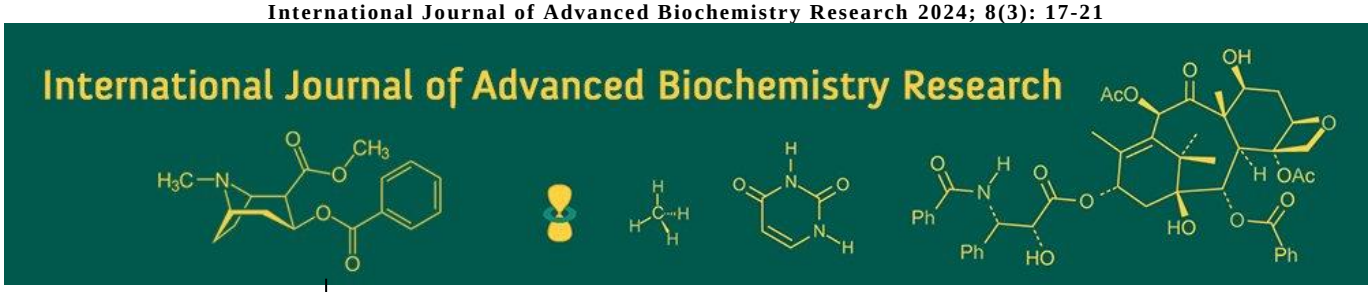

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D-Dimer a biomarker for disease severity in COVID-19 patients

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Abstract
Introduction: The COVID-19 disease has devastating effect in the world since its emergence in Wuhan of the Hubei province in China in December 2019. The world struggled for an early and effective biomarker to predict severity and to improve the management of the disease.
Aim: To estimate the level of D-dimer which could predict disease severity in COVID-19 related disease.
Materials and Methods: This is a Cross sectional study done with D-dimer to predict disease severity in COVID-19 in the department of Biochemistry, Jawaharlal Nehru Institute of Medical Sciences, Imphal, Manipur. The study period is from June 2021 to August 2021. It involved analysis of 144 hospitalised patients of different grades of COVID-19 pneumonia with different ranges of severity. The study population included symptomatic patients of both sexes which are above 18 years with a laboratory confirmed COVID-19 by RTPCR from either throat or nasal swab. All the samples for D-dimer were collected 2-3 days from the period of confirmation. The study population are further divided into three cohorts viz. mild, moderate and severe COVID-19 groups based on the clinical parameters as per ICMR (Indian Council of Medical Research) guide line published at the time.
Results: The study produces results which showed significant differences in the ranges of D-dimer values across the different clinical severities of COVID-19 pneumonia (p<0.001). D-dimer level were found to be more elevated in patients with severe cases than those of mild or moderate cases. The median D-dimer level compared from moderate to severely ill patients showed increase for about 2.5 folds (0.5[0.2-10]mg/L vs 1.7 [0.2-11]mg/L p-<0.001).
Conclusions: D-dimer levels are commonly elevated in symptomatic SARS-CoV-2 patients. Significantly higher levels are seen in severely ill patients. Therefore, D-dimer can be a good prognostic and useful marker in COVID-19 management.

Keywords: COVID-19, D-dimer, COVID-RTPCR, SARS-CoV-2

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly worldwide affecting all ranges of population since the emergence of COVID-19 in December, 2019, in Wuhan, China. This infection can present as asymptomatic carriers or produce common symptoms in the infected individuals such as fever, dry cough, dyspnoea, and fatigue of varying severity. In its most severe manifestation, individuals with COVID-19 can cause Acute Respiratory Distress Syndrome (ARDS) ultimately leading to death if the disease progresses [1]. With wide spectrum of symptoms and among those requiring hospitalization for respiratory support about 20–26% of patients become severe or critically ill with mortality rates varying from 26 to 61.5% [2].

Coagulopathy is more prevalent in critically ill patients of COVID-19. Several studies have shown that SARS-CoV-2 may predispose the infected patients to thrombotic disease of the venous and arterial circulation. This may be due to the pathology of excessive inflammation, platelet activation, endothelial dysfunction, and stasis of the circulation [3].

D-dimer is a product of lysis of cross-linked fibrin after the process of coagulation and fibrinolysis [4]. Elevated D-dimer values correlate with a poor prognosis in patients of acute respiratory distress syndrome (ARDS). Hence there is increased rate of admission to intensive care unit with simultaneous increase in mortality [5, 6].

COVID-19 and Thromboembolism

During the course of management of patients of COVID-19 of varying ranges of clinical severity, several clinicians observe that the prothrombotic state and venous thromboembolic disease events may play a role in COVID-19 symptomology [7-11]. This impression is on the foundation of plenty of reports of large vessel stroke among young patients, recurrent clotting of haemodialysis catheter, reports of occult pulmonary embolism and pulmonary microangiopathy in autopsy of such patients. Also, the pulmonary physiology of these mechanically ventilated COVID-19 patients were also found to be similar to pulmonary vascular disease of such patients mentioned above [12-15].

AIMS

The present study was conducted to estimate the level of D-dimer in COVID 19 positive patients admitted in the hospital and find out the correlation, if any, between the level of D- dimer and the disease severity.

Materials and Method

This is a Cross sectional study done in the department of Biochemistry, Jawaharlal Nehru Institute of Medical Sciences, Imphal, Manipur June 2021 to August. 144 hospitalised patients of varying severity of isolated COVID-19 pulmonary disease who are above 18years (of both sexes) with a RT-PCR confirmed COVID-19 were included in the study. Patients who do not give consent was the exclusion criteria.

Ethical clearance was obtained from the Institutional Ethics committee JNIMS, prior to the study. Informed consent was taken from the patients. All the samples for D-Dimer was collected 2-3 days after RTPCR confirmation of symptomatic patients and clinically categorized into mild, moderate and severe COVID-19 pneumonia as per ICMR guideline. Patient characteristics, comorbidities, on admission and disease severity, were obtained from patients' medical records and reaffirmed with patients clinical assessment.

Statistical analysis

Data were analysed using SPSS software v21. Both continuous and categorical data were expressed as mean and percentage. Test of significance for quantitative data was performed using T tests or Man-Whitney U test. Categorical variables were compared by Chi-square tests or fisher's exact test. Correlation of D-dimer with clinical staging was evaluated by Kendall's coefficient analysis. The Probability value (P-value) of less than 0.05 was taken as significant.

Result

Of the 144 patients in the study, the median age was 58 years (IQR, 49-68), ranging from 24 years to 87years. A total of 43.75% (63/144) patients were more than 60 years and the remaining 56.25% (81/144) patients were less than 60 years of age. The cut-off value for D-dimer was set at the usual normal range of < 0.5 mg/L.

The basic demographic characteristics of the patients such as age, gender and comorbidities are listed in table 1. Generally, the distribution of D-dimer across all ages and gender is the same. As per the cut-off value, 66% (95/144) patients' D-dimer levels were more than 0.5 mg/l, and 34% (49/144) had D-dimer level < 0.5 mg/l (p-0.016). Like any other pneumonia, fever, cough and difficulty in breathing are the usual clinical manifestations of COVID-19 pneumonia. Patients with abnormal D-dimer levels were more likely to have a severe cough and breathing difficulty (p-0.001). No significant difference in the results are noted among the patients with respect to underlying co-morbid condition such as hypertension, diabetes mellitus and renal insufficiency are noted in our present study.

Table 1: General demographic characteristics and clinical manifestations of 144 COVID-19 patients with D-dimer. Normal range of D-dimer: <0.5 mg/L.

Demography	N (%)	D-dimer <0.5 mg/l	D-dimer>0.5 mg/l	P-value
Total	144	49	95	0.016
Age				
<60	81(56.25)	25	55	0.39
>60	63(43.75)	24	40	
Average age(IQR)Y	58.06(49.0,68.0)	59.07	57.6	0.56
Gender				
Male	98(68)	32	66	0.4
Female	46(31.94)	12	34	
Clinical manifestations				
Fever	135(93.75)	46	89	0.31
Cough	83(57.3)	19	64	0.001
Difficulty breathing	129(89.5)	37	92	<0.001
Hypertension	26(18)	8	18	0.9
Diabetes Mellitus	32(22.2)	11	21	0.5
Renal insufficiency	5	1	4	0.41

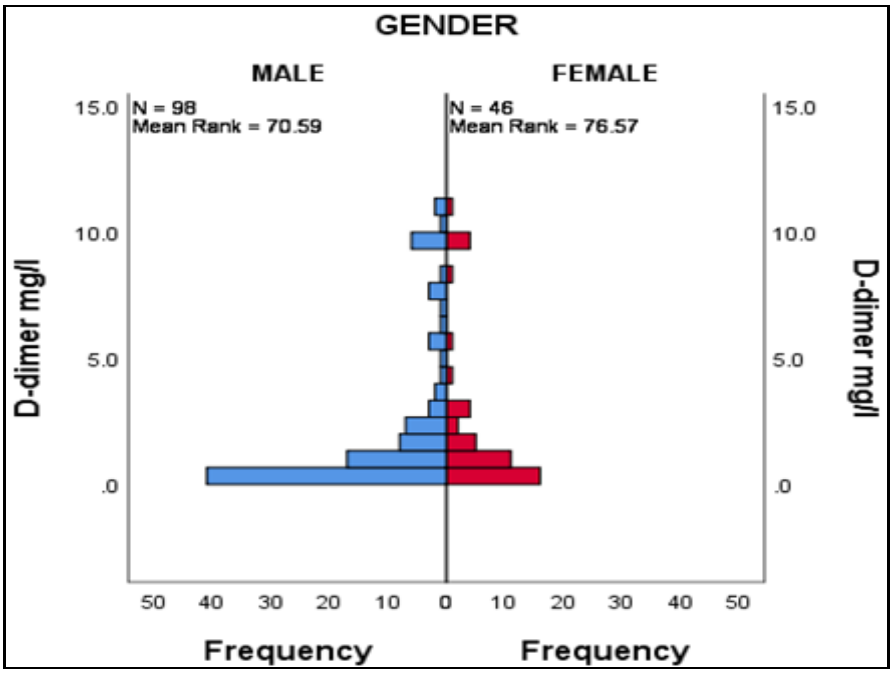

Fig 1: Distribution of D-dimer across gender

Table 2: Relationship between D-dimer level and clinical classification.

Clinical classification	N	D-dimer <0.5 mg/l	D-dimer >0.5 mg/l
Mild	5	5	0
Moderate	51	29	22
Severe	88	15	73
Total	144	49	95
χ^2/p	$\chi^2 = 32.84$ $p<0.001$		

There were significant differences in D-dimer test values for the different clinical classification (p<0.001) as shown in Table. 2. D-dimer level were more likely to be abnormal in patients with severe cases than those with mild or moderate symptoms (Fig. 2).

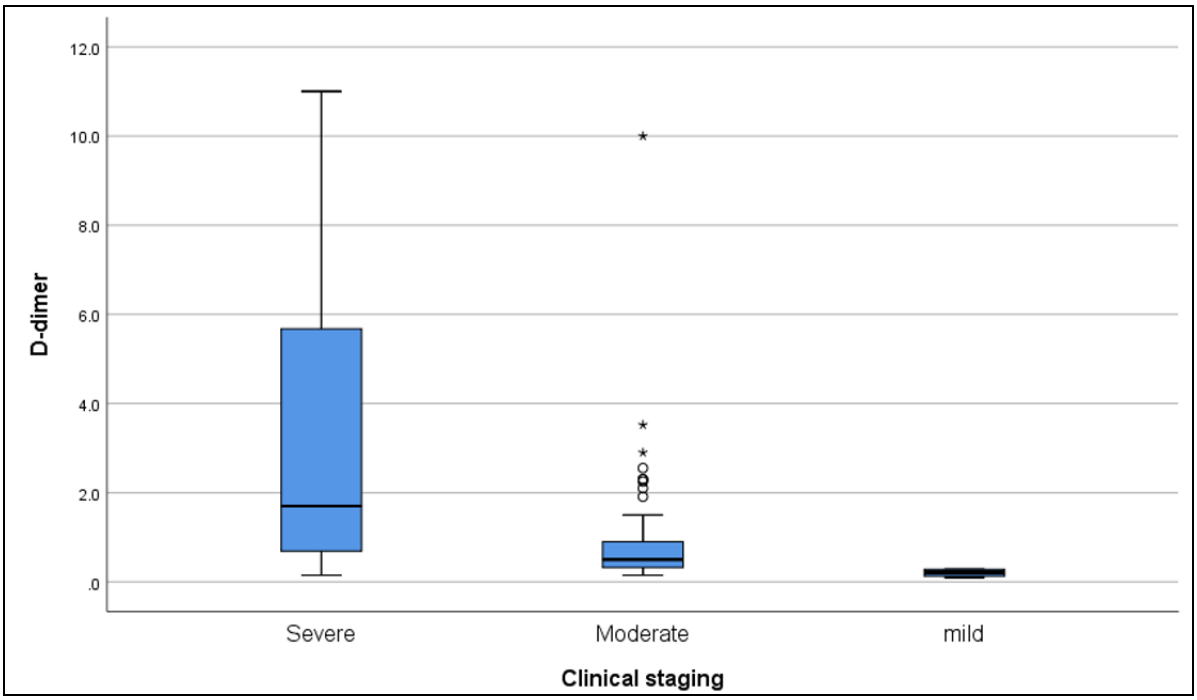

Fig 2: Correlation of D-dimer level with clinical staging.

The comparative values of D-dimer from admission significantly increased with increasing severity of COVID-19 (Kendall's tau-b = 0.46, p-<0.001). The median D-dimer level compared from moderate to severely ill patients showed increase for about 2.5 fold (0.5[0.2-10]mg/L vs1.7 [0.2-11]mg/L p-<0.001).

Discussion

In our study, it is found that elevation of D-dimer level is common among patients of COVID-19 and its elevated values has positive correlation with increased disease severity. D-dimers which is one of the fragments produced when plasmin cleaves fibrin to break down clots is routinely used to exclude thrombosis. Any pathologic or non-pathologic process that increases fibrin production or breakdown thereby increases plasma D-dimer levels [16]. Deep vein thrombosis, pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation and conditions that promotes thrombosis such as pregnancy, inflammation, cancer, chronic liver diseases, post trauma and vasculitis are some the conditions that can cause elevation of D-dimer.

The study lacks the confirmatory assessment for pulmonary embolism or deep vein thrombosis or any other thromboembolism of any part of the body. Nevertheless, elevated D-dimer serves as a diagnostic tool for thromboembolism in the ongoing pathophysiologic milieu of any COVID-19 affected patient. There is also a significant correlation between the elevated D-dimer levels and disease severity stratified by clinical staging according to the interim guideline. High percentage of D-dimer elevation is seen in the present study which may be due to higher percentage of severe cases with the hospital serving as a referral centre.

The study lacks to define the influence of concomitant multisystem and multiorgan dysfunction or injury in the level of D-dimer values. It also lacks the monitoring of increasing or static or perhaps a declining levels of D-dimer in those who recover from severe COVID pneumonia. The effect of several medications and management protocols in D-dimer also merits further evaluation. Hence, further studies are still advocated as to associate the causal mechanisms and the specific effects of SARS-CoV 2 with consequent systemic inflammatory response. It is also worthwhile to note that in SARS-COV-2 infection there is dysregulation of coagulation/anti-coagulation cascades resulting in worsening lung pathology.[17] Ongoing infection promotes the release of pro-inflammatory cytokines such as IL-2, IL-7, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α, thus causing an inflammatory storm [18]. Levels of these were higher especially in the plasma of severe COVID-19 patients and likely so in other illnesses causing SIRS.

Conclusion

D-dimer levels are commonly raised in SARS-CoV-2 infection. Significantly higher levels are seen in patients with severe illness. Therefore D-dimer can be a good prognostic and helpful biomarker to improve the management of COVID-19.

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