)		
Comorbidities	Present	27 (60%)	18 (40%)	45 (60%)	>0.05	Not Significant
	Absent	23 (76.7%)	7 (23.3%)	30 (40%)		
D-dimer	Normal	33 (82.5.%)	7 (17.5%)	40 (60%)	<0.04	Significant
	Raised	17 (48%)	18 (52%)	35 (40%)		

Table 3. Correlation of D-dimer with Severity and Outcome of The Disease

Laboratory Data			Mean	Std. Deviation	P-Value (Mann-whitney U Test)	Statistical Significance
D-dimer	Severity	Mild to Moderate	782.84	386.33	<0.02	Signifcant
		Severe	585.96	533.76		
D-dimer	Outcome	Survivors	466.47	386.33	<0.001	Highly Significant
		Non-Survivors	929.27	589.14		



Bar Graph Showing Mean Value of D-Dimer in Relation with Outcome of the Disease



Bar Graph Showing Mean Value of D-Dimer in Relation with Severity of the Disease

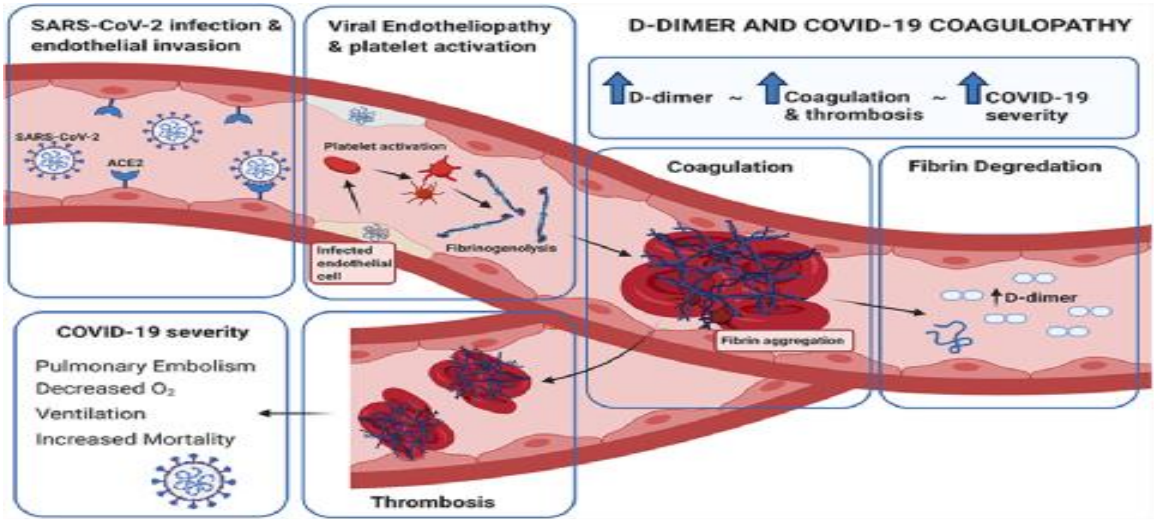


Figure 1. Disease Outcome in COVID-19 Patients with Increase in D-dimer Levels (Bosevski M et.al.,2021)

Our analysis showed us that levels of D-dimer are significantly elevated in severe cases when compared to the mild and moderate course of the disease, and also the level of D-dimer was significantly raised in non-survivors when compared to survivors. Therefore, D-dimer can act as an important predictor of both severity and mortality of the disease at the time of admission.

A study by Zhou et al.,2020, concluded that D-dimer levels >1mg/L on admission in COVID-19-infected patients were independently associated with increased odds of mortality. A study by Bosevski M et al.,2021, also concluded that there are significant differences in D-dimer levels at admission were noted among COVID-19 patients who would require artificial ventilation (1250 ± 210 ng/ml) when compared to those who did not (650 ± 175 ng/ml), respectively.

A meta-analysis conducted by Shah S et al., 2020, included Eighteen studies with a total of 3682 patients who met the inclusion criteria. The risk of mortality was fourfold higher in patients with positive D-dimer versus negative D-dimer ($p< 0.001$), and the risk of developing the severe disease was twofold higher in patients with positive D-dimer levels versus negative D-dimer ($p< 0.001$). There is an increase in mortality and severity of the disease with an increase in D-dimer levels. Our results are concordant with several other studies that concluded that D-dimer is a better predictor of both severity and mortality. And in a study by Poudel A et al., 2021, concluded that the D-dimer value on admission is an accurate biomarker for predicting mortality in patients with COVID-19, and 1.5 µg/ml is the optimal cut-off value of admission D-dimer for predicting mortality in COVID-19 patients.

Our study has some limitations. First, our sample size was small. We describe a modest-sized case series of hospitalized patients. To better define the clinical course of the disease, natural history, and risk factors for mortality, the collection of data for a larger cohort would be needed. Second, in this study, the D-dimer levels were taken on admission. It would be relevant to investigate throughout hospitalization to prevent further complications and better recovery from the disease.

CONCLUSION

In conclusion, there is a significant association between D-dimer and disease severity and mortality. Though the levels of D-dimer have low specificity and can be

increased in other diseases, it serves as an early sensitive marker of DIC and other complications. Therefore, we strongly recommend that the D-dimer be used to screen patients with COVID-19 to evaluate the severity and predict the prognosis and mortality in hospitalized COVID-19 patients during admission and follow-up throughout hospitalization. This will help in better management of COVID-19 patients and can help in preventing severe morbidity and mortality.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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