Research Paper

Determination of D-dimer Levels in Patients Who Survived and Died From COVID-19: A Case-control Study

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ABSTRACT

Background: The COVID-19 has spread worldwide since December 2019 and continues to affect populations today. Studies have shown that changes in blood coagulation, as well as an increases in D-dimer levels, occur in patients with the COVID-19, leading to increased hospitalization and patient mortality. This study was conducted to determine the levels of D-dimer in patients who survived and those who died from COVID-19.

Methods: In this case-control study, the participants were divided into two case and control groups according to the outcome of the disease. This research was conducted at 5th Azar and Sayad Shirazi Hospital in Gorgan from March 20, 2020, to June 20, 2021. A total of 158 patients who were eligible for the study were retrospectively screened. Among these hospitalized patients, 107 were in the survivor group and 51 were in the deceased group. Clinical and laboratory parameters, as well as the results of confirmed cases of COVID-19, were analyzed retrospectively. Data were analyzed using descriptive statistics and SPSS software, version 21.

Results: The mean D-dimer levels of the patients in the survival and death groups were 1.48±2.09 and 2.62±2.55, respectively. This difference was confirmed to be statistically significant (P=0.007). The odds ratio interpretation showed that the chance of death due to COVID-19 in patients with high D-dimer levels is 1.29 times that of patients with lower D-dimer levels.

Conclusion: The D-dimer levels on admission can serve as one of the biomarkers to predict mortality in patients with COVID-19.

Keywords: D-dimer, COVID-19, Coronavirus, Iran

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Introduction

The virus responsible for COVID-19, SARS-CoV-2, is a single-stranded RNA virus belonging to the beta-coronavirus family [1]. SARS-CoV-2 is a new generation of this family that was discovered in 2019 and spread rapidly around the world; this virus had not been identified in humans prior to that time [2]. By the end of March 2020, 600,000 patients worldwide had been diagnosed with a positive coronavirus test [3]. Studies have shown that patients with COVID-19 experience mild infections, but some individuals may develop severe infections, leading to increased hospitalization and mortality. The virus infects host cells using its surface protein (S), which binds to angiotensin-converting enzyme 2 (ACE2). ACE2 is a membrane-bound peptidase expressed in the heart, lungs, gastrointestinal tract and kidneys, playing an important role in immune pathways [4-6]. Common symptoms of infection include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties. In more severe cases, infection can cause pneumonia, acute respiratory syndrome, kidney failure and even death [7-9].

Standard recommendations to prevent the spread of infection include washing hands regularly, covering the mouth and nose when coughing and sneezing, thoroughly cooking meat and eggs and avoiding close contact with people who have respiratory symptoms, such as coughing and sneezing [10]. Most co-morbidities in COVID-19 patients are hypertension, diabetes, heart disease, and chronic obstructive pulmonary disease (COPD) [11]. Studies have shown that changes in blood coagulation, as well as an increase in D-dimer levels, occur in patients with COVID-19 [12, 13]. D-dimer, a breakdown product of fibrin, is a relatively small protein fragment that is present in the blood following the destruction of blood clots by fibrinolysis. The determination of D-dimer concentration is a test used to diagnose thrombotic conditions, including pulmonary embolism and disseminated intravascular coagulation (DIC) [14]. Changes in coagulation factors, such as D-dimer, are among the factors that increase the hospitalization and mortality of patients [15, 16]. Some laboratory abnormalities include decreased white blood cell and lymphocyte counts, neutrophilia, thrombocytopenia, increased C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR) and abnormal procalcitonin (PCT) levels in most patients [17].

Although the role of D-dimer in patients with COVID-19 is not fully understood, studies have shown that patients with COVID-19 who have high levels of D-dimer may develop acute hemorrhagic encephalopathy and ischemic stroke [18, 19]. The threshold value of D-dimer to predict in-hospital mortality was 2.0 µg/mL, with a sensitivity of 92.3% and a specificity of 83.3%. Among the patients, 67 had D-dimer levels ≥2.0 µg/mL, while 267 had levels <2 µg/mL upon admission. Thirteen deaths occurred during hospitalization. Patients with D-dimer levels ≥2 µg/mL had a higher incidence of mortality compared to those with D-dimer levels <2 µg/mL [3]. Therefore, an increase in D-dimer levels in COVID-19 patients is useful for the rapid identification of high disease severity, pulmonary complications, and the risk of venous thromboembolism. This information can assist in risk stratification and the early introduction of therapeutic interventions that may reduce morbidity and mortality from COVID-19. Considering the role of D-dimer in increasing the mortality of patients with COVID-19, this study was conducted to determine the levels of D-dimer in patients who survived and those who died from COVID-19.

Methods

Study design and participants

This case-control study was conducted retrospectively at 5th Azar and Sayad Shirazi hospitals, which serve as referral hospitals for COVID-19 patients affiliated with the Golestan University of Medical Sciences, from March 20, 2020, to June 20, 2021. On consecutive days, the researchers reviewed the medical records of all patients with COVID-19 at the selected hospitals and identified patients who met the inclusion criteria for data extraction.

Inclusion criteria included being at least 18 years old, hospitalization due to COVID-19 with a specialized diagnosis, a positive chest radiograph or PCR test and a D-dimer test performed in the patient's file. Exclusion criteria included pregnancy, cancer, hematologic malignancy, chronic liver disease, acute coronary syndrome, and surgery or trauma within the past 30 days. Cases, in which some patient record information was incomplete were excluded from the study.

Out of the 158 patient files eligible for the study, 107 patients were assigned to the survival group and 51 patients to the death group. Based on the outcome of the disease, the samples were classified into two groups: Those who recovered from COVID-19 (control group) and those who died due to COVID-19 (case group). The D-dimer levels (exposure) were investigated for the presence or absence of a relationship with the increased

Table 1. Demographic characteristics of patients with COVID-19

Variables		No. (%)/Mean±SD	
		Survived Group (n=107)	Death Group (n=51)
Gender	Male	46(43)	29(56.9)
	Female	61(57)	22(43.1)
Comorbidity disease	Yes	67(62.6)	40(78.4)
	No	40(37.4)	11(21.6)
Hospitalization history	Yes	88(82.2)	48(94.1)
	No	19(17.8)	3(5.9)
Drug history	Yes	66(61.7)	36(70.6)
	No	40(37.4)	15(29.4)
Drug abuse	Yes	16(15)	15(29.4)
	No	75(70.1)	32(62.7)
BMI (kg/m^2)		25.74	28.16
Age (y)		55.64±17.41	64.49±19.27

BMI: Body mass index.

risk of death due to COVID-19, hospitalization history, drug history, and drug abuse. The items raised in the research exclusion criteria could be considered confounding factors in the study; therefore, they were treated as exceptions and removed.

Statistical analysis

The normality of continuous measurements was assessed, and results were expressed as Mean±SD. Categorical variables were expressed as numbers (percentages). A logistic regression analysis was performed between the case and control groups, and the odds ratio was reported. We used SPSS software, version 21 for all analyses, and two-tailed P<0.05 were considered statistically significant.

Results

A total of 158 eligible samples were included in this study, of whom 43% were men and 57% were women in the survivor group, while 56.9% were men and 43.1% were women in the death group. The average age of the samples in the survival and death groups was 55.64±17.41 and 64.49±19.27 years, respectively. Table 1 shows the basic clinical characteristics of the patients, including age, gender, chronic disease, history of hospitalization, history of drug use, and drug use on admission.

The mean D-dimer levels in the surviving group was 1.48±2.09 µg/mL,while the death group showed mean D-dimer levels of 2.62±2.55 µg/mL, (P=0.007; Table 2), and the two groups were significantly different regarding D-dimer levels.

Table 2. Mean D-dimer levels in the survived and death groups

Variable		Mean±SD	P
D-dimer levels (µg/mL)	Survived	1.48±2.09	0.007
	Death	2.62±2.55	

Table 3. Logistic regression analysis results

Variables	Logistic Regression Analysis Results			95% CI	
	df	P	Exp (B)	Lower	Upper
Hospitalization history	1	0.176	1.222	0.914	1.633
Drug history	1	0.066	2.373	0.945	5.959
Drug abuse	1	0.439	1.471	0.554	3.909
D-dimer levels	1	0.006	1.283	1.075	1.532
Constant	1	0	0.114	-	-

Based on the fitted model given in Table 3, the significance of the Wald test for D-dimer was <0.05 and significant. The interpretation of the odds ratio (Exp [βi]) is as follows: The chance of death due to COVID-19 in patients with high D-dimer levels is 1.29 times that of patients with lower D-dimer levels. The P for hospitalization history, drug history and drug abuse were >0.05, indicating that these variables did not significantly predict in-hospital death for patients with COVID-19.

Discussion

The main finding of this study was that D-dimer levels on admission were an independent predictor of in-hospital death for patients with COVID-19. The interpretation of the odds ratio indicated that the probability of death due to COVID-19 in patients with high D-dimer levels was 1.29 times that of patients with lower D-dimer levels. Guan et al. analyzed 1099 patients with laboratory-confirmed COVID-19 from more than 550 hospitals in China and found that D-dimer levels were significantly higher in non-survivors than in survivors [20]. Huang et al. showed that D-dimer levels on admission were higher in patients who required intensive care support than in patients who did not, with a mean level of 0.5 µg/mL [6]. This finding is consistent with the results of our research, which reported D-dimer levels in deceased patients with an average of 2.62 µg/mL and in recovered patients with an average of 1.48 µg/mL. The average D-dimer levels in deceased patients were significantly higher compared to recovered patients.

Zhang et al. suggested that for patients with significantly elevated D-dimer levels (cutoff of 2.0 µg/mL; fourfold increase), hospitalization and close monitoring should be considered, even in the absence of other severe symptoms [3]. High D-dimer has always been associated with adverse effects [21, 22]. Previously, the lack of specificity was considered a weakness of D-dimer. However, this low specificity has become one of its advantages in prognostic assessment [23]. Poudel et al. showed that the mean D-dimer levels among patients who survived were 1.067±1.705 µg/mL, compared to 3.208±2.613 µg/mL among patients who died. This represents a statistically significant difference (P<0.001, independent samples t-test). This study found that higher D-dimer levels at hospitalization were significantly associated with in-hospital mortality in COVID-19 patients [24].

Unlike the present study, several other studies found that D-dimer levels were not related to the severity of the disease, showing no significant difference in D-dimer levels between patients with severe and mild forms of COVID-19. The difference between the results of the present study and the findings of these studies can be due to the difference in the sample sizes. In the study by Lui et al. the number of patients with severe disease was 7; in the study by Qian et al. it was 9 and in the study by Jian et al. it was 13. Therefore, these studies had limited statistical power to investigate the relationship between dimer-D levels and mortality and disease severity [25-27]. On the other hand, the results of a series of studies showed that an increase in D-dimer levels at the onset of hospitalization in patients with COVID-19 infection is associated with an increased risk of severe disease progression and death [28-30].

A systematic review published in August 2020 found that COVID-19 patients with elevated d-dimer levels were at increased risk of severe disease and mortality, noting that no cutoff value had been defined to predict adverse events [31]. A retrospective study in the US involving 1065 hospitalized patients found that each 1 µg/mL increase in D-dimer levels during hospitalization was associated with a hazard ratio of 1.06 for all-cause

mortality. However, D-dimer was a poor prognostic marker for predicting mortality [32].

This research had limitations. Our study may have a selection bias because it was a retrospective study. Despite our efforts to include all eligible patients, some were excluded from admission due to missing D-dimer levels in their medical records. A multi-parameter prediction model that includes D-dimer and other variables may provide better predictive capabilities for COVID-19 patients.

Conclusion

The D-dimer levels on admission are an accurate biomarker for predicting mortality in patients with COVID-19. Therefore, D-dimer levels can be an easy and cheap laboratory indicator for the prognosis of COVID-19. Monitoring D-dimer levels will be a crucial approach in the clinical management of COVID-19 infection.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Golestan University of Medical Sciences (Code: IR.GOUMS.REC.1400.243) and in coordination with the treating physicians. All information was kept confidential by the researcher, and no interventions were made on patients. All other procedures adhered to the standards of Golestan University of Medical Sciences.

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Authors' contributions

Study design: Forough Faroughi, Mahnaz Modanloo and Iman Taghizadeh Firozjaie; Data collection: Mohammad Sadeghi, Forough Faroughi and Iman Taghizadeh Firozjaie; Data analyses: Mahnaz Modanloo, Forough Faroughi, Behnaz Khodabakhshi and Iman Taghizadeh Firozjaie; Writing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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