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D-Dimer Level on Admission as an Outcome Predictor of COVID-19 Patients in Intensive Care Units in Bangladesh

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Abstract

Purpose: This study investigated the D-dimer level on admission as a significant predictor of outcomes for COVID-19 patients. **Setting:** This cross-sectional study was conducted among purposively selected RT-PCR-positive 52 COVID-19 patients in the Intensive Care Unit at Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh, between July 2020 and June 2021. **Methodology:** The analysis was done using SPSS software version 24. Continuous variables were analyzed for inferential statistics using the Mann-Whitney U and Kruskal-Wallis tests. Pearson's correlation analysis was done on D-dimer and many hematological and biochemical markers in COVID-19 patients. **Primary and secondaryoutcome:** The primary outcome was in-hospital mortality, and secondary outcomes included a comparison between D-dimer levels and chances of mortality. **Results:** The mean±SD of the patient's age was 58.09±10.01 years (34-88 years), with 42 (80.8%) being over 50 years old and the majority of them were male 30 (57.7%). A maximum 36 (69.2%) patients fell into the severe COVID-19 category; 36 (69.2%) of the total patients died after 28 days of admission. On admission, D-dimer levels were more significant in death patients compared to those who survived (7.96±7.40 vs 0.98±1.88 µg/mL, p <0.001). **Conclusions:** On admission, D-dimer levels are strong predictors of COVID-19 severity and death. However, experimental research is needed to explore the actual scenario. **Strengths and Limitations:** This was a study to predict mortality among COVID-19 patients. Long-term follow-up was not undertaken because it was outside the study's scope, and the D-dimer's half-lifewas around 8 hours. It was a single-centered study. **Data Availability Statement:** Datasets prepared during and analyzed during the current study are available from the corresponding author upon reasonable request.

Keywords: Coronavirus, COVID-19, D-dimer, Diabetes, Mortality.

INTRODUCTION

D-dimer, a substance produced when blood clots break down, is involved in the clotting and inflammation in people with COVID-19. High D-dimer levels are linked to more severe COVID-19 and worse outcomes [1]. Patients with D-dimer levels over 1000 ng/ml have a 20 times higher risk of dying compared to those with lower levels. However, the main reason behind increased clotting in COVID-19 patients has not been fully discovered. D-dimer is commonly used in medical practice to rule out deep vein and lung blood clots with confirmation of widespread blood clotting. Most people with severe blood clots have high D-dimer levels. D-dimer levels can be high in both normal and abnormal situations, such as during pregnancy, cancer, inflammation, and after surgery [2].High D-dimer levels have been found to strongly predict death in COVID-19 patients in intensive care units (ICUs) in Bangladesh. These high levels are strongly linked to more severe illness and a greater risk of dying. Studies indicated that D-Dimer levels ≥376 ng/mL significantly increase mortality risk by 22.4 times, with a sensitivity of 82.6% and specificity of 82.5%. A D-Dimer cutoff of ≥308 ng/mL is associated with severe disease, enhancing the risk of complications [3].

A study found that D-dimer levels above 1415 ng/mL reported a high likelihood of receiving invasive mechanical ventilation [4]. Another study also found a strong link between D-dimer levels and the severity of COVID-19 and clinical symptoms like cough, joint pain, and muscle pain. To predict survival, the optimal D-dimer cutoff point was <1059 µg/L, with a sensitivity of 75.44% and a specificity of 58.70%. For predicting disease severity, the cutoff point was <2244 µg/L, with an 85.9% sensitivity and a 30.4% specificity [5].Monitoring D-Dimer levels can inform clinical decisions regarding mechanical ventilation and potential anticoagulant therapy, as thrombotic events are prevalent in severe cases.D-Dimer levels are a reliable predictive tool, with studies showing that higher levels correlate with longer ICU stays and increased mortality [6].

A recent study showed that COVID-19 increases the risk of complications like deep vein thrombosis (DVT), venous thromboembolism (VTE), and pulmonary embolism (PE) by up to 25%. The excessive inflammation triggered by severe lung injury in COVID-19 can lead to VTE due to factors such as cytokine storm, endothelial and macrophage activation, DIC, immobilization, and hypoxia. D-dimer levels can effectively predict severe and fatal COVID-19 cases. Moreover, complicated clinical outcomes such as all-cause mortality, ICU hospitalization, ventilation, or acute respiratory distress syndrome (ARDS) [7]. COVID-linked fatalities are connected mainly to increased blood clotting and a heightened risk of blood clot events in the veins, leading to clot-related inflammation in severe cases. Consequently, blood clotting markers could signal the seriousness of the disease and the likelihood of death and assist in determining patient prioritization, treatment approaches, and prognosis monitoring [8].

A study showed that D-dimer levels could predict outcomes in COVID-19 patients. They studied 1643 patients in China, including 691 with high D-dimer levels. Most of these patients had symptoms like fever, dry cough, and issues with breathing, digestion, or the nervous system. They found that 12% patients had too few lymphocytes, while 32.1% had too many of them. Patients with raised D-dimer levels have a higher probability of death and stay in the hospital for an average of 20 days. Elevated D-dimer levels could potentially be an early sign of severe illness and a higher risk of death.Tang *et al*. studied 183 severe COVID-19 patients and found that non-survivors had significantly higher D-dimer and FDP levels [9]. Poude*et al*.also suggested that D-dimer levels greater than 2.0µg/mL could effectively predict in-hospital mortality in COVID-19 patients [10]. The predictive importance and ideal threshold value of D-dimer levels upon admission to reliably predict outcomes have yet to be determined, indicating a need for more study in this field. As a result, this study aimed to investigate D-dimer levels as a predictor of survival of COVID-19 patients [11]. However, more information is needed about the sensitivity and specificity of D-dimer as a predictor of outcomes, particularly when compared to other predictive criteria in our specific situation. Elevated D-dimer levels in COVID-19 patients might be attributed to the body's reaction to viral infections and endothelial cell failure, which causes greater clotting. D-dimer has been shown to have a 77% predictive value for severity and a 75% predictive value for death in COVID-19, with specificity of 71% and 83%, respectively. This study investigated the D-dimer level on admission as a significant predictor of outcomes for COVID-19 patients.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted among 52 RT-PCR-positive COVID-19 patients in the Bangabandhu Sheikh Mujib Medical University Intensive Care Unit from July 2020 to June 2021. The objective was to determine the outcomes of COVID-19 patients concerning D-dimer level on admission. Patients older than 18 years and willing to participate were included purposively in the study. RT-PCR-positive COVID-19 patients who had pregnancy, active cancer &significant surgery, and trauma within the last 30 days were excluded from the study. After describing the detailed purpose and procedure of the study to the patients or their attendant's, informed written consent was obtained from each patient or their accompanying attendant. Data was collected through face-to-face interviews using a pre-tested, observation-based, peer-reviewed, semi-structured questionnaire and checklist. Socio-demographic data with detailed history of the participants' clinical manifestations and comorbidities, which were recorded for each respondent in a separate questionnaire. After maintaining proper personal protective equipment, optimum relevant physical examinations were performed. Patients' blood samples were collected for CBC, CRP, D-dimer, ALT, AST, Serum urea, Serum creatinine, and Serum ferritin. D–dimer level was detected by standard procedure on the first day of admission by SYSMAX CS-1600 analyzer in the fibrinogen equivalent unit (FEU), and other investigations were performed in the Department of Hematology, Department of Biochemistry BSMMU. Clinical, Hematological, and biochemical information were recorded on separate checklists. The severity of COVID-19 was categorized according to the WHO classification. All patients were treated according to protocol of the National Guideline of Bangladesh. Discharge criteria were two negative reports of RT-PCR at 24 hours apart. Patients were categorized as mild illness, moderate, severe, and critical.

Statistical Analysis

After collecting the necessary data, it was extensively reviewed for inconsistencies before being edited, coded, and categorized. The data were then tabulated using SPSS software version 24. Descriptive statistics for numerical data

included mean, median, and standard deviation, while frequencies and percentages were used for categorical data. Continuous variables were evaluated using the Mann-Whitney U and Kruskal-Wallis tests. Pearson's correlation analysis was also done on D-dimer and many hematological and biochemical indicators in COVID-19 patients. The statistical significance criterion was established at 95% confidence. A p-value of less than 0.05 was judged statistically significant.

Ethical Implication

Patients and significant families were properly informed about the study's scope and limitations. It was conveyed to them that there would be no bodily or social danger to the volunteers and that they may withdraw from the research at any time. Every stage of the investigation was conducted using proper safety procedures. The patient provided informed written consent.The participants received no inducement to participate in the study. Written approval was also obtained from the relevant department where the study was conducted. BSMMU's Institutional Review Board (IRB) provided ethical approval for the current study. Memo-BSMMU/2020/9137, dated 17/10/20.

RESULTS

The cross-sectional study was conducted within 1-year duration among 52 RT-PCR-positive COVID-19 patients to assess outcomes of COVID-19 concerning D-dimer level on admission. The study results are described below.

Table1:Socio-demographic characteristics of the participants (n=52)

Variables	Frequency (f)	Percent (%)
Age (years)		
34-40	2	3.8
41-50	8	15.4
51-60	22	42.3
61-88	20	38.5
Total	52	100
Mean±SD = 58.09±10.01		
Gender		
Male	30	57.7
Female	22	42.3
Total	52	100

The mean age of all patients was 58.09±10.01 years. The majority, 42.3% (n=22) of participants, belonged to the age 51-60 years, followed by 38.5% (n=20) ofthe age 60 years or more. By gender, the majority, 57.7% (n=30) of participants were male, and the rest, 42.3% (n=22), were female presented in Table1.

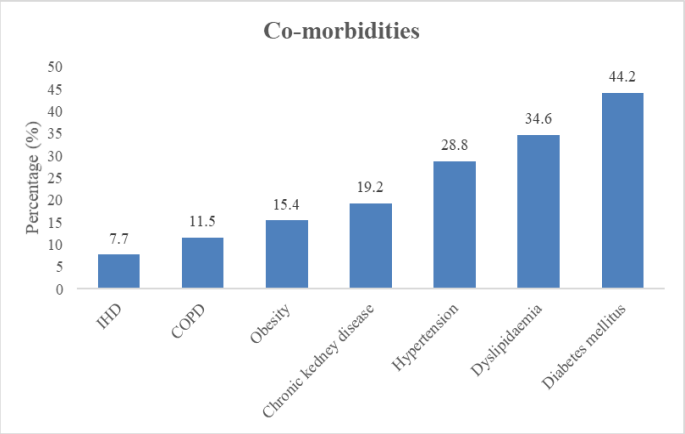

Figure 1: Distribution of comorbidities among study patients (n=52)

Multiple Response

Regarding comorbidities among the participants, the most common comorbidity in 44.2% (n=22) was diabetes mellitus, followed by dyslipidemia in 34.6% (n=18), hypertension in 28.8% (n=15), chronic kidney disease in 19.2% (n=10), obesity in 15.4% (n=8), COPD in 11.5% (n=6) and ischemic heart disease in 7.7% (n=4) of participants illustrated in Figure1.

Table2: Distribution of mean clinical parameters of COVID-19 patients (n=52)

Variables	Mean±SD (median, range)/ f (%)
PF ratio	113.75±31.29 (113.50, 65-202)
SpO2 (%)	86.87±7.21 (86.50, 67-98)
Heart Rate (bpm)	84.27±12.98 (88, 60-110)
SBP (mmHg)	126.69±16.51 (120, 100-180)
DBP (mmHg)	80.77±9.01 (80, 60-100)
RR (breaths/min)	23.65±5.40 (22, 18-38)
Basal crepitation	f (%)=13 (25%)

Mean PF ratio, SpO2, heart rate, and respiratory rate were 113.75±31.29, 86.87±7.21%, 84.27±12.98/min, and 23.65±5.40 breaths/min, respectively. Basal crepitation was found in 25% (n=13) of patients shown in Table2.

Table3: Biochemical and radiological findings of COVID-19 patients (n=52)

Investigations	f (%)
Chest x-ray	
Bilateral pneumonia	10 (19.2)
Unilateral pneumonia	36 (69.2)
Biochemical parameters	**Mean±SD**
Haemoglobin (gm/dL)	10.78±1.51
WBC (per mm^3)	9356.15±3442.17
Platelet (per mm^3)	145923.08±93646.99
C-reactive protein (mg/L)	64.54±26.06
Serum creatinine (mg/dL)	1.11±0.28
Neutrophil (%)	41.24±31.39
Lymphocyte (%)	35.38±26.32
Neutrophil Lymphocyte Ratio (NLR)	4.78±8.13
ALT (IU/L)	63.92±20.74
AST (IU/L)	59.06±27.45
Serum LDH (IU/L)	447.44±235.15
Serum Ferritin (µg/L)	948.39±702.79
D-dimer(µg/mL)	5.87±6.98

Considering radiological and biochemical findings, unilateral pneumonia was found in most patients, 69.2% (n=36). Mean hemoglobin was 10.78±1.51 gm/dL, WBC was 9356.15±3442.17/mm3, Platelet was 145923.08±93646.99/mm3, CRP was 64.54±26.06 mg/L, Serum creatinine was 1.11±0.28 mg/dl, Neutrophil was 41.24±31.39%, Lymphocyte was 35.38±26.32%, NLR was 4.78±8.13, ALT was 63.92±20.74 IU/L, AST was 59.06±27.45 IU/L, LDH was 447.44±235.15 IU/L and D-dimer was 5.87±6.98 µg/ml presented in Table3.

Table4: Distribution of patients by severity and outcome of COVID-19 (n=52)

Variables	Frequency (f)	Percent (%)
Severity		
Moderate	3	5.8
Severe	36	69.2
Critical	13	25
Total	52	100
Outcome		
Expired	36	69.2
Survived	16	30.8
Total	52	100

According to WHO criteria, the majority, 69.2% (n=36) of participants, were in the severe category of COVID-19, followed by 25% (n=13) and 5.8% (n=3) in critical and moderate categories, respectively. Considering the outcome, 69.2% (n=36) of patients expired within 28 days, as stated in Table4.

Table5: Comparison of mean D-dimer on admission with severity and outcome of COVID-19 (n=52)

D-dimer (in µg/mL)	Moderate(n=3)	Severe(n=36)	Critical(n=13)	p-value*
Mean±SD	0.40±0.05	4.11±6.17	11.77±6.60	<0.001[a]
Median	0.40	0.80	10	
Minimum	0.35	0.35	1.60	
Maximum	0.45	19	21	
D-dimer (in µg/mL)	**Expired(n=36)**	**Survived(n=16)**		**p-value**
Mean±SD	7.96±7.40	0.98±1.88		<0.001[b]
Median	5	0.5		
Minimum	0.45	0.35		
Maximum	21.00	8		

p-value was determined by [a]Kruskal-Wallis test &[b]Mann-Whitney U test.

**p-value <0.01 is highly significant.

On admission, D-dimer level was higher (11.77±6.60 µg/mL) among critical COVID-19 patients compared to severe (4.11±6.17 µg/mL) and moderate (0.40±0.05 µg/mL) COVID-19. These differences in mean D-dimer level with the severity of COVID-19 were statistically significant (p <0.01).On admission, D-dimer level was higher (7.96±7.40) among patients who expired within 28days compared to COVID-19 patients who survived (0.98±1.88 µg/mL). D-dimer level on admission was statistically associated with the severity of COVID-19.

Table6:D-dimer Correlation with Blood Markers in COVID-19 (n=52)

Parameters	R	p-value
Haematological parameters		
Lymphocyte count	+0.113	0.427
Neutrophil Lymphocyte Ratio (NLR)	+0.409	0.003**
Platelet count	-0.340	0.014*
Biochemical parameters		
C-reactive protein	+0.440	0.001**
AST	-0.073	0.606
ALT	0.219	0.119
Serum LDH	+0.481	0.001**
Serum Ferritin	+0.351	0.011*

**p-value <0.01 is highly significant. *p-value <0.05 is significant.

Pearson correlation analysis showed that serum D-dimer had a significant positive correlation with NLR, CRP, serum LDH, and ferritin (p<0.05). At the same time, serum D-dimer had a significant negative correlation with platelet count (p<0.05), as shown in Table6.

DISCUSSION

In this study, the mean age of all patients was 58.09±10.01 years (range: 34-88 years), with the maximum belonging to >50 years of age (42.3%) which was similar to the other studies [12]. Besides, male preponderance 30 (57.7%) was observed in this study as in other similar studies, probably due to high mobility and socialization among males compared to females [13]. Studies have indicated that women are less vulnerable to viral infection than males, presumably because of the protection of the X chromosome and sex hormones, which play a crucial role in innate and adaptive immunity [14].The most common comorbidity was diabetes mellitus 22 (44.2%), followed in decreasing order dyslipidemia 18 (34.6%), hypertension 15 (28.8%), chronic kidney disease 10 (19.2%), obesity 8 (15.4%), COPD 6 (11.5%) and ischemic heart disease 4 (7.7%) respectively. Multiple studies and meta-analyses also stated a higher disease burden of COVID-19 in patients with concurrent diseases such as cardiovascular disease, hypertension, and diabetes [15,16].

In the current study, the maximum number of study patients, 36 (69.2%), were in the severe category of COVID-19, followed by the critical 13 (25%) and moderate 3 (5.8%) category. The mean-on-admission D-dimer level was 5.87±6.98 µg/mL. In the current research project, it was observed that D-dimer level was significantly higher among critical COVID-19 patients (11.77±6.60 µg/mL) compared to severe (4.11±6.17 µg/mL) and moderate (0.40±0.05 µg/mL) COVID-19 as p-value <0.05. A similar studybyGao*et al*. explored a strong correlation between D-dimer levels and the

severity of COVID-19 [17]. They observed that patients with severe and critical stages of the disease tend to have higher mean D-dimer values than those with mild symptoms. For instance, severe cases showed higher mean D-dimer values than mild cases (0.6 mg/L vs 0.3 mg/L, respectively; p<0.001). This indicates that D-dimer levels tend to rise with the severity of the disease, which could be valuable in assessing the progression of COVID-19 [18].In this study, the 28-day death rate of COVID-19 patients was 36 (69.2%), which was substantially higher than previous Bangladeshi studies [19,20]. The findings may be due to the high percentage of inclusion of severe and critical COVID-19 patients in the study. Reports worldwide suggest that COVID-19-related lung damage may differ from traditional ARDS, indicating that standard ARDS mechanical ventilation techniques may be less effective [21,22].

In this investigation, on admission, D-dimer level was substantially higher among patients who perished within 28 days compared to COVID-19 patients who lived (7.96±7.40 vs 0.98±1.88 µg/mL, p <0.001). In parallel to present research findings, several studies have found that people who did not survive had higher D-dimer levels than those who did. For example, in one study, non-survivors had significantly higher D-dimer levels compared to survivors (4.6 µg/mL versus 0.6 µg/mL) [23]. Similarly, another study showed that when admitted to the hospital, non-survivors had notably higher D-dimer levels compared to survivors and the overall population (2.12 µg/mL versus 0.66 µg/mL and 0.61 µg/mL, respectively; p<0.001). These findings suggest a potential link between higher D-dimer levels and negative outcomes in these patient groups [24].In this investigation, Pearson correlation analysis indicated that serum d-dimer had a significant association with neutrophil-lymphocyte ratio (NLR), platelet count, C- reactive protein (CRP), serum LDH, and ferritin as p-value <0.05. Previous research has detected similar correlation patterns of d-dimer, NLR, CRP, serum LDH, and ferritin [25].The study's limitations were cross-sectional, and the half-life of D-dimer was 8 hours. Moreover, it was a single-centered study. The sample size was small due to the COVID-19 situation.

CONCLUSION

The in-hospital mortality rate was 69.2%. On admission, D-dimer level had a substantial connection with the severity and mortality of COVID-19. Further cohort investigation with a greater sample size is suggested. COVID-19 patients with high on-admission D-dimer levels should be treated more extensively.

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