

A study regarding D-dimer as a biomarker for disease severity in COVID-19 patients in tertiary care hospital of Southwest Bihar

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Received: 27-03-2021

Accepted: 14-04-2021

How to cite this article:

Pathak R, Kumar M, Ojha R, Sangwan J. A study regarding D-dimer as a biomarker for disease severity in COVID-19 patients in tertiary care hospital of Southwest Bihar. Int J Adv Integ Med Sci 2021;6(2):6-9.

Source of Support: Nil,

Conflicts of Interest: None declared.

Background: Coronavirus disease has been declared a Public Health Emergency of International Concern. After the outbreak of the coronavirus disease 2019 (COVID-19) over 120,941,264 cases of coronavirus have been reported from December 2019. We aim to assess the use of D-dimer as a biomarker for disease severity and clinical outcome to improve the management of COVID-19 patients. **Aim and Objective:** The aim of the present study was to evaluate whether elevated D-dimer levels could predict the disease severity and mortality in patients with COVID-19. **Methods:** Patients with laboratory-confirmed COVID-19 were prospectively enrolled in Narayan Medical College and Hospital from September 12, 2020 to April 30, 2021. **Results:** In the present study the majority of patients were men in the 40–59 age group with a D-Dimer value of between 500 and 1000 ng/ml. The majority of female patients were in the 40–59 age group with a D-Dimer dose of between 1000 and 2000 ng/ml. However, the difference was found to be statistically significant ($P < 0.05$) at a 95% significance level. D-dimer at a reception $> 2.0 \mu\text{g/mL}$ (fourfold increase) can effectively predict mortality in patients with COVID-19, indicating that D-dimer may be the first and most helpful marker of improving Covid-19 patient management. **Conclusion:** D-dimer was commonly elevated in COVID-19 positive patients. D-dimer levels correlate with disease severity and are a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19.

KEY WORDS: Biomarker, corona virus disease, D-dimer, SARS-CoV-2, severity

INTRODUCTION

Coronavirus has been declared a Public Health Emergency of International Concern. On December 31, 2019, the Wuhan Municipal Health Commission, Hubei Province, China, reported the presence of 27 cases of patients with undiagnosed etiology, related diseases, and the local market for wildlife and

seafood.^[1] After a laboratory investigation, on January 7, 2020, the causative agent of these diseases was identified, identified as the new CoV in 2019, and officially designated by the World Health Organization (WHO) as 2019-nCoV.^[2] Subsequently, the Global Infectious Disease Development Committee renamed 2019-nCoV as SARS-CoV-2.^[3,4] COVID was declared a pandemic by the World Health Organization on March 11, 2020. In India, the first case of coronavirus disease 2019 (COVID-19) was reported on 30 January 2020 in Kerala.^[2,3]

Coronaviruses (CoVs) are the largest group of viruses in the family Coronaviridae,^[5,6] introducing a single type of RNA genome.^[7] The genome is surrounded by a helical capsid and a lipoprotein envelope containing several spicules of glycoprotein which together give the virus the appearance

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of a crown. Thus comes the word “corona,” in Latin, meaning crown.^[8] When infecting people, CoVs can cause a variety of diseases, from upper respiratory infections such as the common cold, liver, enteric, neurological, and lower respiratory infections such as pneumonia, bronchitis, and acute respiratory syndrome (SARS).^[5,7,9] SARS can be caused by the strongest respiratory coronavirus (SARS-CoV),^[10] the Middle East respiratory coronavirus (MERS-CoV),^[11] and more recently the coronavirus of - acute respiratory syndrome 2 (SARS-CoV-2).^[1]

The SARS-CoV-2 infection creates a profound inflammatory response that causes coagulation breakdown. Cascade coagulation rehabilitation in COVID-19 patients is associated with a non-invasive condition and adverse clinical outcomes including death. Previous studies of community-acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) patients have shown that D-dimer levels are high in severe cases and can be used as a prognostic biomarker,^[1,2,11] and D-dimer > 1-1 µg/ml is one of the leading causes of death in older patients with COVID-19.^[10] D-dimer is a biomarker of fibrin formation and degradation that can be measured in whole blood or plasma. Healthy people have lower levels of D-dimer circulation, and higher levels are found in cases associated with hypercoagulation and increased fibrinolytic activity. Coagulopathy was reported, and elevated D-dimer was observed in 3.75–68.0% of COVID-19 patients.^[6,9,10] Currently, the best laboratory diagnostic marker of COVID-19 - corresponding to hemostatic abnormalities (CAHA) is considered D-dimer.

However, the role of D-dimer in COVID-19 patients has not been fully investigated. Therefore, the aim of this study was to evaluate the risk factors in clinics to quickly predict the severity and death of COVID-19 and to apply it. In this study, we demonstrated D-dimer levels in patients and also evaluated the role of D-dimer as a biomarker of disease severity and clinical outcome. Our study may help establish a different treatment and individual treatment route for COVID-19 patients.

MATERIALS AND METHODS

Study Design

A prospective study conducted at Narayan Medical College and Hospital (Sasaram, Bihar) on laboratory-confirmed COVID-19 patients between September 10, 2020, and April 30, 2021.

Laboratory Assay and Interventions

A total of 241 blood samples were collected in light blue color Vacutainer containing Sodium citrate as anticoagulant for the estimation of D-dimer level (As per the WHO guidelines on drawing blood: best practices in phlebotomy 2010, Geneva: WHO; 2010) from each patient at the time of admission. Plasma separated from the samples centrifuged at 3000 rpm for 5min

and test was carried out in Fully Automated Immunoassay System-VIDAS using enzyme-linked fluorescence assay technology as per manufacturer instruction at the time of presentation and during the hospital stays every 48 and 72 hourly till discharge or death.

Statistical Analysis

Collected data were entered in MS Excel spreadsheet, coded appropriately and later cleaned for any possible error and analyzed in Statistical Package for Social Studies for windows version 22.0. All tests were performed at 95% significance level, thus an association was significant if the value was <0.05 ($P < 0.05$).

RESULTS

Studies show that, Of the 241 patients in total, 160 of the patients (66.4%) were male, among them most 80 (33.2%) were in the 40–59 age group with a majority of 51 (31.875%) with D-Dimer value ranging from 500 to 1000 ng/ml. Of the 81 women aged 40–59 most of the 22 (27.2%) had D-Dimer levels ranging from 1001 to 2000 ng/ml. as shown in Tables 1 and 2.

The distribution of patients in terms of D-dimer value for their survival and ICU admission, suggests that non-survivors had a higher D-dimer for ICU admission than survivors (discharged). As shown in Tables 3 and 4.

However, the difference was found to be statistically significant ($P < 0.05$) at a 95% significance level.

Table 1: Gender and age of the patient

Gender	Age of the patient						Total
	0–19	20–39	40–59	60–79	80–99	100 and above	
Male	1	34	80	38	6	1	160
Female	2	12	41	25	1	0	81
Total	3	46	121	63	7	1	241

Table 2: D-dimer value (ng/ml) and gender

D-dimer value (ng/ml)	Gender		Total
	Male	Female	
<500	37	17	54
500–1000	51	15	66
1001–2000	28	22	50
2001–3000	14	4	18
3001–4000	8	7	15
4001–5000	1	5	6
5001–10000	8	9	17
>10000	13	2	15
Total	160	81	241

Table 3: D-dimer value (ng/ml) and survivor/dead

D-dimer value (ng/ml)	Survivor/Dead		Total
	Survived	Dead	
<500	54	0	54
500–1000	65	1	66
1001–2000	49	1	50
2001–3000	16	0	16
3001–4000	13	0	13
4001–5000	5	1	6
5001–10000	8	11	19
>10000	8	9	17
Total	218	23	241

Table 4: D-dimer Value (ng/ml) and patient admitted in ICU and discharged/death

D-dimer value (ng/ml)	Patient admitted in ICU		Total
	Yes	No	
<500	0	54	54
500–2000	3	111	114
2001–5000	31	3	34
5001–10000	8	0	8
>10000	8	0	8
Discharged			
Total	51	167	218
Death			
Total	23	0	0
Total	74	167	241

DISCUSSION

A key finding of this study is that in the acceptance of a D-dimer level $>2.0 \mu\text{g/mL}$, it was an independent predictor of hospital mortality in patients with COVID-19. These findings provide a well-established set of cuts to identify those COVID-19 patients with poor prognosis at baseline. Elevated D-dimer levels have been reported as one of the most common laboratory symptoms noted in COVID-19 patients requiring hospitalization. The findings of the study show similar results to that in various studies conducted by Guan *et al.*,^[9] Ning *et al.*,^[1] Fei *et al.*,^[3] Huang *et al.*^[5] D-dimer levels at admission were higher in patients requiring critical care support than those who did not need (median, $0.5 \mu\text{g/mL}$).

Elevated D-dimer levels indicate a hypercoagulable condition in a patient with COVID-19, which may be caused by a number of factors: First, viral infections are often accompanied by a violent inflammatory response and inadequate control of the anti-inflammatory response.^[4] It can cause endothelial cell dysfunction, which leads to overproduction of thrombin.^[12] Second, hypoxia found in severe COVID-19 can promote thrombosis by not

only increasing blood viscosity, but also a hypoxia-inducible-dependent signaling pathway.^[13,14] Third, hospitalized patients, especially severe COVID-19 patients, were more likely to have age, lower status, prolonged bed rest, and aggressive treatment, which were all risk factors for dealing with hypercoagulation or thrombosis.^[15-17] As evidence, segregation of a critical patient's lung with COVID-19 reported closure and formation of microthrombosis in small lung vessels.^[18] In fact, some patients may develop sepsis-induced coagulopathy or even develop intravascular coagulation.^[1,19] In all cases, high D-dimer was always associated with adverse events.^[20-22]

This study has several limitations. First, our study may have a preferred option because it was a single entity, even if it had sufficient potential to detect significant differences between groups at death. Second, a multi-parameter prediction model including D-dimer and other variables can provide a better predictive capability for COVID-19 patients.

CONCLUSION

D-dimer at a reception $>2.0 \mu\text{g/mL}$ (four times more than normal) can effectively predict mortality in patients with COVID-19, indicating that the value of D-dimer could be the first and most helpful marker of improving COVID-19 patient management.

ACKNOWLEDGMENT

The authors would like to thank all the people who helped or supported Narayan Medical College & Hospital to combat the emergence of the novel coronavirus. Thanks to everyone who participated in this project to make this study a success.

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