Study to Determine a Prognostic Cutoff Values of the Coagulation Analyte D-dimer for ICU Admission among COVID-19 Patients

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Abstract

Introduction: The measured D-dimer levels in coronavirus disease-2019 (COVID-19) patients have no specific cutoff to find the progression of coagulopathy and severity.

Aim: This study aimed to determine prognostic cutoff values of D-dimer for intensive care unit (ICU) admission among COVID-19 patients.

Materials and methods: This cross-sectional study was conducted in Sree Balaji Medical College and Hospital, Chennai, during a period of 6 months. This study included 460 COVID-19-positive individuals.

Results: The mean age was 52.2 ± 12.53 years. Patients with mild illness have D-dimer value 461.8 ± 221, whereas moderate and severe COVID illness patients have D-dimer values of 1915.2 ± 699.9 and 7937.6 ± 2045.2, respectively. D-dimer cutoff value of 1036.9 is shown to be a prognostic cutoff value for COVID-19 patients admitted in the ICU with 99% sensitivity and 17% specificity. The area under curve (AUC) was considered excellent (AUC $= 0.827$, 95% CI: 0.78–0.86, p-value < 0.0001) indicative of high sensitivity.

Conclusion: The D-dimer value of 1036.9 ng/mL was found to be the optimum cutoff for the patients to predict the severity of the COVID-19-positive patients admitted in the ICU.

Keywords: Coronavirus disease-2019, D-dimer, Intensive care unit, Prognosis, Prognostic cutoff.

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Highlights

The D-dimer levels in COVID-19 patients have no specific cutoff to find the progression of coagulopathy and severity. This study states that the D-dimer value of 1036.9 ng/mL was found to be the optimum cutoff to predict the severity of the COVID-19-positive patients in the ICU.

Introduction

Coronavirus disease-2019, an infectious respiratory illness caused by the severe acute respiratory syndrome-corona virus 2 (SARS-CoV2) that first appeared in India in 2019, has now spread to several other countries.[1] Coronavirus is a member of the corona viridae family, which is known to cause mild respiratory diseases in humans.[2] On March 12, 2020, the first COVID-19-related death in India was reported. The virus is most commonly transmitted via droplets, either directly or indirectly via fomites.[3] The disease's average or median incubation period is 5–6 days. There might be around 20 days of an infective period during which the patient can continue to shed the virus even after symptom resolution. Fever is probably one of the most common manifestations of COVID-19 disease. Anosmia, loss of taste, anorexia, diarrhea, abdominal pain, myalgia, and dyspnea were the other symptoms of this disease.[4] The transmission, infectivity, and symptom manifestation of the disease varies a lot. Few patients developed ARDS and needed ICU admission and treatment. Patients with mild-to-moderate COVID-19, newly diagnosed diabetes, and severe hyperglycemia in newly diagnosed diabetes were all common.[5] There are many markers to predict the severity of COVID-19 disease like C-reactive protein (CRP), interleukin-6 (IL-6), D-dimer, etc.[6]

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D-dimers are one of several fragments formed when plasmin, a fibrinolytic enzyme, cleaves fibrin to break up clots. It is made up of two covalently bound fibrin D domains that were cross-linked during the clotting process by factor XIII. This fragment forms distinct epitopes that monoclonal antibodies can recognize in D-dimer assays to confirm that the coagulation cascade is producing thrombin. Because D-dimer is formed by fibrin cross-linking, it is regarded as a sensitive biomarker for ruling out venous thromboembolism.[7] D-dimer elevations occurred in 3.75–68% of COVID-19 patients.[8]

D-dimer levels that are abnormal in COVID-19 patients are associated with a poor prognosis. D-dimer reference intervals have been established to detect deep vein thrombosis and pulmonary

embolism. However, there is no specific cutoff point for determining the progression of coagulopathy and thus the severity in the COVID-19 patients.

This study aims to determine prognostic cutoff values of the coagulation analyte D-dimer for ICU admission among COVID-19 patients. This can provide valuable information for developing clinical management protocols for patients with coagulopathy and will provide the impetus to perform further biological research to develop novel therapeutic strategies.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted in the Department of General Medicine and Biochemistry, Sree Balaji Medical College and Hospital, Chromepet, Chennai, during the period of 6 months (January 2021–June 2021).

The groundwork for the study was started after getting clearance from the Research Committee and the Institutional Human Ethical Committee (Ethical clearance number: 002/SBMC/IHEC/2021/1616) of Sree Balaji Medical College and Hospital, Chromepet, Chennai. This study included 460 COVID-19-positive individuals. They were divided into three groups depending on the severity of the COVID illness. COVID-19's severity was graded as follows: mild: no pneumonia on lung CT, mild clinical symptoms; moderate: fever, cough, and lung CT with pneumonia; and severe: respiratory distress (respiratory rate >30/min, oxygen saturation 93% at rest).[9]

Group A – Mild COVID illness.
Group B – Moderate COVID illness.
Group C – Severe COVID illness.

Inclusion Criteria

Male and female patients with COVID-19 of 21–70 years age-group.

Exclusion Criteria

- Patients with a previous history of deep vein thrombosis (DVT) and pulmonary embolism (PE) (DVT was diagnosed using lower limb Doppler studies and pulmonary embolism with computed tomography (CT) chest. Patients with D-dimer values >500 ng/mL should undergo other detection tests for DVT and PE).
- The study was explained to all patients who had registered for it. Consent was obtained from COVID patients of groups A and B. Informed consent from COVID patients with severe illness was not obtained. A 3-mL venous blood sample was collected from the antecubital vein of each subject using appropriate vacutainer tubes under aseptic conditions. Analyses of D-dimer were done by automated turbidimetric immunoassay using monoclonal antibodies bound to latex beads to detect plasma D-dimer. The results are given in terms of D-dimer concentration (ng/mL). Normal of D-dimer level is <500 ng/mL. This study included D-dimer values done on the 3rd day of admission.

Data Analysis

The Statistical Package of Social Service was used to analyze the data (SPSS 22.0). Data with normally distributed continuous variables were presented as mean ± SD, while categorical variables were expressed as percentages. Analysis of variance (ANOVA) was used to compare the differences in illness severity stages among COVID-19 patients. For all statistical tests, a p-value of 0.05 was used to indicate a significant difference. Receiver operating characteristic (ROC)

Table 1: Distribution of subjects according to sex

Sex	N	%
Male	308	66
Female	152	33
Total	460	100

Table 2: Comparison of mean ± SD of the D-dimer between the different stages of severity of illness among COVID-19 patients

Parameter	Group A (mild)	Group B (moderate)	Group C (severe)	p-value
D-dimer (mean ± SD)	461.8 ± 221	1915.2 ± 699.9	7937.6 ± 2045.2	<0.0001***

***p-value of <0.05 is significant

Table 3: ROC analysis of D-dimer

Marker	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p-value
D-dimer	1036.9	99%	17%	0.827	0.78–0.86	<0.0001

curve was created to evaluate the risk of COVID-19 by measuring D-dimer levels.

RESULTS

This study included 460 COVID-19-positive patients.

The mean age of COVID patients in this study was 52.2 ± 12.53 years age.

Table 1 shows that among 460 COVID-19-positive patients, about 66 % were males and 33% were females.

Table 2 shows that the mean values of D-dimer were found to be significantly elevated with the severity of illness among COVID-19 patients. Patients with mild illness have dimer value of 461.8 ± 221, whereas moderate and severe COVID illness patients had d-dimer values of 1915.2 ± 699.9 and 7937.6 ± 2045.2, respectively.

Receiver operating characteristic curve was created to evaluate the risk of COVID-19 by measuring D-dimer levels. D-dimer cutoff value of 1036.9 is shown to be prognostic cutoff value for COVID-19 patients admitted in the ICU with 99% sensitivity and 17% specificity. The AUC was considered excellent (AUC = 0.827, 95% CI = 0.78–0.86, p-value < 0.0001) indicative of high sensitivity.

Table 3 shows the ROC analysis of D-dimer. The AUC – 0.5: no discrimination; 0.7–0.8: considered acceptable; 0.8–0.9: considered excellent; and >0.9: outstanding. In this study, AUC is 0.8, which is considered excellent.

DISCUSSION

The 460 COVID-19-positive patients admitted in the ICU were estimated for D-dimer values. Based on the severity of the infectious condition, the patients were classified as mild, moderate, and severe. Among these groups, the difference in the levels of D-dimer was analyzed and found that patients in severe conditions have a higher mean value of D-dimer compared with moderate and mild, which was also statistically significant. D-dimer was a part of the investigation panel in COVID-19 patients. It is usually estimated on the day of admission and thereafter, depending on the severity of the disease. Prior

to the 2019 COVID-19 pandemic, despite some evidence to the contrary, D-dimer was not thought to be a useful biomarker for bacterial or viral pneumonia.[10] However, elevated D-dimer levels and thrombotic complications in COVID-19 patients have been widely reported. D-dimer levels greater than 0.5 gm/mL were found in 260 of 560 patients (46%) by Guan et al.[11] Zhang et al. in China concluded that D-dimer could be an early useful marker for predicting in-hospital mortality in patients in a study that included 343 patients. They discovered that 2 gm/mL was the best cutoff point for D-dimer.[12] A systematic review published in August 2020 discovered that COVID-19 patients with high D-dimer values had an increased risk of severe disease and mortality and that there was no consistent cutoff value to predict adverse events.[13] This study showed that the patients with mild illness have dimer value 461.8 ± 221, whereas moderate and severe COVID illness patients have D-dimer values of 1915.2 ± 699.9 and 7937.6 ± 2045.2, respectively. Studies have found that D-dimer and the concentration of fibrinogen increase three- to fourfold increase from the early stage to severe.[14,15] Yao et al. discovered that elevated D-dimer levels are associated with disease severity and serve as a prognostic marker for hospital mortality in COVID-19 patients.[16] Similar to our outcome study by Yu et al., a case–control study showed that severe COVID-19-positive individual had higher D-dimer levels that nonsevere patients.[17] Yu et al. discovered elevated levels of D-dimer in patients with community-acquired bacterial pneumonia (CAP) and COVID-19, but the increase was more pronounced in COVID-19-positive individuals compared with CAP, which was also statistically significant.[18] In this study, an optimum cutoff for D-dimer was found as 1036.9 ng/mL which states the severity of the disease with increase in the number of days of ICU stay in the hospital. A study by Poudel et al. showed that 1.5 µg/mL is the cutoff D-dimer value for the admission of COVID-19 patients.[19] Another study used a disseminated intravascular coagulation (DIC) and sepsis-induced coagulopathy (SIC) score to forecast the severity of COVID-19.[20] The DIC scoring system or the SIC score can be used to determine the severity of coagulopathy. The presence or absence of a few parameters, namely fibrinogen level, D-dimer level, and sequential organ failure assessment (SOFA) score, causes the difference between the two. In their study, Zirpe and Bamne discovered that DIC score 1, SIC score 2, and D-dimer level 600 ng/mL for PE; and DIC score , SIC score 1, and D-dimer level 990 ng/mL for mortality prediction in COVID-19 disease.[21] A case series on clot formation in COVID-19 has stated that acute ischemic stroke and lower limb arterial thrombosis are very common among COVID patients and D-dimer levels have to be monitored for better prognosis of patients.[22]

LIMITATIONS OF THE STUDY

The study population can be expanded because it was relatively small.

CONCLUSION

This study found that D-dimer elevation was common in COVID-19 patients and was related to disease severity. The D-dimer value of 1036.9 ng/mL was found to be the optimum cutoff for the patients to predict the severity of the COVID-19-positive patients admitted in the ICU. Hence, the estimation of D-dimer value predicts the severity state of the COVID-19 patients, which would be an early predictor of the severity of the COVID-19 patients.

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