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D-Dimer As A Predictive Biomarker Of Clinical Severity In Covid-19 Patients: Analysis Of 840 Cases

Arun Prabhakaran C[1], Arunalatha P [2], Subachitra T[3], Raasi S[4]*
[1,4]Assistant Professor, [2]Professor and Head, [3]Associate Professor,
Department of Pathology, Stanley Medical College,
Chennai, Tamil Nadu, India

***Corresponding Author:**
Raasi S
Assistant Professor, Department of Pathology,
Government Stanley Medical College, Chennai, Tamil Nadu

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] causes coagulation dysfunction in COVID-19 disease and is associated with increased mortality worldwide. Our study aims to highlight the correlation between D-Dimer values and clinical severity in COVID-19 patients and to evaluate the usefulness of D-Dimer as a predictive hematological biomarker for early detection of thromboembolic complications.

Methodology: This cross-sectional study was conducted in Stanley medical college in hospitalized 840 confirmed COVID-19 patients. D-Dimer values were correlated with clinical severity.

Results: Elevation of D-Dimer of more than 2000 ng/ml is more common in males (54%) of 46-60 years age group with severe COVID-19 disease. There is significant fourfold increase in D-Dimer levels of more than 2000 ng/ml in severe COVID-19 disease. The mean D-Dimer value of 4280 ng/ml is observed in deceased patients of severe clinical severity.

Conclusion: There is significant difference between D-Dimer values of mild, moderate and severe COVID-19 disease ($p<0.05$). D-Dimer level more than 2000 ng/ml is seen in almost all cases of severe COVID-19 disease in our study. Hence serial monitoring of D-Dimer levels will reduce the mortality associated with thromboembolic events.

Keywords: Coagulation dysfunction, COVID-19, D-Dimer, Prothrombotic state

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces prothrombotic state due to innate tropism for ACE II receptors in endothelium and lungs [1]. Clinically, patients are categorized as mild, moderate and severe COVID-19 disease. Acute respiratory distress syndrome (ARDS) in COVID-19 may progress to a composite end-point in the form of severe disease requiring intensive care management [2]. Failure of early detection of the prothrombotic state may even lead to death of the patient [3]. Our study aims to highlight the correlation between elevated D-dimer values and the clinical severity of the disease in RTPCR proven COVID-19 patients. D-dimer can be used as a potential prognostic tool to prevent thromboembolic complications at an early stage by guiding anticoagulant therapy and it positively influences clinical outcome of coronavirus disease (COVID-19).

Materials And Methods:

Study design: Cross sectional study.

Study population: The study was conducted in a total of 840 in-patients who are diagnosed positive for COVID-19 by RTPCR from April 2021 to June 2021 and hospitalized in Stanley medical college hospital.

Ethical committee approval was obtained from the Institutional Ethics Committee.

Inclusion Criteria:

1. RTPCR positivity for COVID -19.
2. Age more than 18 years.
3. Hospitalized in-patients.

Exclusion Criteria:

1. Cases less than 18 years of age.
2. Cases of known coagulation disorders.
3. Coagulopathy secondary to other causes.

Methodology:

Blood samples were collected from admitted Covid -19 positive in-patients. 2 ml of fresh venous blood was collected in Citrate tube and processed in ERBA ECL-760 fully automated coagulation analyzer at the Central Clinical Pathology lab. Routine Internal Quality Control (QC) for both normal and pathologic values of D-Dimer and sample integrity were done. D-Dimer values obtained were registered in D-Dimer register and in Microsoft Excel worksheet.

D-Dimer values were correlated with following variables such as

1. Age of the patient.
2. Sex of the patient.
3. Clinical severity of the disease and its outcome.

Data were summarized using percentages, mean and standard deviation. Significance between D-Dimer values of mild, moderate and severe disease will be assessed using Kruskal-Wallis test at p value < 0.05. All data were entered into Excel format and statistical analysis was done through SPSS version 22. Figures and graphs were expressed using Microsoft Excel.

Results:

Of the total 840 COVID-19 hospitalized patients, 596 patients (71%) had elevated D-Dimer levels > 500 ng/l. Mild increase in D-Dimer levels (501 to 1000 ng/ml) is seen in 18% of cases. Moderate increase in D-Dimer levels (1001 to 2000 ng/ml) is seen in 18% of cases and severe increase (>2000 ng/ml) in 35% of cases (Figure 1).

Elevation of D-Dimer is more common in males (54%) when compared to females (46%). Most of our cases (n=293) have increased D-Dimer levels more than 2000 ng/ml with male predominance (52%) in it as shown in Figure 2.

Among males (n=320), 47 % of cases (n=151) have D-dimer levels more than 2000 ng/ml. Among females (n=276), 51 % of cases (n=142) have D-dimer levels more than 2000 ng/ml (Table 1). Markedly elevated D-Dimer levels are common in males of more than 60 years age group and females of 46 to 60 years age group (Tables 2 and 3).

Clinically, patients are categorized as mild, moderate and severe COVID-19 based on parameters which include respiratory rate, hypoxia and breathlessness. Mild and moderate clinical severity are seen in 47% and 19% cases respectively. 34% of cases are diagnosed as severe COVID-19 disease (Figure 3). Severe COVID-19 disease is common in males of 46 to 60 years age group in our study (Figure 4). It is associated with D-Dimer levels more than 2000 ng/ml (range of 2008 ng/ml to 11187ng/ml).

The overall population mean D-Dimer in our study is 2046 ng/ml with 95% confidence interval and standard deviation is 2198. The mean D-Dimer levels in mild, moderate and severe categories are 708, 1417 and 4526 ng/ml with 95% Confidence Interval respectively. Kruskal-Wallis test demonstrated a significant difference between D-Dimer levels of mild and severe cases with H statistic of 299.5695 and p value is <.00001. There is also significant difference between D-Dimer levels of moderate and severe cases with H statistic of 298.2674 and p value is <.00001. Results are significant at p <0.05. D-Dimer levels are markedly elevated in severe COVID-19 disease. We observed a significant fourfold increase in D-Dimer levels of more than 2000 ng/ml in severe COVID-19 disease and in 50% of deceased patients. The mean D-Dimer value of 4280 ng/ml was observed in deceased patients of severe clinical severity in our study population.

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Table 1: Genderwise distribution of elevated D-Dimer values

GENDER	D-DIMER 501-1000	D-DIMER 1001-2000	D-DIMER >2000
MALE	61%	51%	51%
FEMALE	39%	49%	47%

Table 2: Categorization of elevated D-Dimer values in males

MALE	501-1000ng/ml	1001-2000 ng/ml	>2000 ng/ml	TOTAL
18 to 30 years	6	4	7	17
31 to 45 years	28	30	48	106
46 to 60 years	32	17	44	93
more than 60 years	27	25	52	104
Total	93	76	151	320

Table 3: Categorization of elevated D-Dimer values in females

FEMALE	501-1000ng/ml	1001-2000 ng/ml	>2000 ng/ml	TOTAL
18 to 30 years	7	11	23	41
31 to 45 years	11	11	23	45
46 to 60 years	30	30	56	116
more than 60 years	11	23	40	74
Total	59	75	142	276

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Figure 1: D-Dimer categorization in the study population

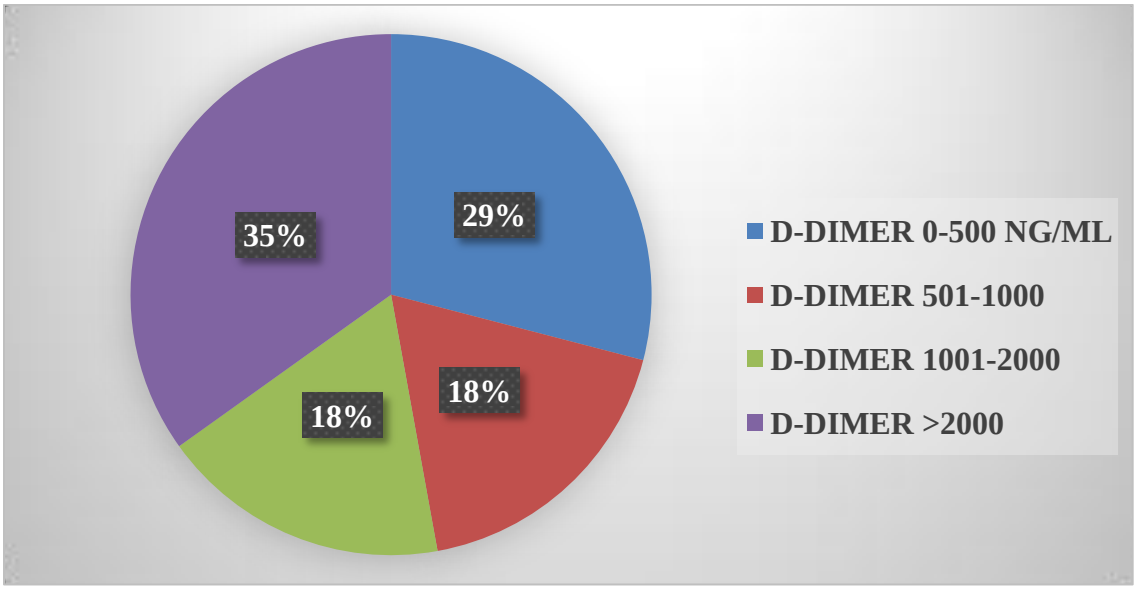

Figure 2: Gender wise distribution of D-Dimer values

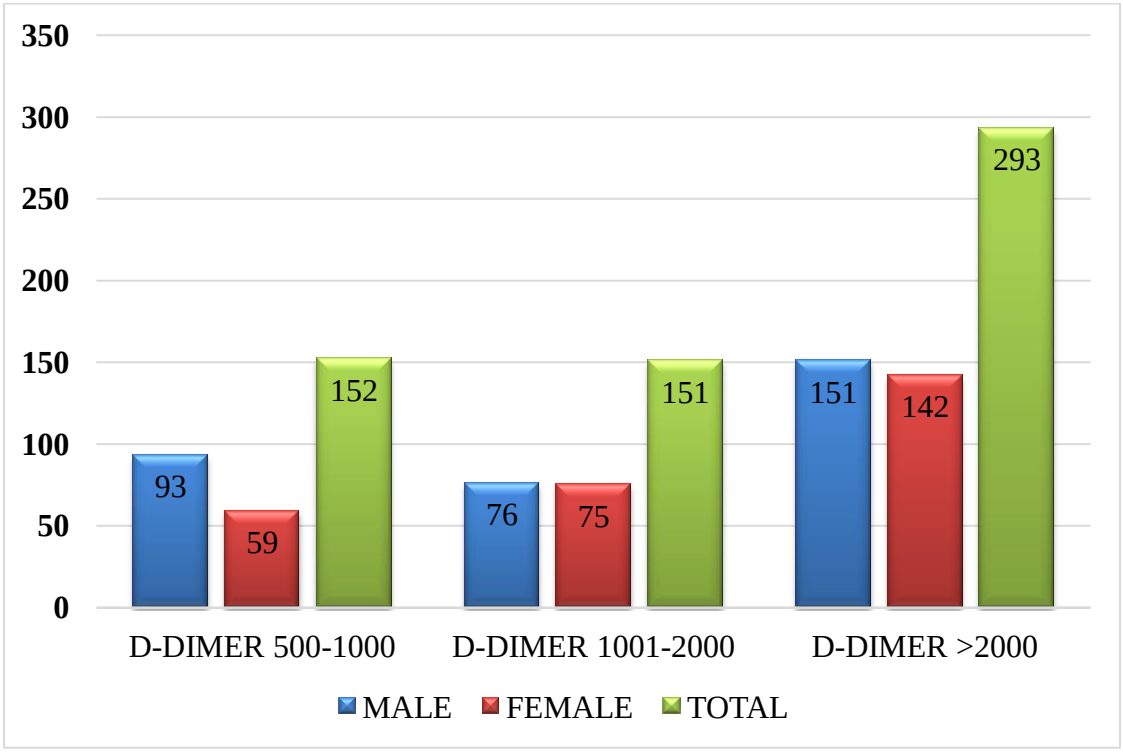

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Figure 3: Covid 19 cases based on clinical severity

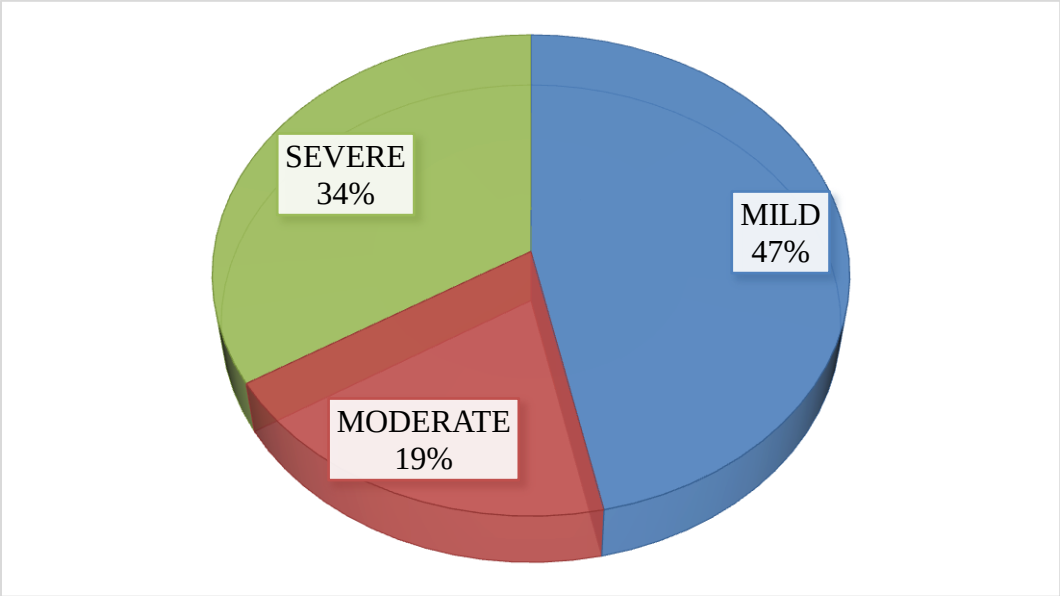
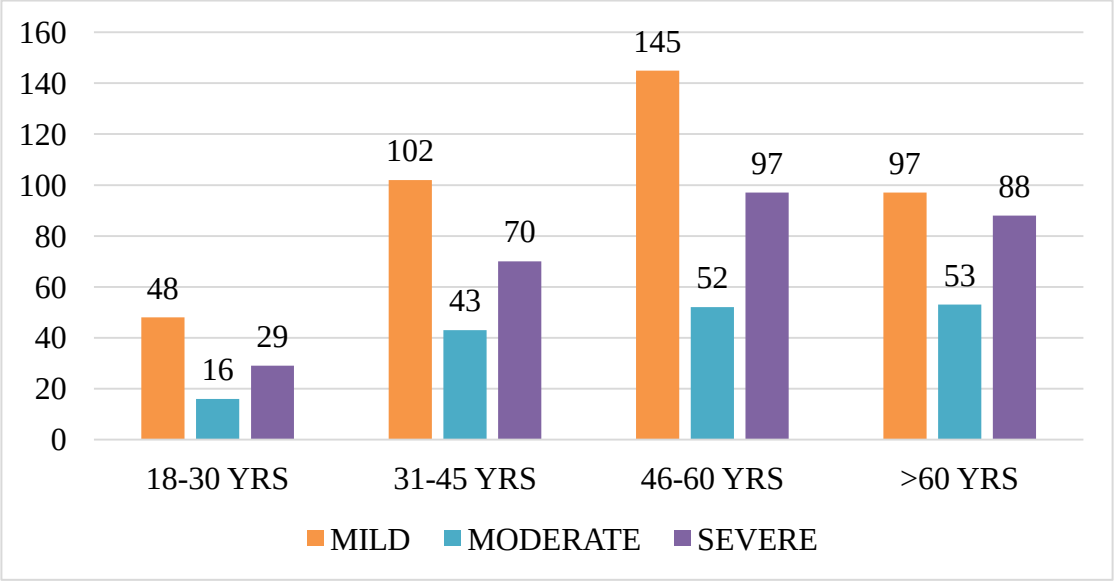


Figure 4: Age wise distribution of cases based on clinical severity



Discussion:

Coagulation dysfunction is common in COVID 19 patients due to innate tropism of the SARS-CoV2 virus for ACE2 receptors located on vascular endothelial cells [1]. D-Dimer, a fibrin degradation product, is released into the blood when there is blood clot degradation by fibrinolysis [2]. D-dimer levels are elevated due to activation of coagulation cascade and can be seen in association with deep vein thrombosis, pulmonary embolism or disseminated intravascular coagulation [3]. Jecko Thachil et al stated lungs as epicenter for COVID-19 associated hypercoagulability and proposed three stages of hemostatic abnormalities as follows [4]:

Stage 1 – elevation of D-Dimer.

Stage 2- elevation of D-Dimer with mild prolongation of PT/INR, APTT and mild thrombocytopenia.

Stage 3- critically ill with laboratory parameters of classic DIC.

The association between SARS-COV2 and coagulation dysfunction is further supported by studies on prophylactic and therapeutic anticoagulant

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administration. Tang et al reported a lower 28-day mortality in patients with D-dimer >3000 ng/mL treated with therapeutic doses of heparin when compared to COVID-19 non-users [p=0.017][5].

Older age is associated with increased mortality in COVID-19 due to decreased immunity and associated comorbidities [6,7]. In our study, elevated D-Dimer levels are seen mostly in 46 to 60 years age group. Risk factors for increased mortality include co-morbidities such as diabetes, hypertension and coronary heart disease [6,7]. Zhou et al reported that elevated D-Dimer levels are used in early clinical diagnosis of COVID-19 and levels >1.0 µg/mL are associated with increased mortality.[7] In our study, D-Dimer levels more than 2000 ng/ml are associated with increased severity of the disease. Tan et al in his study on SARS epidemic in 2003, reported that elevated D-Dimer levels are due to upregulation of fibrinogen expression in lung epithelial cells by SARS-COV 3A protein [8]. Kawaguchi et al in his study reported that D-dimer values < 1.5 mg/l are associated with low morbidity due to deep vein thrombosis [9]. In our study, patients with D-Dimer levels less than 1000 ng/ml had a mild clinical severity.

Huang et al reported the fivefold increase in D-Dimer levels with median of 2.4 mg/L [0.6–14.4] on hospital admission in severe COVID-19 disease and the pathogenesis is mainly related to cytokine storm due to release of proinflammatory cytokines [10,11]. This is similar to our study as we reported a fourfold increase in D-Dimer levels [more than 2000 ng/ml] in all cases of severe COVID-19 disease with the mean value of 4526 ng/ml.

Chen et al in his study found markedly higher D-dimer levels in the deceased group than in survivors [12]. This is similar to our study as we observed significantly higher D-Dimer levels of more than 2000 ng/ml and mean of 4280 ng/ml in the deceased group. Zhang et al reported significantly higher mean D-Dimer values of 0.4 µg/ml in severe cases [13]. Han et al found higher mean ± SD D-dimer levels in the infected group than in the control group with p<0.001, increase of D-dimer levels with disease severity and significant difference between mild and severe disease with p<0.05[14]. Similar corroborative findings are observed in our study which include increased D-dimer levels with clinical severity and higher mean values in the severe group with significant differences at p<0.05 when compared to other groups.

Al-Samkari et al found that initial D-dimer >2.5 µg/mL was helpful in prediction of thromboembolic complications [15]. Ayusha Poudel et al reported that D-dimer value of 1.5 µg/ml on admission can be used as optimal cutoff for predicting mortality in COVID-19 patients [16]. M.Soni et al in an analysis of 483 cases found that D-dimer value > 2.01 µg/mL can predict in-hospital mortality in COVID-19 patients [17]. In our study based on analysis of 840 COVID-19 cases with serial monitoring of D-Dimer levels, D-Dimer values > 2000 ng/ml can be used as optimal cutoff for predicting clinical severity and mortality. Our study demonstrated statistically significant differences [p <0.05] between D-Dimer values of mild, moderate and severe COVID-19 patients which is similar to study by Hary Gustian et al [18]. Thus, our study findings are concordant with previous studies.

Conclusion:

There is significant difference between D-Dimer values of mild, moderate and severe COVID-19 disease (p<0.05). D-Dimer level more than 2000 ng/ml is seen in almost all cases of severe COVID-19 disease in our study. Patients with a 3 to 4 -fold increase in D-dimer should be considered at risk for venous thromboembolic events (VTE) and other complications related to procoagulant state seen characteristically in severe COVID-19 disease. Early clinical diagnosis of severe disease with serial monitoring of D-Dimer levels will reduce the in-hospital mortality in COVID-19 disease.

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