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Original Article

Elevated D-Dimer Levels Are Strongly Associated With High Mortality Rate In COVID-19 Patients: An Observational Study

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ABSTRACT

Severe acute respiratory syndrome called COVID-19, was declared as global health emergency and a pandemic due to its worldwide distribution and frightful spread. Patients are presented with severe respiratory illness along with thrombotic disorders. Elevated d-dimer level (>2000ng/ml) is a potential predictive biomarker of the disease outcome and prognosis. **Objective:** To find the association of high D-dimer levels and mortality rate in COVID-19 patients to establish the optimal cutoff value for use in clinical setting. **Methods:** Present study enrolled 318 COVID-19 patients admitted to Mayo Hospital, Lahore, Pakistan and confirmed by RT-PCR. On admission D-dimer level of enrolled patients was measured by fluorescence immunoassay and reported in ng/ml. The enrolled subjects were divided in groups based on their age, gender, on admission d-dimer levels (<2000ng/ml and >2000ng/ml), outcome (survivors, non-survivors) and variant (α, β, and γ). Wilcoxon test was used to check the D-dimer level difference in survivor and non-survivor group. **Results:** 81% patients (257/316) died and were categorized as non-survivors while 19% (61/318) were discharged after recovery and were categorized as survivors. Mean D-dimer level for survivor group was 2070ng/ml (±3060ng/ml) whereas for non-survivor group was 8010ng/ml (±5404ng/ml) and mean difference was statistically significant ($p<0.05$). **Conclusion:** D-dimer level was highest (upto 20,000ng/ml) in second wave (β -variant) as compared to other two waves and caused highest number of deaths (n=163).

INTRODUCTION

Corona virus (SARS-CoV-2) has caused the deadly pandemic of the 21st century and globally affected 195 countries. The disease made a start in December 2019 when a few patients with severe respiratory ailments were identified in Wuhan, China linking it to the novel SARS CoV-2 and called the disease as COVID-19 [1-3]. The World health Organization marked it as global health emergency on January 30, 2020 [4] and it was declared as a pandemic on March 11, 2020 [5]. The virus spreads among human beings through physical contact and aerosols and requires strict social isolation to inhibit its hastening growth. Therefore, the disease enforced sudden social isolation over the globe and poses destructive effects not only on physical & mental health but also trembled education system and all types of business. Till now, 24 million cases and 4 million deaths have been reported by world health organization in different geographical areas of the world [6]. This deadly virus encloses single stranded RNA as the genetic material [7]. The coronavirus is known to occur with four subfamilies explicitly as alpha, beta, gamma, and delta [8,9,10]. So far, Pakistan has been hit by three variants of corona virus with the threat of several more. First wave of COVID-19 arose in

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Pakistan in the middle of March and July 2020, reaching to the maximum in mid-June diagnosing approximately 4000–6000 active patients of COVID-19 daily. A fall was seen in the active cases by the start of September with a subsequent resurgence in the second wave starting in October 2020 till February 2021. Then there was a transitory period in March alongside the third wave of active cases from March and May 2021.The positive cases of COVID-19 began to increase once more in June and in July 2021, Pakistan entered the fourth wave [11].COVID-19 patients are presented with fever and lower respiratory tract infection including dry cough, and dyspnea which are comparable to the symptoms of two other coronavirus-related diseases as the severe acute respiratory syndrome (SARS) as well as the middle east respiratory syndrome (MERS)[12].

Although, the etiology is not fully understood, studies report the presence of coagulopathies or thrombotic complications in these patients. Mechanism of intravascular coagulopathy occurring in COVID-19 patients is not fully understood but studies suggest that cytokine storm, cause by superinfection or organ dysfunction, activates the coagulation cascade [13,14]. Outcome of COVID-19 patients can be predicted by specific laboratory tests including higher D-dimer levels, C-reactive protein (CRP), LDH, and elevated sensitivity cardiac troponin I [15].The fibrinolytic system is responsible for the breakdown of the fibrin mesh following clot formation. Activation of plasmin enzyme results in the production of D-dimer consisting of two D fragments of fibrin which is indicative of the presence of damaged fibrin in the blood stream. Presence of D-dimer embodies the stimulation of coagulation accompanied by the fibrinolysis systems [16]. In COVID-19 infection the stated evidence of coagulopathy revealed elevated concentrations of D-dimer, lactate dehydrogenase with mild to no changes in PT and PTT accompanied by elevated levels of antiphospholipid antibodies [17,18].

The D-dimer test is a biomarker-based assessment that determines the amount of coagulation that is occurring at any time. A few studies have also found that patients having COVID-19 with high D-dimer concentration at the time of admission to the hospital have a greater risk for fatality [19].Very few systematic reviews and meta-analysis have been conducted to compile the current data and utilized the on-admission D-dimer levels to assess the mortality risk in COVID-19 patients. There are also fluctuations in the d-dimer levels during the three waves of corona virus. Normal D-dimer level is considered less than 500ng/ml is usually increases with age, in pregnancy and in severe community acquired pneumonia [20]. Few recent studies reported the d-dimer as an indicator of severity in COVID-19 patients [21-24]. Therefore, the present study was designed to evaluate the association of high d-dimer levels with the severity and mortality during first, second and third wave of COVID-19.

METHODS:

Present study was approved from ethical review committee of Mayo hospital, Lahore, Pakistan (Reference No. 5471-500) and the study design was as per the principles of declaration of Helsinki to conduct research on human beings. The present study initially recruited 350 patients admitted at Mayo Hospital, Lahore, Pakistan with symptoms of COVID-19 and initially tested positive with antibody test during September 2020 to March 2021. Written informed consent was obtained from all patients and they were informed that the research will cause no added benefits or harms to them. Study enrolled patients of three COVID-19 waves caused by three different variants of SARS-CoV-2 virus. Only patients with positive RT-PCR test for the presence of SARS-CoV-2 virus were finally included in the study. Patients previously diagnosed for deep vein thrombosis, pulmonary embolism, inflammatory, autoimmune, and cardiovascular disorders were excluded from the study.

Clinical and demographic data of the enrolled patients was obtained from medical record review. Patients enrolled in the study were divided in two major groups as survivors and non-survivors. Survivor group included those patients who besides disease severity survived and were discharged from the hospital while non-survivors could not fight with the virus and expired within one or two weeks of admission to the hospital. D-dimer levels in all enrolled subjects were measured by immunofluorescence assay and reported in ng/ml. To check the data normality Shapiro-wilk test was used. Wilcoxon test was used to detect the statistically significant difference in D-dimer levels of two groups (survivors and non-survivors). Results from D-dimer comparison in survivor, non-survivor groups and three waves of COVID-19 are presented in the form of bar graphs, scatter plots and pie charts.

RESULTS:

Present study enrolled 350 patients initially admitted to Mayo Hospital, Lahore, Pakistan with symptoms of COVID-19 and 318 patients confirmed for the presence of SARS-CoV-2 by RT-PCR test were finally included in the study. Patients with any inflammatory, autoimmune, and cardiovascular disorders were excluded from the study. The summary of

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demographic characteristics and clinical symptoms of the enrolled subjects are given in the Table 1. Briefly, 61 patients were in survivor group as they were discharged after treatment while 257 could not survive and expired within 10 days of admission to the hospital and were grouped as non-survivors. Majority of the non-survivors were males and older in age than the survivor group. 82% of non-survivors were above 45 years of age while only 18% were under 45 years. Disease severity was noted to increase with age, and very few patients (<5%) were less than 40 years old in critically ill patients. Fever, dyspnea, myalgia, fatigue, and cough were the most significant features seen in both survivors and non-survivors while headache, nausea and diarrhea were least common. To analyze the data normality Shapiro-wilk test was used and data was found to be non-normally distributed ($p<0.05$) and rejected the null hypothesis that data is normally distributed. Non-parametric Wilcoxon test found the statistically significant difference ($p<0.05$) in D-dimer levels of survivors and non-survivors.

Characteristics	Non-survivors	Survivors
Total	257	61
Male	171	34
Female	86	27
Age		
< 45 years	8	7
> 45 years	249	54
Mean d-dimer level		
(SD)(ng/ml)	8010	2872
Symptoms		
Fever	254	56
Dyspnea	255	50
Dry Cough	230	41
Fatigue	252	52
Myalgia	219	35
Ageusia	176	28
Headache	136	18
Nausea	97	3
Diarrhea	30	1
COVID-19 Waves in Pakistan		
First wave (α-variant)	39	19
Second wave (β-variant)	163	13
Third wave (γ-variant)	55	29

Table 1: Characteristics of COVID-19 patients

Distribution of D-dimer levels (ng/ml) in two age groups of survivors and non-survivors is shown in the Figure 1 A. It can be clearly interpreted from the scatter plot of the age groups that D-dimer levels are higher in more than 45 years age group for both survivor and non-survivors. A very few patients with higher D-dimer levels were under 45 years age group. We report the poor prognosis and higher mortality rate in patients above 45 years age and higher d-dimer levels (>2000ng/ml) concurrently. However, no significant association was found between d-dimer levels in different genders (male/female) of survivor and non-survivors as shown in the Figure 1(B), the distribution of patients d-dimer levels is same in both genders which supports the hypothesis that both genders have equal mortality risk caused by higher d-dimer levels.

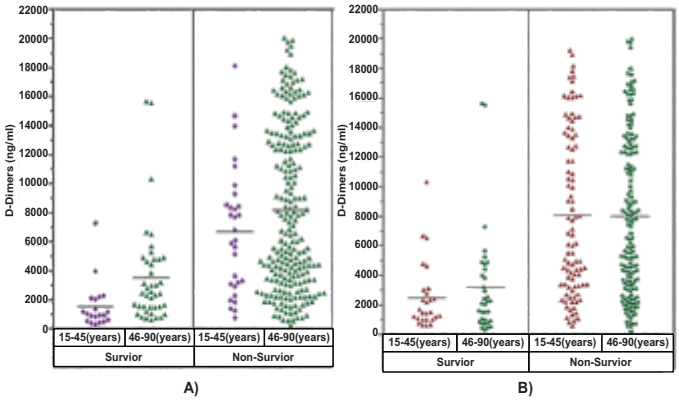

Figure 1: (A) Distribution of D-dimer levels (ng/ml) in two age groups (15-45 Years, 46-90 Years) of survivor and non-survivors of COVID-19 patients. (B) Distribution of D-dimer levels (ng/ml) in two genders of survivor and non-survivors of COVID-19

Survivor and non-survivor groups were further sub-divided in 5 groups according to their d-dimer levels as a) less than 1000 ii) 1000-2000 iii) 2000-5000 iv) 5000-15000 and v) more than 15000ng/ml. As shown in the Figure 2A more patients survived (n=17) with D-dimer level less than 1000ng/ml as compared to non-survivors of the same sub-group (n=10). It was noticed that the patients with D-dimer level less than 1000ng/ml and could not survive were above 60 years ago and had a history of comorbidities. In other four sub-groups number of non-survivors exceeds the survivors with increasing D-dimer levels. 73 deaths were observed with the D-dimer levels in the range of 2000-5000ng/ml while only 23 survived. Highest number of deaths (n=124) were reported in the sub-group of D-dimer level between 5000-15000 ng/ml while only 7 patients survived in this group. Only one patient with more than 15000ng/ml D-dimer was able to survive and all other patients with this higher level of D-dimer died (n=29). Number of deaths in each sub-groups confirms the association of high D-dimer level with high mortality rate of COVID-19. A cut-off value of D-dimer was set as 2000ng/ml and data was again divided in two groups as below 2000ng/ml and above 2000ng/ml to check the mortality associated with these two groups. Interestingly, there was

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an approximately equal number of patients in below 2000ng/ml group who survived (n=30) and died (n=31). However, there was an obvious difference in number of survivors (n=30) and deaths (n=226) in more than 2000ng/ml group as shown in Figure 2B. Majority of the patients with D-dimer levels greater than 2000ng/ml died within a week of admission to the hospital which establishes a link between high mortality risk and D-dimer levels of COVID-19 patients.

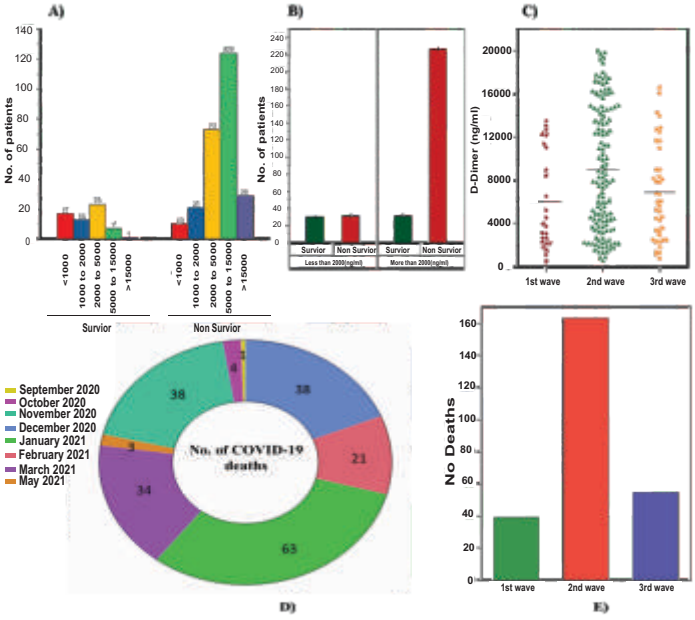

Figure 2: (A) Comparison of survivors and non-survivors of COVID-19 based on their D-dimer sub-groups. (B) Bar graph of survivors and non-survivors of COVID-19 patients with D-dimer levels below and above 2000ng/ml. (C) D-dimer distribution in three waves of COVID-19 in Pakistan. (D) No. of COVID-19 deaths occurred from May2020 to March 2021 at Mayo Hospital, Lahore, Pakistan. (E) No. of deaths caused by three waves of COVID-19.

Effect of different variants of SARS-CoV-2 on D-dimer levels was checked by categorizing the data in three waves according to the presence of variant. 1st wave was caused by SARS-CoV-2 α-variant while second and third waves were caused by β and γ variants respectively. Figure 2C shows distribution of D-dimer levels in three waves of COVID-19. It can be interpreted from the figure that highest number of deaths (n=163) were reported in second wave (β-variant). Majority of the patients in this category were with D-dimer levels above 2000ng/ml. Fewer patients were observed with high D-dimer level in first and third wave. We concluded that β-variant was more strongly associated with formation of D-dimers, and this increased the D-dimer level cause death in COVID-19 patients. Number of deaths caused by different variants of COVID-19 from May 2020 to March 2021 are shown in the Figure 2D while deaths occurred in three waves on COVID-19 are shown in Figure 2E. High level of D-dimer was found to be strongly associated with high mortality rate of COVID-19 in all three waves of COVID-19 in Pakistan.

DISCUSSION:

An insight to the current study comprising of 319 patients having COVID-19 with a known outcome as survivor or non-survivor revealed that increased D-dimer levels at the time of admission were substantially linked with a higher risk of mortality. According to the findings of current study, patients with COVID-19 having increased D-dimer levels at the time of admission had a substantially greater chance for mortality. D-dimer exist as fragment formed during clot disintegration by the breakdown of fibrin by means of plasmin [25]. As a result, elevation in D-dimers might imply enhanced fibrinolysis showing signs of intravascular coagulation and thrombotic illness, and perhaps the development of sepsis, as observed in the clinical presentation of COVID-19 [26,27]. Recent data also suggests that individuals with acute COVID-19 have an elevated risk of pulmonary embolism and deep vein thrombosis during the disease's course[28-30].The prediction of mortality employing the D-dimer levels at the time of hospital admission necessitates cautious interpretation. Patient factors including age, ethnicity, ongoing malignancy, immobility, and previous thromboembolic disorders all impact baseline D-dimer levels[31-33]. We discovered that patients who could not survive COVID-19 disease were significantly older than survivors and had a higher incidence of underlying illnesses and modifications in these potential confounders were not achievable in our analysis. Men are more prone than women to contribute to unhealthy behaviors including smoking and drinking alcohol [34,35] accompanied by higher age related pre-existing co-morbidities, which are linked to a poor COVID-19 prognosis. Moreover, after even adjusting for age, the result of co-morbidities on COVID-19 mortality was higher for men as compared to women [36]. Our study also shows similar results as there are a high number of male cases with increased severity and fatality as compared to women. A previous study reported the D-dimer levels more than 1g/ml are associated with an increased risk of mortality and possible risk factors included age [37].They found that possible risk indicators such as older age and D-dimer levels more than 1 g/L might assist physicians in identifying patients with poor prognosis. We reported that D-dimer levels above 2000ng/ml are highly associated with increased

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mortality. Furthermore, a fourfold increase in D-dimer level as compared to normal anticipated to be good interpreter of mortality in patients with COVID-19 [38]. Elevation in the D-dimer concentration may owe to the inflammatory processes in viral infections, damage in the endothelial cells due to raised thrombin formation. Moreover increase in age and the underlying morbidities followed by prolonged hospital stay and hypoxia which leads to elevation in both viscosity and the transcription factor-dependent signaling pathway increases the patient risk of coagulation disorders [23].The current study's findings indicate that an increased D-dimer level on admission (> 2000ng/ml) may identify patients at higher risk for in-hospital mortality and hence advise clinicians about appropriate candidates for intensive care and early intervention. Early assessment of D-dimer levels can be a source to predict the progression of the disease and may lead to better prognosis and treatment of the affected people.

Limitation of the study

The limited sample size of the current study is one of its limitations. This is a unicentric research conducted at a medium-sized hospital across a relatively small geographical area. Furthermore, we have reached the statistical significance limit for calculating mortality disparities. As a result, our findings must be interpreted with care. However, we feel that the results obtained are significant since they may be indicative of many comparable centers in the Mediterranean region.

CONCLUSION:

The D-dimer level on admission has a potential diagnostic accuracy for predicting COVID-19 patients' all-cause death. Despite variations in threshold values throughout publications, patients with increased D-dimer levels on admission had a greater than five-fold increase in all-cause death when compared to those with normal levels. Although our study shows that determining mortality risk using a D-dimer cut-off value of 2000ng/mL is achievable, a consensus d-dimer concentration cut-off must be developed before practical adoption. Although the reason of this occurrence has yet to be determined, we feel that it is worth noting given the critical role that d-dimer has taken on as a diagnostic and prognostic biomarker in COVID-19 patients.

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