Letter to the Editor

Survival Analysis of COVID-19 Patients Based on Different Levels of D-dimer and Coagulation Factors

Abolfazl Zendehdel[1], Saeidreza Jamalimoghadamsiahkal[2], Maedeh Arshadi[3], Forough Godarzi[3], Shokouh SHahrousvand[3], Hamidreza Hekmat[4], Ehsan Sekhavatimoghadam[4], Seyedeh Zahra Badrkhahan[5], Mina Riahi[6], Isa Akbarzadeh[3,#], and Mohammad Bidkhori[3,#]

COVID-19 is a systemic disease that affects the respiratory, gastrointestinal, cardiovascular, hematopoietic, and immune systems[1]. Several studies have shown that the SARS-CoV-2 can cause blood clots (thrombosis) in veins and arteries. Therefore, COVID-19 patients are prone to deep vein thrombosis (DVT) and pulmonary embolism (PE)[2]. Arterial and venous thrombotic complications and coagulation disorders represent one of the major causes of mortality, especially in patients admitted to the intensive care units, patients hospitalized for long durations, and those on artificial respiration[3]. Approximately 20% of patients with COVID-19 have significant coagulation disorders and about one quarter of patients who are prone to thrombotic events and hospitalized in the intensive care unit receive anticoagulant prophylaxis[4]. Among the deceased COVID-19 patients, 71.4% displayed symptoms of diffuse intravascular coagulation and only 0.6% of patients with diffuse intravascular coagulation symptoms survived[5].

Coagulation Factors such as D-dimer levels, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) are currently considered to be the most important prognostic tools and the best indicators of a laboratory diagnosis for homeostasis abnormalities related to COVID-19. D-dimer is the product of fibrin protein degradation by the enzyme, plasmin. The presence of D-dimer levels in the blood indicate the activation of coagulation systems and fibrinolysis. Studies have shown that high levels of D-dimer at the time of admission and a 3–4-fold increase over time have a significant relationship with mortality due to diffuse intravascular coagulation disorder (DIC), cytokine storm, limb failure and infection/ sepsis[1,2].

Over 6.5 million people worldwide have died due to COVID-19 since the beginning of the pandemic. Therefore, the use of survival analysis models will help to identify risk factors related to patient death. When time-to-event (or survival) data are available, an option is to use the Cox Proportional Hazards Model. In the logistic regression model, final outcome is a binary variable; however, in the Cox model, the exact time of each outcome and the duration between the outcomes are also investigated. Therefore, the estimate obtained from the Cox model has greater validity than the logistic model. A better understanding of the pathogenic mechanisms created by the COVID-19 virus and predicting the prognosis of the disease through validated biomarkers will help to more appropriately manage patients with COVID-19 and develop more suitable treatment strategies. In Iran, there have been limited studies on laboratory signs and predictors of mortality from SARS-CoV-2 (especially in high sample sizes). Therefore, the aim of this study was to determine how levels of D-dimer and coagulation factors affect the risk of COVID-19 mortality by Cox regression.

This study was a retrospective cohort of patients hospitalized with COVID-19 at Ziaeian Hospital in Tehran. Patients in this study displayed one of the

doi: 10.3967/bes2022.122

1. Geriatric Department, Associate professor of internal medicine, Ziaeian Hospital, Tehran University of Medical Sciences, Tehran, Iran; 2. Ziaeian Hospital, Tehran University of Medical Sciences, Tehran, Iran; 3. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; 4. Department of Cardiology, School of Medicine, Ziaeian Hospital, Tehran University of Medical Sciences, Tehran, Iran; 5. Department of Geriatric Medicine, School of Medicine, Ziaeian Hospital, Tehran, Iran; 6. Department of Health Services Management, School of Health Managment and Information Sciences, Iran University of Medical Sciences, Tehran, Iran

laboratory or radiological signs of COVID-19, a typical COVID-19 appearance on a CT scan, or a positive PCR test, and were hospitalized. The required initial information was extracted from the patients' records. Hospitalized patients were followed up, until discharge or death occurred.

Background information, symptoms, and underlying diseases were recorded in patients' files (by asking patients or their families). The patients' laboratory data, including blood factors (PTT, INR, D-dimer, and white blood cells) were measured at the time of hospital admission. PT and PTT were measured using a coagulation analyzer. The international sensitivity index and mean PT normal range were defined as 1.02 and 13.5, respectively and the INR was obtained D-dimer levels in the plasma were measured using a commercial qualitative test kit (SARANTASHKHIS). The decision regarding the categories of laboratory parameters was made based on the guidelines issued by the Iranian Ministry of Health and Medical Education, expert opinion, and upper limit of normal defined by our hospital laboratory. Hospitalization category was divided into two categories as ward and others (emergency, ICU, and ICU-ward). The patients' information was extracted from the patients' files during the hospitalization period using a researcher-created data collection checklist. All missing or unknown records were covered by reviewing the hospital medical record units or asking patients and their families. Missing blood parameter values were completed by reading the blood test results in the patients' medical files.

Since the necessary data for the present study were extracted from the hospital data of hospitalized patients, the sample size included all 1,050 patients admitted due to COVID-19 at Ziaeian Hospital in Tehran. This study was approved by the ethics committee of Tehran University of Medical Sciences (registered as: IR.TUMS.MEDICINE.REC.1400.379).

Percentage and frequency were used to describe qualitative variables and the mean and standard deviation were used for quantitative variables. A Cox proportional hazards model was used in this study because follow-up information was available. Since Cox models use the exact time of the event, they are more efficient compared to logistic and Poisson regression models. The effect size obtained from the Cox hazards ratio indicates how many times the variables affect the probability of dying. Before performing the analysis, the proportional hazard (PH) assumption was examined using the log-log of survival and the statistical test based on Schoenfeld residuals. If the PH assumption was met, the association between the included variables and the time to event (death was investigated using a Cox proportional hazard model). First, a univariable analysis using single variables at each model was performed ($\alpha = 0.2$). In the next step, significant variables were entered into the multivariable Cox regression model ($\alpha = 0.05$). D-dimer levels were investigated separately and adjusted only for age and sex due to a high number of missing data. Data were analyzed using STATA 14.

A total of 870 COVID-19 patients were included in this study. The mean age was 56.8 years and the majority of the participants were male (58.0%), married (51.3%), and hospitalized on ward (77.3%). The mean white blood cells (WBC) was 7.33×10^9/L and 43.7% of participants were D-dimer negative. Most of the patients displayed between 1.0 to 1.1 (82.9%) for INR, and a PTT of 25 and 36 s (83.5%) (Table 1).

The number of deaths was 43 (28.7%) in patients with an INR greater than 1.1 and 76 (10.6%) for INR between 1.0 to 1.1. Mortality in patients with PPT ≤ 24 s, 25–36 s, and > 36 s was 21.4%, 12.2%, and 20.9%, respectively. A total of 8.6% of patients negative for D-dimer died and the highest percentage of death was in patients with high D-dimer level (1,600 to 3,200) (Table 2).

The majority of surviving patients: 86.12% had INR = 1.0–1.1, 84.9% had PTT = 25–36 s, and 45.42% had negative D-dimer. However, in the majority of deceased patients: 63.86% had INR = 1.0–1.1, 74.78% had PTT = 25–36 s, and 31.25% were negative for D-dimer levels.

At the first the univariable analysis using single variables was performed. As shown in Table 3, all variables except sex and PTT were statistically significant in this analysis. In the next step, significant variables were entered into the Cox proportional hazard model. Based on these results, age, INR, hospitalization section, and D-dimer levels were statistically significant in the fitted multivariable model ($P < 0.05$). Based on the adjusted hazard ratio (HR), each year increase in age increased the probability of dying by 1.01 times. In addition, those with an INR of 1.0–1.1 were 1.99 times more likely to die than those with an INR higher than 1.1. The risk of mortality in hospitalized patients was 4.69 times higher than in other patients.

Due to the high number of missing data for D-dimer levels compared to other variables, it was investigated separately. The HR for the univariable

analysis was 1.37 for D-dimer, which was statistically significant (P = 0.02). Consequently, an adjustment for only age and sex was performed and the results showed an HR of 1.29 (P = 0.01). This data indicates that for every increase in the level of D-dimer, hazard of mortality increases by 29%.

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Clinical manifestations of COVID-19 include fever, cough, diarrhea, shortness of breath, fatigue, and pneumonia. Most patients exhibit non-severe illness; however, some can develop serious COVID-19. In severe cases, SARS-CoV-2 infection can lead to acute respiratory distress syndrome and even death. COVID-19 causes

Table 1. Baseline characteristics of under study patients

Variable	COVID-19 patients (n = 870)	Missing (n)
Age (years), mean ± SD	56.84 ± 17.96	–
Sex, *n* (%)		
Male	505 (58.05)	–
Female	365 (41.95)	
Marital status, *n* (%)		
Single	411 (47.85)	11
Married	441 (51.34)	
Divorced	7 (0.8)	
Hospitalization, *n* (%)		
Ward	673 (77.36)	–
Other	197 (22.64)	
Outcome, *n* (%)		
Discharged	751 (86.32)	–
Died	119 (13.68)	
INR		
1.0–1.1	720 (82.95)	2
> 1.1	148 (17.05)	
PTT (seconds)		
≤ 24	14 (1.61)	–
25–36	727 (83.56)	
> 36	129 (14.83)	
WBC ($\times 10^9$/L)†, mean ± SD	7.33 ± 5.68	–
D-dimer (ng/mL), *n* (%)		
Negative (< 200)	174 (43.72)	472
One-plus (200−399)	127 (31.91)	
Two-plus (400−99)	50 (12.56)	
Three-plus (800−1,599)	29 (7.29)	
Four-plus (1,600−3,200)	18 (4.52)	

Note. INR, international normalized ratio; PTT, prothrombin time test (seconds); WBC, white blood cells. †Adjusted for age and sex.

Table 2. Clinical characteristics according to patient survival

Variable	Survivors, *n* (%)	Non-survivors, *n* (%)
INR		
1.0–1.1	664 (89.4)	76 (10.6)
> 1.1	107 (71.3)	43 (28.7)
PTT (seconds)		
≤ 24	11 (78.6)	3 (21.4)
25–36	638 (87.8)	89 (12.2)
> 36	102 (79.1)	27 (20.9)
D-dimer (ng/mL), *n* (%)		
Negative	159 (91.4)	15 (8.6)
One-plus	119 (93.7)	8 (6.3)
Two-plus	40 (80)	10 (20)
Three-plus	20 (69)	9 (31)
Four-plus	12 (66.7)	6 (33.3)

Note. INR, international normalized ratio; PTT, prothrombin time test (seconds).

thrombosis in the veins and arteries, and thus, COVID-19 patients are prone to deep vein thrombosis and pulmonary embolism. This study aimed to investigate the relationship between D-dimer levels and mortality rate in hospitalized COVID-19 patients using a survival analysis.

Based on the results of this study, D-dimer and INR levels were associated with the survival of COVID-19 patients. Patients with a negative D-dimer test result had a lower risk of dying from COVID-19, and this risk increased in association with higher D-dimer levels. According to one meta-analysis, D-dimer levels were found to be significantly higher in patients with severe clinical conditions. Moreover, patients who died had higher D-dimer levels compared to surviving patients[3]. Elevated D-dimer levels in COVID-19 patients might be attributed to several factors, including viral infections. Viral infections can cause an uncontrolled inflammatory response in the body and lead to the production of excess thrombin via endothelial cell dysfunction[6,7].

One of the other factors evaluated in the present study was hospitalization and the risk of death from COVID-19. The results demonstrated that there was a significant association between hospitalization and the risk of death in patients. The clinical condition of those who were hospitalized was confirmed to be more severe.

In the current study, INR was associated with patient survival. According to the results of this study, COVID-19 patients with an INR greater than 1.1 was found to increase the hazard of mortality by approximately two times compared to those with values less than 1.1. Another meta-analysis also showed that COVID-19 patients with severe clinical conditions or those who died during follow-up had a significantly prolonged INR during the first days of admission compared to those with mild disease[8]. Although COVID-19 often affects the respiratory system, it can also cause other serious complications, such as thrombosis. In addition, a high INR and coagulation system disorders can cause ischemia, heart failure, and dysfunction in other organs. High INR and dysfunction of the coagulation system can cause ischemia, heart failure, disorders in other organs, and even death.

The results of a retrospective cohort study revealed that abnormal PTT was significantly associated with patient mortality[9]. However, no significant relationship was found in the present study. The results of another meta-analysis study showed that no differences were found regarding the levels of PTT between two groups of patients with severe and non-severe clinical conditions, as well as surviving and deceased patients. According to meta-analysis results, PTT is unlikely to have an effect on the severity and mortality of COVID-19 patients.

This study had some limitations. First, the patient information was extracted from medical records and was not available for some variables. Second, since this study was conducted at a single center, its generalizability is limited. However, the hospital under study is a referral hospital for COVID-19 patients in Tehran, the capital of Iran.

The results of this study revealed that higher D-dimer and coagulation factor levels were associated with a lower survival among COVID-19 patients. Since thrombosis and blood clots represent serious complications of COVID-19, there is a need to diagnose these disorders early in COVID-19 patients. Therefore, it is recommended that coagulation factor tests, including D-dimer and INR levels be performed on patients who require hospitalization. Furthermore, patients with high levels of these factors should be treated with anticoagulants to reduce the risk of death.

Funding Details This project was not supported by any institution and did not receive any funding.

Conflict of Interest The authors declare no conflict

Table 3. Cox Survival analysis results

Covariates (Baseline group)	Univariable			Multivariable		
	Hazard ratio	95% *CI*	*P*-value	Hazard ratio	95% *CI*	*P*-value
Sex (female)	1.00	(0.69, 1.45)	0.900			
Age	1.02	(1.01, 1.04)	< 0.001	1.01	(1.00, 1.02)	0.004
WBC	1.02	(1.01, 1.04)	0.002	1.00	(0.97, 1.03)	0.633
INR (1.0–1.1)	2.79	(1.90, 4.09)	< 0.001	1.99	(1.30, 3.04)	0.001
PTT	1.37	(0.90, 2.09)	0.125	1.36	(0.91, 2.04)	0.102
Hospitalization (ward)	5.50	(3.65, 8.29)	< 0.001	4.69	(3.09, 7.12)	< 0.001
D-dimer (negative)	1.37	(1.12, 1.68)	0.02	1.29[†]	(1.04, 1.59)	0.010

Note. INR, international normalized ratio; PTT, prothrombin time test (seconds); WBC, white blood cells (cell per microliter). [†]Adjusted for age and sex.

of interest.

Acknowledgement The authors would like to express their deepest gratitude to the Ziaeian Hospital.

[#]Correspondence should be addressed to Isa Akbarzadeh, Tel: 98-903-601-8200, E-mail: iakbarzade@razi.tums.ac.ir; Mohammad Bidkhori, Tel: 98-990-250-7302, E-mail: Bidkhori.mohammad93@gmail.com

Biographical note of the first author: Abolfazl Zendehdel, male, born in 1979, Doctor, Associate Professor, faculty member of Tehran University of Medical Sciences, internist.

Received: June 29, 2022;

Accepted: August 29, 2022

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