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Association between D-Dimer Level and Severity of Covid-19 Infection

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ABSTRACT

Background: The COVID-19 pandemic has presented a major challenge in critical care, especially in identifying patients at high risk for complications and poor outcomes.

Objective: Given the pressing need to identify biomarkers that predict disease severity and outcomes, this study evaluates the association between D-dimer levels and the severity of COVID-19 infection in intensive care unit (ICU) patients, providing insights into its potential as a prognostic marker.

Patients and methods: A prospective cohort of 120 COVID-19 patients was studied at Menoufia University hospitals' ICU. D-dimer levels, measured upon admission, were analyzed alongside disease progression, clinical scores, Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), complications, ICU length of stay, and mortality.

Results: Demonstrated a significant positive correlation between elevated D-dimer levels and increased disease severity, with critically ill patients exhibiting markedly higher levels. Elevated D-dimer was associated with a greater incidence of complications, including deep vein thrombosis, pulmonary embolism, and multi-organ dysfunction, as well as a longer ICU stay and higher mortality. ROC analysis identified a D-dimer cutoff of 2505.4 ng/mL, yielding 74.2% sensitivity and 98.3% specificity for predicting mortality.

Conclusion: D-dimer serves as a valuable, prognostic biomarker for risk stratification and identifying patients likely to experience severe outcomes. D-dimer monitoring is recommended to improve clinical outcomes in critically ill COVID-19 patients by enabling early intervention, targeted treatment and resource allocation.

Keywords: COVID-19, D-dimer, ICU.

INTRODUCTION

The COVID-19 pandemic has had a significant impact, with over 150 million confirmed cases and more than 3 million fatalities worldwide, placing an immense strain on healthcare systems worldwide [(1-3)].

COVID-19 critically ill people have a higher risk of complications, poor outcomes, and death. The variables that lead to the development of major clinical problems, which indicate high disease severity, must be identified. This would lessen the existing strain on health care systems, enhance patient outcomes, and assist in guiding clinical decision-making [(4,5)].

COVID-19 exerts widespread systemic effects through complex immune and inflammatory responses (a 'cytokine storm'), resulting in widespread inflammation, endothelial injury, promoting a hypercoagulable state that can cause significant tissue damage, thromboembolic events, multi-organ dysfunction and leads to mortality [(6-8)].

A very tiny protein fragment called the D-dimer, a fibrin degradation product, is seen in the blood when blood clots are broken down by fibrinolysis. It is employed as a biomarker to identify and track thrombotic disorders. Determination of D-dimer levels is important as diagnostic and prognostic marker of COVID-19 severity, risk of complications and mortality, growing in importance as a tool for COVID-19 patient care [(9-11)].

This study aimed to evaluate the role of D-dimer as a biomarker for assessing COVID-19 disease severity.

PATIENTS AND METHODS

This prospective observational cohort study took place at Menoufia University hospitals, targeting adult COVID-19 patients admitted with confirmed diagnoses. The study included a cohort of 120 patients admitted to the ICU with confirmed COVID-19 infection through real-time reverse transcription polymerase chain reaction (RT-PCR) assay, or Computed Tomography of COVID-19 Reporting and Data System (CT CO-RADS) classification[(12,13)].

Inclusion criteria: Adults (18-70 years old) with laboratory confirmation of COVID-19 by respiratory or blood specimens positive for SARS-CoV-2 by (RT-PCR).

Exclusion criteria: Patients with a history of cancer, pregnancy, ACS, recent surgery or trauma within 30 days, or severe chronic illnesses such as hematologic malignancy, chronic liver disease, and patients without D-dimer testing upon admission or patients lost to follow-up.

All demographic, clinical, and outcome data were recorded for each patient. Although D-dimer levels were measured only upon admission, the value of this biomarker extends as a predictive marker for disease progression, in assessing how elevated D-dimer levels at admission correlate with the changes in disease severity (remeasured after 3 days of admission), and with development of complications (e.g., deep vein

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thrombosis (DVT), pulmonary embolism (PE), shock and organ dysfunction), and final outcomes (e.g., length of ICU stay and mortality), even without repeated D-dimer testing during hospitalization.

Ethical approval:

This study was ethically approved by the local Research and Ethical Committee of the Anesthesia Department, Faculty of Medicine, Menoufia University (11/2021 ANET 56). All participants provided written informed consent. The Helsinki Declaration was followed throughout the course of the investigation.

Statistical analysis:

In order to conduct statistical analysis, SPSS 24.0 for Windows was utilized. Participants' clinical, laboratory, and demographic information was compiled using descriptive statistics. The Kolmogorov-Smirnov test was utilized to verify that the data were in accordance with the normal distribution. Normality was used to determine the median (min-max) and mean ± standard deviation (SD) for continuous data. Kruskal-Wallis test and the paired t-test were used to compare them. The χ^2-test was utilized to examine the categorical variables, which were represented as frequencies and percentages. The Spearman rank correlation technique was used to conduct the correlation analysis. To forecast D-Dimer's effectiveness in terms of mortality in COVID-19 patients, ROC curve analysis was employed. It was decided that $p < 0.05$ was the significant criterion.

RESULTS

This study included 120 adult patients with COVID-19 infection who were admitted to ICUs at Menoufia University hospitals (**Figure 1).**

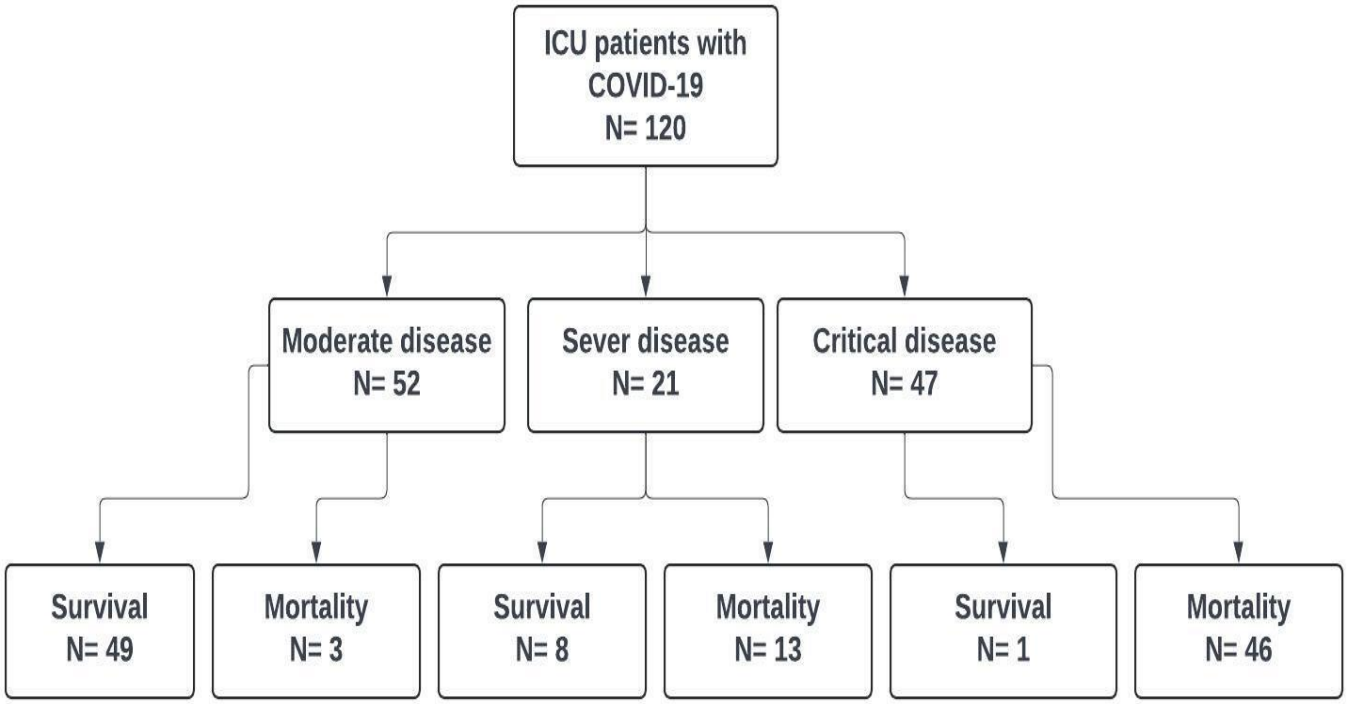


Figure (1): Study flowchart.

The age of the included patients ranged between 22 – 70 years with a median of 52.5 years. 74 patients (62%) were males, and the median BMI was 28.1 kg/m². The patients were divided into three groups: moderate, severe, and critical cases according to disease severity on admission. There were 52 patients with moderate disease, 21 with severe, and 47 critical cases. More comorbidities, including hypertension (HTN), chronic respiratory diseases, chronic kidney disease (CKD), and the history of exposure to COVID-19 cases were found in patients with critical cases as compared to those with moderate and severe COVID-19. On admission, 47.5% of patients had a history of exposure to COVID-19 cases. Based on the CT findings, the level of suspicion of COVID-19 infection is graded from low or CO-RADS 2 (0.8%) up to very high or CO-RADS 5 (40%). It was observed that patients with critical disease had significantly higher levels of WBC count, creatinine, urea, troponin, partial pressure of carbon dioxide (pCO2) compared to those with moderate or severe disease. The differences among the three groups were statistically significant ($p < 0.001$). Hemoglobin (Hb), platelets (Plt), and bicarbonate (HCO3) levels were significantly lower in the critical group, indicating more severe clinical conditions. Additionally, critically ill patients had notably higher SOFA and APACHE II scores, reflecting greater disease severity (**Table 1).**

Table (1): Demographics, Comorbidities, CO-RADS classification, Laboratory data and Clinical scores of the patients.

Variables		Total N= 120	Moderate disease (N= 52)	Severe disease N= 21	Critical disease N= 47	P- value
Gender	Male	74 (62%)	33 (63.5%)	13 (61.9%)	28 (59.6%)	0.92
	Female	46 (38%)	19 (36.5%)	8 (38.10%)	19 (40.4%)	
Age (years), median (min-max)		52.5 (22-70)	52 (22-67)	52 (25-68)	58 (29-70)	0.001*
BMI (kg/m²), median (min-max)		28.1 (19.4-34.2)	24.4 (19.4-33.8)	27.7 (20.3- 33.9)	29.9 (20.7-34.2)	<0.001*
Comorbidities						
HTN		60 (50%)	17 (32.7%)	15 (71.4%)	28 (59.6%)	0.003*
DM		66 (55%)	30 (57.7%)	12 (57.1%)	24 (51.1%)	0.78
History of CVS		68 (56.7%)	29 (55.8%)	12 (57.1%)	27 (57.4%)	0.98
Chronic respiratory Diseases		64 (53.3%)	25 (48.1%)	11(52.4%)	28 (59.6%)	0.52
History of CVS		63 (52.5%)	28 (53.8%)	14 (66.7%)	21 (44.7%)	0.24
CKD		58 (48.3%)	20 (38.5%)	10 (47.6%)	28 (59.6%)	0.11
Epidemiological History						
History of exposure to COVID-19 case.		57 (47.5%)	16 (30.8%)	12 (57.1%)	29 (61.7%)	0.009*
Imaging						
CT Chest scan (CO-RADS Score)	CO-RADS 2	1 (0.8%)	1 (1.9%)	0 (0%)	0 (0%)	<0.001*
	CO-RADS 3	50 (41.7%)	50 (96.2%)	0 (0%)	0 (0%)	
	CO-RADS 4	21 (17.5%)	1 (1.9%)	20 (95.2%)	0 (0%)	
	CO-RADS 5	48 (40%)	0 (0%)	1 (4.8%)	47 (100%)	
Laboratory data						
Hb (g/dL)		10.5 (6.6 – 16.5)	11.6 (9.8 - 13.8)	14.2 (12.6 - 16.5)	8.4 (6.6 - 9.9)	<0.001*
Plt (10^3/µL)		168 (52- 442)	198.5 (104- 325)	291 (151- 442)	143 (52- 193)	<0.001*
WBC count (10^3/µL)		11.1 (2- 28.1)	9.3 (3- 19.9)	9.3 (3.5- 11.5)	18.3 (2- 28.1)	0.004*
pH		7.3 (6.8- 7.5)	7.3 (7.3- 7.5)	7.4 (7.4- 7.5)	7 (6.8- 7.2)	<0.001*
PCO2 (mm Hg)		42.6 (30- 89.7)	37.4 (30- 44.9)	39 (35.2- 43.8)	70.1 (50.3- 89.7)	<0.001*
HCO3 (mmol/L)		19.5 (14.1 - 27.9)	20.35 (18.1 - 23.7)	24.5 (22.3 - 27.9)	16.9 (14.1 - 19.9)	<0.001*
INR		1.3 (0.8- 4.6)	1.7 (1- 4.6)	1.3 (0.9- 3.4)	1.1 (0.8- 4.6)	<0.001*
ALT (U/L)		119 (13- 199)	104 (13- 192)	142 (16- 199)	133 (14- 199)	0.61
AST (U/L)		137 (21- 238)	118 (21- 238)	161 (39- 233)	154 (43- 236)	0.49
Urea (mg/dL)		44 (8- 119)	40 (30- 50)	12 (8- 18)	102 (83- 119)	<0.001*
Creatinine (mg/dL		1.7 (0.6- 4.9)	1.5 (1- 2)	0.9 (0.6- 1.3)	3.2 (2- 4.9)	<0.001*
Troponin (ng/mL)		0.08 (0- 1.9)	0.07 (0.04- 0.1)	0.02 (0- 0.04)	1.1 (0.5- 1.9)	<0.001*
Clinical Scores						
SOFA		5 (3- 15)	3 (3- 6)	3 (3- 4)	13 (10- 15)	<0.001*
APACHE II		14 (10- 39)	12 (10- 14)	13 (10- 14)	34 (25- 39)	<0.001*

Median and range: Non-parametric test.

BMI: Body mass index, HTN: Hypertension, DM: Diabetes Mellitus. CVS: Cardiovascular Diseases. CKD: Chronic kidney disease, CT CO-RADS: Computed Tomography of COVID-19 Reporting and Data System, Hb: Hemoglobin, Plt: Platelets, WBC: white blood cell, pCO2: Pressure of carbon dioxide,HCO3: Bicarbonate, INR: International Normalised Ratio, ALT: Alanine Aminotransferase,, AST: Aspartate Aminotransferase SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II. *Statistically significant at P<0.05.

Interestingly, D-dimer levels were markedly elevated in critically ill patients, with a median value of 6477.2 ng/mL (range: 3023.7-9828.4), compared to 1176.8 ng/mL and 781.1 ng/mL in the moderate and severe groups, respectively **(Figure 2)**.

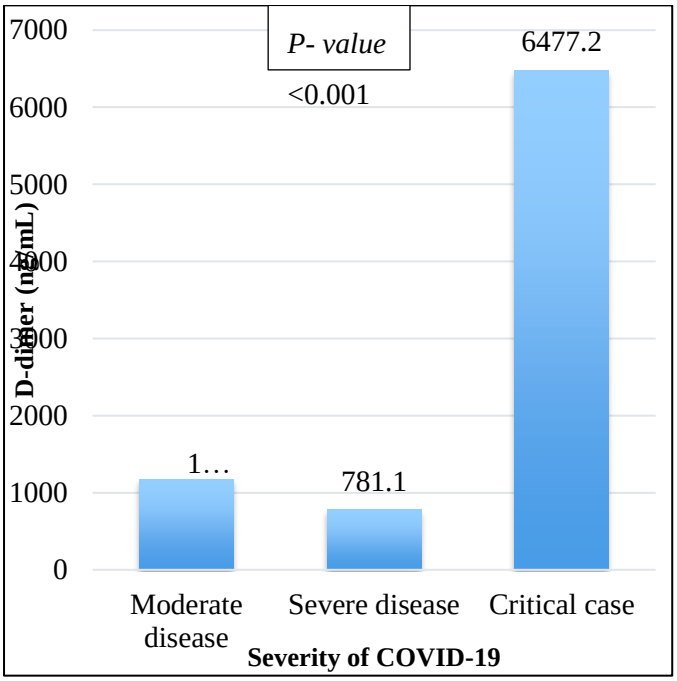


Figure (2): Distribution of d-Dimer across COVID-19 severity levels.

Table (2) showed a strong positive correlation between D-dimer levels and the SOFA score and APACHE II score, also showed a moderate positive correlation with disease severity after three days, and a weak-to-moderate correlation with length of ICU stay (**Table 2)**.

Table (2): Correlation between D-dimer levels and clinical scores, severity after 3 days and length of ICU Stay.

Correlation	Spearman rank correlation	P-value
SOFA	0.765	<0.001*
APACHE II	0.710	<0.001*
Disease Severity (after 3 days)	0.56	<0.001*
Length of ICU Stay (days)	0.401	<0.001*

SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II. *Statistically significant at P<0.05.

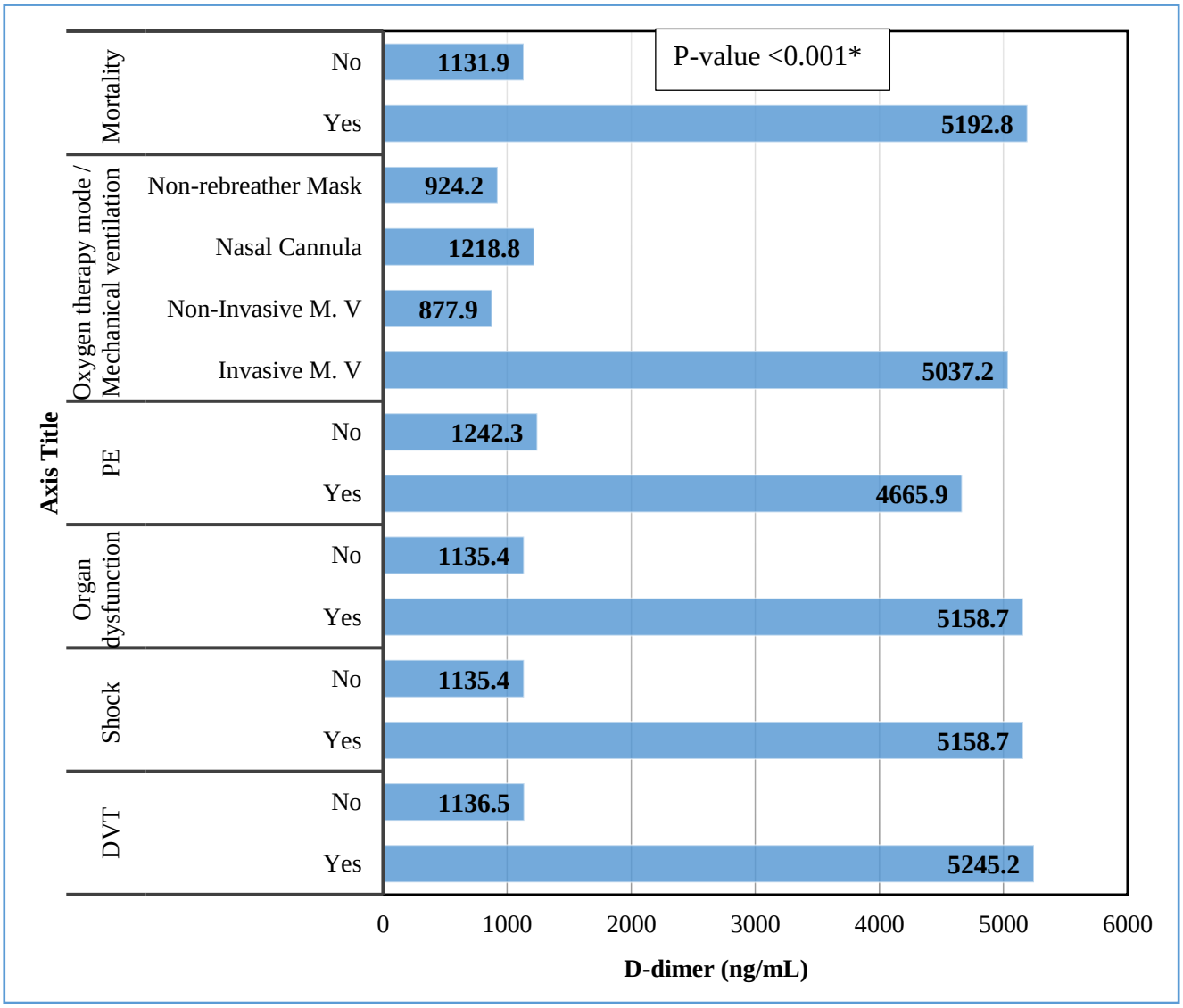
There was a significant decrease in the MAP among the 120 patients after three days of admission compared to their initial values. The respiratory rate (RR) showed a statistically significant increase after 3 days. In contrast, no significant changes were observed in heart rate (HR), oxygen saturation (SpO_2), or PaO_2/FiO_2 over the same period (**Table 3).**

Table (3): Changes in clinical data after 3 days of admission of all patients.

Variable	On admission	After 3 days	Mean difference	P-value
MAP (mmHg)	75.28 ± 7.059	70.90 ± 9.018	4.383	<0.001 *
HR (beats/min)	101.72 ± 20.67	104.11 ± 20.6	-2.392	0.083
RR	24.89 ± 8.99	26.21 ± 9.3	-1.317	0.017*
SpO_2 %	90.14 ± 6.57	89.72 ± 6.6	0.425	0.173
PaO2/FiO2	251.33 ± 96.39	266.15 ± 203.9	-14.817	0.395

MAP: Mean Arterial Pressure, HR: Heart Rate, RR: Respiratory Rate, SpO_2 %: Saturation of peripheral oxygen, PaO_2/FiO_2: The ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration. The data were expressed as Mean ± SD. *: Statistically significant.

The results showed that patients who developed complications such as DVT, PE, shock, invasive MV, organ dysfunction, or death had significantly higher D-dimer levels upon admission compared to those without complications. For all comparisons, the p-values were less than 0.001, indicating a strong statistical association between elevated D-dimer levels and the occurrence of these complications **(Figure 3).**



*: Statistically significant.

Figure (3): Distribution of D-dimer levels between patients with and without complications and mortality.

D-dimer significantly predicted in-hospital mortality in COVID-19 patients ($p < 0.001$).

The ROC analysis was used to assess the ability of D-dimer to predict in-hospital mortality. The AUC value for D-dimer was 0.794 (95% CI: 0.704-0.885).

Youden's index was used to establish the optimal D-dimer cutoff value based on the findings of the ROC analysis.

The cutoff value of D-dimer for this outcome was estimated as 2505.4 ng/mL, with 74.2% sensitivity and 98.3% specificity (**Figure 4)**.

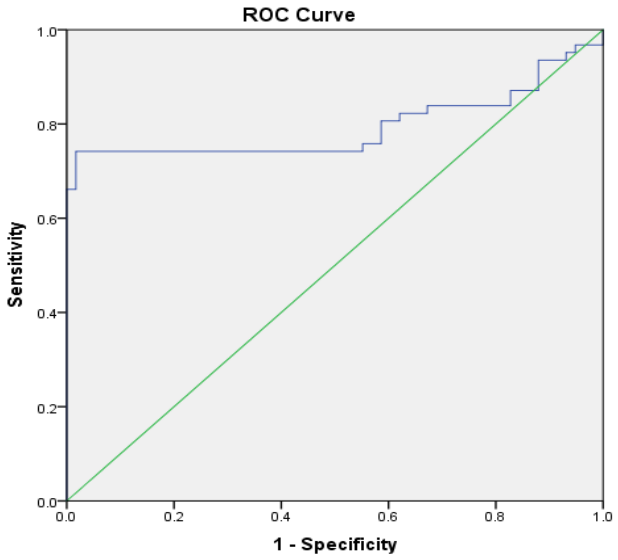


Figure (4): Receiver operating characteristic curve of D-dimer in predicting in-hospital mortality in patients with COVID-19.

DISCUSSION

Particularly in critically sick patients, COVID-19 is a very variable illness that can cause anything from minor symptoms to severe respiratory failure and multi-organ dysfunction [4]. Predicting which patients are most at risk of complications, poor outcomes, and mortality is one of the main issues in handling severe COVID-19 cases in intensive care units [5]. D-dimer, a marker of fibrin degradation, has emerged as a potential prognostic marker in this context. Researchers have linked elevated D-dimer levels to coagulopathy and adverse outcomes in critically ill patients [11].

This study aimed to explore the correlation between D-dimer levels and the severity of COVID-19 infection in ICU-admitted patients. Our findings demonstrated a significant association between elevated D-dimer levels and increased severity of illness, complications, prolonged ICU stays, and increased mortality. These results highlight the role of D-dimer as a valuable prognostic marker in predicting COVID-19 progression and outcomes and therefore guiding clinical decisions in COVID-19 management. In line with previous studies [4, 5, 11], our findings underscore the potential of D-dimer as a tool for early risk stratification and management in critically ill COVID-19 patients.

Patients with critical COVID-19 showed significantly elevated D-dimer levels. The median D-dimer levels were 6477.2 ng/mL in critical patients (range: 3023.7-9828.4), compared to 1176.8 ng/mL and 781.1 ng/mL in the moderate and severe groups, respectively ($p < 0.01$). Several studies have highlighted the significant correlation between D-dimer levels and disease severity.

The study of **Baroiu *et al.*** [14] on 849 COVID-19 patients that was prospective, observational, and actively controlled, added to our findings because it found that in severe instances, the average D-dimer level was 2.4 mg/L, whereas in light cases, it was 0.5 mg/L ($p<0.0001$).

Huang *et al.* [15] also found higher D-dimer levels are associated with more severe COVID-19. They found that D-dimer levels were five times higher in people in the ICU with serious disease (0·6-14·4 mg/L) than in people without serious disease (0·3-0·8 mg/L); $p<0·0042$.

Afrin *et al.* [16] also demonstrated that elevated D-dimer levels are a reliable predictor of the severity of COVID-19 symptoms. They found that the average D-dimer level in COVID pneumonic patients was 4.26±3.60 mg/L, and in COVID patients, it was 0.59±1.08 mg/l (P value = <0.001).

Zhan *et al.* [17] carried out research to investigate the connection between D-dimer levels and illness severity. They discovered that D-dimer levels are frequently high in severe COVID-19 patients, which is consistent with our findings. In contrast, **Yu *et al.*** [18] found fewer correlations between D-dimer and illness severity in retrospective research. They concluded that increased baseline D-dimer levels had limited predictive value for thrombosis and are linked to inflammation in COVID-19 patients. This discrepancy could be explained by differences in the patient populations, including non-ICU patients with less severe disease suggesting that D-dimer's predictive value may be more relevant in critically ill populations.

We discovered a strong link between D-dimer levels and clinical severity scores, such as SOFA ($r = 0.765$) and APACHE II ($r = 0.710$) ($p < 0.01$). This suggests a probable correlation between worsening organ dysfunction and higher D-dimer levels. This fits with what **Short *et al.*** [19] found in a large multicenter cohort study. Additionally, they found a clear association between greater D-dimer levels and a higher risk of mortality, as evidenced by the substantial correlation they found between SOFA scores and D-dimer levels in ICU patients.

Erol *et al.* [20] similarly observed that greater APACHE II scores in non-survivors were substantially correlated with increasing D-dimer levels.

Additionally, to the early link between D-dimer levels and illness severity, our study found a somewhat favorable correlation between D-dimer levels upon admission and disease severity three days after ICU admission ($r = 0.56$, $p < 0.001$). This indicates that elevated D-dimer levels are associated with worsening disease severity in critically ill COVID-19 patients. Moreover, there was a significant reduction in MAP after three days, with a mean difference of 4.383 mmHg ($p < 0.001$), and a statistically significant increase in RR ($p = 0.017$). These physiological changes were indicative of the worsening condition among patients with higher D-dimer levels, further supporting the role of D-dimer as a predictor of disease progression in the ICU. Previous investigations found that higher D-dimer levels are related with more severe COVID-19 presentations.

However, only one study by **Berger *et al.*** [21] and ours, which explored the link between D-dimer levels and disease severity progression, found that rises in D-dimer levels after ICU admission were related with greater disease progression in critically sick COVID-19 patients. Our study specifically evaluates the correlation between the initial D-dimer levels, which are measured only upon admission, and the changes in disease severity, which are remeasured after 3 days of admission.

D-dimer levels were predictive of complications, such as DVT, PE, and multi-organ dysfunction. Patients who developed DVT had a median D-dimer level of 5245.2 ng/mL, while those with PE had a median level of 4665.9 ng/mL, while those with organ dysfunction had a median level of 5158.7 ng/ml. This finding is consistent with **Weinberg *et al.*** [22], who also demonstrated that critically sick COVID-19 patients who had elevated D-dimer values (over 20 times the upper normal range) were more likely to experience thromboembolic events. **Zhang *et al.*** [23] similarly showed that in severely sick COVID-19 patients, increased D-dimer levels are linked to the development and progression of organ failure.

Our study revealed that 47% of patients required invasive MV, with 84% of critical patients needing ventilator support. Elevated D-dimer levels (> 5037.2 ng/mL) were associated with a greater likelihood of requiring mechanical ventilation. This agrees with **Ali *et al.*** [24], who found that elevated D-dimer levels predict invasive ventilation demand ($p = 0.001$). **Zhao *et al.*** [25] similarly demonstrated that MV was positively associated with D-dimer ($p < 0.001$).

Patients with higher D-dimer levels also had longer ICU stays, and a moderate positive correlation was observed between D-dimer levels and ICU stays ($r = 0.401$, $p < 0.001$). **Maulana *et al.*** [26] similarly showed a substantial association exists between initial D-dimer levels and the length of ICU hospitalization ($p = 0.023$).

In contrast, **Cidade *et al.*'s** [27] found no significant correlation between D-dimer levels and ICU stay duration. The authors found that the D-dimer profile has no prognostic value for patient survival and should not be used as a stand-in for ICU length of stay. It is not without restrictions, though. The study was conducted at a single location and had a limited sample size. Furthermore, there was no registration of any possible ICU issues that would have justified elevated D-dimer values and had nothing to do with COVID-19 infection.

Our ROC analysis revealed that a D-dimer cutoff value of 2505.4 ng/mL had a sensitivity of 74.2% and specificity of 98.3% for predicting in-hospital mortality. Patients with D-dimer levels above this threshold had significantly higher mortality rates. This is consistent with **He *et al.*** [28], who demonstrated that in severely sick COVID-19 patients, higher D-dimer levels are highly predictive of mortality. It was shown that the ideal probability cutoff for a prediction of death was 2.025 mg/L.

Poudel *et al.* [29] also showed consistent findings to ours. They said the optimum D-dimer level for predicting mortality in COVID-19 patients is 1.5 µg/ml, and the D-dimer level upon admission is a useful biomarker for predicting death in COVID-19 patients.

The median age of our cohort was 52.5 years, with 62% being male. Comorbidities such as hypertension (50%) and chronic respiratory diseases (53.3%) were more common among critical patients. These results are in line with earlier research that showed comorbidities and advanced age are risk factors for serious COVID-19 outcomes [30]. Approximately 47.5% of patients reported contact with confirmed COVID-19 cases. These patterns align with global studies that highlight exposure and travel history as key risk factors for severe COVID-19 [31].

Seventy-five percent of critically ill patients had CO-RADS scores of 5, indicating a high likelihood of COVID-19 infection based on CT findings. Moderate cases had CO-RADS scores of 3 or 4. This distribution is consistent with previous studies, which demonstrate that higher CO-RADS scores are linked to more severe disease [32]. The lab results showed that critical patients had higher D-dimer levels (median 6477.2 ng/mL), as well as higher WBC counts, creatinine, and troponin levels, with lower hemoglobin and platelet counts. These trends are consistent with previous studies, where elevated markers of inflammation and coagulopathy were associated with worse outcomes in severe COVID-19 cases [33].

Our findings emphasize the clinical value of D-dimer as a prognostic biomarker for critically ill COVID-19 patients. Routine D-dimer measurement upon ICU admission can guide early interventions, including anticoagulation and intensive monitoring. Given its predictive value for complications, mechanical ventilation, and mortality, D-dimer testing should be included in normal clinical practice to identify high-risk patients and modify treatment methods accordingly.

This study's strengths include its prospective design, the use of standardized severity scores (SOFA, APACHE II), and the comprehensive data collection from a well-defined cohort of ICU patients. The large sample size adds robustness to the statistical analysis and enhances the generalizability of the findings.

CONCLUSION

In critically ill COVID-19 patients, D-dimer can serve as a valuable indicator of COVID-19 severity and as a prognostic biomarker for patient outcomes, supporting its potential effectiveness in risk assessment and personalized management strategies to improve clinical outcome.

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No Competing Interests.

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