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Level and relation of D-dimer with COVID-19 patients disease outcome: A study from Khyber Pakhtunkhwa

Safia Khanam[1], Maria Azam[1], Uzma Hidayat[2], Haleema[1] ✉

[1]Khyber Girls Medical College, Peshawar - Pakistan [2]Lady Reading Hospital Peshawar - Pakistan

Corresponding Author
Haleema
Khyber Girls Medical College, Peshawar - Pakistan
E-mail:
khaleema024@gmail.com

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A B S T R A C T

Background: The activation of the plasmin enzyme produces the D-dimer, and elevated levels signal a hypercoagulable state and secondary fibrinolysis in the body, which is extremely valuable for thrombotic illness diagnosis. COVID-19 patients have been reported to be hypercoagulable.

Methodology: A total of 250 COVID-19 patients from two hospitals in Khyber Pakhtunkhwa were included in this study. The study participants were chosen randomly regardless of their age and gender. For analysis, all data was extracted from patient record files and entered into SPSS version 20.

Results: The present study included 250 confirmed COVID-19 patients. Age of study cases were from 16 to 87 years with mean age of 43.6 ± 14.145. All the study cases were confirmed as COVID-19 cases by real-time reverse transcription-polymerase chain reaction (PCR). Majority of the study cases 153 (61.2%) were male and maximum numbers were from age group of 36 to 45 years. This study reveals lower plasma D-dimer level in 184 (73.6%) of the selected patients, whereas high D-dimer level was found in 66 (26.4%) of the study cases, which was declared as significant biomarker for final outcome of COVID-19 disease with a p-value is 0.00001 which is significant value.

Conclusion: D-dimer levels are frequently higher in SARS-CoV-2-infected individuals. The optimum threshold accepted value of D-dimer as a predictor of death in COVID-19 patients is 1.5 µg/ml, which has good sensitivity and specificity. Significantly greater D-dimer value is found among individuals with severe illness and may be considered as a predictive marker for mortality among hospitalized patients. Thus, D-dimer may be a rapid and low-cost laboratory indicator for COVID-19 diagnosis.

Key words: SARS-CoV-2; D-dimer; COVID-19; Biomarker; Peshawar

Introduction

At the end of 2019, a new pandemic began when Wuhan, China, which served as the disease's origin, identified the first suspicious case as COVID-19. The whole situation started on December 29, 2019, when Chinese doctors received the first case with pneumonia symptoms, which they identified and reported to the World Health Organization (WHO) on December 31, 2019 as COVID-19 case.[1] COVID-19 is mostly a respiratory condition, but it can also impact the gastrointestinal, hepatic, cardiovascular, neurological, and renal systems. Leukopenia, lymphocytopenia, high CRP, high D-dimer, extended PT, and high fibrinogen levels have all been documented in the early stages of COVID-19 infection. COVID-19, the pandemic disease produced by infection with the new virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), can now be added to the long list of disorders linked to high D-dimer levels. Physicians in Wuhan, China, were the first to notice that D-dimer levels were increased in COVID-19.[2] According to a study, D-dimer was high in many of the 191 COVID-19 patients hospitalised in Wuhan in January 2020 at the start of the pandemic. The extent of the elevation was most significant in those who did not survive.[3]

D-dimer is raised in people with severe COVID-19, and it is highest in those who are most critically ill and those who do not survive, according to several subsequent studies conducted around the world. Over the last few months, much of COVID-19 research has been focused on determining the importance of D-dimer elevation and the COVID-19-related coagulopathy that is thought to be the cause of the elevation.

Covid19 has been linked to hemostatic problems in various studies, and COVID patients have been found to have significantly higher D-dimer levels. D-Dimer is a fibrin degradation (fibrinolysis) product circulates in blood plasma at low concentrations in healthy people. D-dimer has proven to be a therapeutically relevant biomarker of thrombotic illness since active blood coagulation and subsequent fibrinolysis are linked to increased plasma D-dimer content. D-dimer is a fibrin breakdown product commonly utilised as a thrombotic biomarker. The activation of the plasmin enzyme results in the formation of the D-dimer.[4] This suggests that degraded fibrin is present in the bloodstream. After the clot has formed, the fibrin mesh is broken down by the fibrinolytic system. The D-dimer represents the coagulation and fibrinolysis systems' activity. To rule out deep vein thrombosis (DVT), pulmonary embolism (PE), and to confirm the diagnosis of disseminated intravascular coagulation (DICO), the D-dimer test is often used in clinical practice. D-dimer levels rise in nearly all individuals with severe DVT. D-dimer levels are also elevated in physiological situations such as pregnancy and pathological diseases such as cancer, inflammation, and surgery. Normal D-dimer levels are less than 0.5 g/mL, and this level may grow with age and pregnancy. Following the advent of the COVID-19 pandemic, D-dimer was established as a possible predictor of COVID-19 patient prognosis.[5]

The management of COVID-19 can considerably benefit from reliable and readily available prognostic biomarkers. The purpose of this study is to determine if D-dimer elevation at the time of admission may be utilized as a prognostic predictor of mortality in COVID-19 patients.

Methodology

There were 250 confirmed COVID-19 patients in this study. Subjects were chosen randomly regardless of their age. This study covered patients of both genders. All data were extract from patient files and lab reports. Data include demographic, clinical, and disease outcome of each patient. For research purposes, all data was entered into specially designed proforma. The patient's result was reported as either a primary outcome (survival discharged if PCR negative) or a secondary out-come (non-survival) (mortality due to any cause). The overall length of stay in the hospital was the secondary outcome variable. SPSS version 22 was used to enter and evaluate all of the collected data. The mean and ± standard deviation of continuous variables was calculated. Variables of a categorical nature were shown as n (%). To compare categorical variables, a chi-square test was applied. Only variables that produced significant findings in the univariate analysis were used to calculate the adjusted hazard ratio after the univariate analysis. The best-fit model was also used for analysis purposes. With a 95% confidence interval, Cox proportional hazards regression analysis was carried out. A p-value of 0.05 or less declared as statistically significant value for all analysis.

Results

In this study a total of 250 confirmed COVID-19 cases were included which include 61.2% male whereas remaining 38.8% were female. Majority of study cases (34.4%) belongs to age group 36 to 45 years, followed by 23.6% with age more than 55 years. In the present study co-morbidities also studied and results shows that Diabetes Mellitus found in 80 (32.0%) cases, Hypertension in 111 (44.4%), COPD in 40 (16.0%), Hypothoirodism in 63 (25.2%), Chronic Liver Disease in 28 (11.2%), Tuberculosis in 25 (10.0%), whereas cardiovascular Diseases found in 55 (22.0%) of the study cases (Table 1).

D-dimer value was the main findings of this study and 1.5µg/ml is the optimal cutoff value for it. In the present

Table 1. Baseline characteristics of study cases

Characteristics	Frequency	Percentage
Gender		
Male	153	61.2
Female	97	38.8
Age group	43.6 ± 14.145	
≤ 25	33	13.2
26 – 35	37	14.8
36 – 45	86	34.4
46 – 55	35	14.0
>55	59	23.6
Diabetes Mellitus		
Yes	80	32.0
No	170	68.0
Hypertension		
Yes	111	44.4
No	139	55.6
COPD		
Yes	40	16.0
No	210	84.0
Hypothoirodism		
Yes	63	25.2
No	187	74.8
Chronic Liver Disease		
Yes	28	11.2
No	222	88.8
Tuberculosis		
Yes	25	10.0
No	225	90.0
Cardiovascular Diseases		
Yes	55	22.0
No	195	78.0
D-Dimer Level		
Lower than 1.5 µg/ml	184	73.6
Equal/greater than 1.5 µg/ml	66	26.4
Mortality		
Yes	49	19.6
No	201	80.4
Total	250	100.0

study, 184 (73.6%) patients have lower D-dimer value than 1.5µg/ml whereas remaining 66 (26.4%) show d-dimer level equal/greater than 1.5µg/ml. Mortality rate among study cases remain 19.6% (Table 1).

Univariate and multivariate regression performed to find out different factors related with D-dimer level. Table 2 showed effect of different factors with D-dimer level of study cases. Significant positive association (P-value 0.000) was found among gender and level of D-dimer level. Significant associated (P-value <0.005) was also found among age group more than 60 years with level of D-dimer. Diabetes Mellitus also show significant association (P-value < 0.005) with D-dimer level. Positive significant association was also found among Hypothyroidism (P-value 0.005), Tuberculosis (P-value 0.005), Cardio-vascular Diseases (P-value 0.000) and D-dimer level. Strong positive association was also found

Table 2. Crosstabulation between different factors and D-dimer level

Variables	Total	D-dimer < 1.5µg/ml N = 184 (73.6%)	D-dimer 1.5µg/ml N = 66 (26.4%)	Odd Ratio (OR)	95% Confidence Interval		P-Value
					Lower	Upper	
Gender							
Male Female	153 97	132 (52.8%) 52 (20.8%)	21 (8.4%) 45 (18.0%)	5.440	2.958	10.04	0.000
Age (Mean ±SD)	43.6 ± 14.145						
Age < 60 years Age ≥ 60 years	184 66	167 (66.8%) 17 (6.8%)	36 (14.4%) 30 (12.0%)	8.186	4.083	16.41	<0.005
Patients with Underlying conditions							
Diabetes Mellitus							
Yes No	80 170	44 (17.6%) 140 (56.0%)	36 (14.4%) 30 (12.0%)	0.262	0.145	0.473	<0.005
Hypertension							
Yes No	111 139	75 (30.0%) 109 (43.6%)	36 (14.4%) 30 (12.0%)	0.573	0.325	1.011	0.53
COPD							
Yes No	40 210	23 (9.2%) 161 (64.4%)	17 (6.8%) 49 (19.6%)	0.412	0.204	0.832	0.012
Hypothyroidism							
Yes No	63 187	35 (14.0%) 149 (59.6%)	28 (11.2%) 38 (15.2%)	0.319	0.173	0.588	0.000
Chronic Liver Diseases							
Yes No	28 222	17 (6.8%) 167 (66.8%)	11 (4.4%) 55 (22.0%)	0.509	0.225	1.153	0.101
Tuberculosis							
Yes No	49 201	19 (7.6%) 165 (66.0%)	30 (12.0%) 36 (14.4%)	0.138	0.070	0.272	0.000
Cardiovascular Diseases							
Yes No	61 189	22 (8.8%) 162 (64.8%)	39 (15.6%) 27 (10.8%)	0.094	0.048	0.182	0.000
Death							
Yes No	49 201	14 (5.6%) 170 (68.0%)	35 (14.0%) 31 (12.4%)	0.073	0.035	0.151	0.000

between mortality and high D-dimer level.

This study reveals high plasma D-dimer levels in 66 patients (26.4%), which was a significant biomarker for COVID-19 diagnosis with a p-value is 0.0000 which is less than 0.05.

Discussion

D-dimer is produced when fibrin is broken down by a process called fibrinolysis. Elevated levels of D-dimer signify secondary fibrinolysis and a hypercoagulable condition in the body, which is very helpful for thrombotic illness diagnosis. In the present study, it was found that raise in D-dimer level at time of admission was prevalent in patients with COVID-19 and was linked to both increased disease severity and in-hospital mortality. The tests are frequently performed as a part in a diagnostic process to rule out the presence of thrombosis. However, level of D-dimer is also increased by any pathologic or non-pathologic procedure that boosts fibrin synthesis or breakdown. Examples include arterial thrombosis, disseminated intravascular coagulation, deep vein thrombosis/pulmonary embolism, pregnancy, inflammation, cancer, chronic liver disorders, post-trauma and post-surgery state, and vasculitis.

Different studies also point out the importance of D-dimer and suggest that levels of D-dimer also linked to the severity of community-acquired pneumonia and final outcome of the disease. D-dimer hasn't, however, been used as a biomarker for viral pneumonia. Similarly raise in D-dimer level has been point out in many studies that reporting the clinical characteristics of COVID-19, it has not been investigated if the amount of D-dimer is a marker of severity.

Based on real-time reverse transcription-polymerase chain reaction (PCR), the current study comprised patients with a mean age of 43.6 ± 14.145 and a confirmed COVID-19 diagnosis ranging from age from 14 to 85 years. These all patients visited hospital for their treatment. Majority of the study cases were male (61.2%). As male face increase option of illness so chances of disease catchment is more as compared to female. In the present study all age group individuals were suffered from this disease.

Another important finding of this study was to find out different co-morbidities among the study cases. Different co-morbidities i.e. Diabetes Mellitus, Hypertension, COPD, Hypothoirodism, Chronic Liver Disease, Tuberculosis, and Cardiovascular Diseases were studied. Diabetes Mellitus was found among 80 (32.0%) of study cases. Hypertension was found among 111 (44.4%) of the study cases. COPD was present among 40 (16.0%) among the studied patients. Hypothoirodism is another co-morbidity which was found in (63) 25.2% of the studied cases. Chronic Liver Disease was found among 28 (11.2%) of the study cases. Tuberculosis was also found among 25 (10.0%) of the patients and Cardiovascular Diseases was found among 55 (22.0%) of the cases. According to a study conducted by Karyono DR and Wicaksana AL, older COVID-19 patients and COVID-19 patients with hypertension, diabetes, and other cardiovascular illnesses had a greater death rate.[6] Hypertension (55.4%), diabetes (37.3%), and hyperlipidemia (18.5%) were the three most common comorbid conditions among COVID-19 fatalities in NY, USA. Frequencies of comorbidities in this study were somewhat higher as compared with the present study. In a another study, similar results were also found which showed that the most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%).[7] A study conducted by Richardson et al found that comorbidities were also found with different frequencies i.e. hypertension (42.31%), cardiovascular disease (30.77%) and diabetes (28.21%).[8]

The death rate among the studied patients in the current study was 19.6%. In the current tertiary care hospital, these people died as a result of COVID-19 illness. In comparison to a research by Diaharuddin et al, which revealed a death rate of 17.18%, the mortality rate in the current study was a little higher.[9] Our study's high death rate is a sign of the disease's severity and the existence of concomitant illnesses. In a US trial, where mortality was 21%, a similar death rate was discovered.[8] Compared to the current research's death rate of 28%, another study from China had a higher mortality rate.[10]

The current study highlights a substantial association between admitted COVID-19 patients and mortality among these patients and greater D-dimer values. D-dimer is a byproduct of fibrin breakdown that is primarily used to identify and treat thrombotic diseases. Despite some evidence to the contrary, D-dimer was not thought to be a helpful biomarker for viral or bacterial pneumonia prior to the 2019 COVID-19 pandemic.[11] However, since then, several individuals with COVID-19 have reported having high D-dimer levels and thrombotic problems. D-Dimer level among the studied cases showed that 184 patients (73.6%) show lower level of D-Dimer than 1.5µg/ml and 66 (26.4%) of the studied cases showed greater level of D-Dimer than 1.5µg/ml. A study conducted by Zhou et al. reported that value of D-dimer greater than 1µg/ml is a risk factor for mortality.10A similar study was conducted by Guan et al which reported that value of D-dimer more than 0.5µg/ml was found in 46% of the study cases and positively associated with mortality.[12] The one difference is that the cut off value of D-dimer is different as compared to the findings of present

study. Several other studies also point out the relationship between the D-dimer levels and the severity of illness. According to a study conducted by Zhang et al, D-dimer may be a good early marker for predicting patient in-hospital death. They discovered that 2µg/ml was the ideal cutoff value for D-dimer.[13] A D-dimer concentration of more than 2µg/ml at the time of admission, according to another study conducted in China, was linked to a higher risk of death.[14] According to a comparable study conducted in India, the ideal D-dimer cutoff value for predicting hospital mortality at the time of admission was 1.44µg/ml, whereas the optimal value for the highest D-dimer measurement during the course of the hospital stay was 2.01µg/ml.[15] According to a systematic review released in August 2020, COVID-19 patients who presented with high D-dimer readings were at an elevated risk of developing severe illness and dying. In this review It was also observed that no reliable cutoff value had been established to forecast unfavorable occurrences.[16] A retrospective analysis among hospitalized patients in the United States reported a hazard ratio of 1.06 (95% CI 1.04-1.08, p0.001) for all-cause death for every 1µg/ml rise in admission D-dimer. However, they observed that D-dimer was a subpar prognostic test for predicting death, with just a 0.678 area under the ROC curve for D-dimer trend.[17] The average D-dimer level was found to be 0.58µg/ml in 1551 individuals with moderate illness and 3.55µg/ml in 708 patients with severe disease, according to a systematic study by Rostami et al.[18] According to Gungor et al meta-analysis, patients with elevated D-dimer levels at the time of admission were at an increased risk for both death and disease severity than those with normal levels of D-dimer.[19] According to a comparable meta-analysis, using 0.5µg/ml as the threshold value, the relative risk of death was 4.60 (95% CI 2.72-7.79).[20] Another meta-analysis of six studies indicated that patients with COVID-19 who had increased D-dimers had poorer clinical outcomes, including as all-cause death, ICU hospitalisation, and acute respiratory distress syndrome (ARDS).[21]

There is currently disagreement in the research on the ideal admission D-dimer cutoff value for mortality prediction. Using ROC curves, several researches have determined the best cutoffs, although the values range from 0.67 to 2.025 µg/ml, with significant sensitivity and specificity variations.[13,15,17,22-24] The threshold value for admission D-dimer was determined to be 1.113 µg/ml by a French multicenter research that was published in May 2021. Based on the distance between each point on the ROC curve and the top left corner of the graph, the ideal cutoff value for our study was determined. An excellent blend of sensitivity and specificity is offered by this. 1.5µg/ml was shown to be the ideal value in our investigation, with a sensitivity of 70.6% and a specificity of 78.4%. The D-dimer value at this cutoff is three times higher than the typically accepted upper limit value of 0.5 µg/ml for normal.

According to a recent research, the lab values' trajectory, which included D-dimer, accurately predicted patients' death and the severity of COVID-19.[25] More research is required in this area, although considering the D-whole dimer's trajectory during hospital admission may provide higher predictive value than admission D-dimer alone.[26]

Patients with other medical conditions and the elderly are most frequently affected. The individuals may be more susceptible to thrombosis as their age grow and have other medical comorbidities including hypertension, diabetes mellitus, and cardiovascular disorders. It is significant to highlight that findings only confirm associations between D-dimer levels and disease severity and mortality. Regarding the underlying causative processes and whether the correlations represent particular effects of SARS-CoV-2 infection or are results of a systemic inflammatory response, there is currently a lack of evidence.[27] An abnormal coagulation system, comprising both the cellular and protein components, is responsible for the pathogenesis of influenza by enhancing viral replication and immunological pathology.[28] The pathological characteristics of COVID-19 are strikingly similar to those of SARS and MERS coronavirus infections. They include extensive alveolar damage with cellular fibromyxoid exudates, pneumocyte desquamation and hyaline membrane development, pulmonary edema with hyaline membrane formation, and lymphocyte-dominated interstitial mononuclear inflammatory infiltrates.[29,30] The observed rise level of D-dimer points out an elevated inflammatory response occur due to SARS-COV-2 infection as well as a hyperfibrinolysis condition.

The present study reveals that D-dimer, is an excellent predicting biomarker for predicting mortality among COVID-19 admitted patients. This biomarker is widely acceptable and easy to perform in laboratory with reasonable price. It serves as a base and one of the main predicting marker for the detection of disease during emergency cases and may also use for the management purposes. As COVID-19 is one of the main issue during these days and become of the greatest global health issue, use of D-dimer in routine practice among the COVID-19 patients might be beneficial.

Conclusion

In conclusion, SARS-CoV-2-infected individuals frequently have high D-dimer levels. The optimum threshold value for admission D-dimer for predicting death in COVID-19 patients is 1.5 µg/ml, which has good sensitiv-

ity and specificity. Significantly greater levels are detected in individuals with severe illness and may be utilized as a predictive marker for mortality among hospitalized patients. Thus, D-dimer may be a quick and low-cost laboratory indicator for COVID-19 prediction.

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