Original Article

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Prolonged Elevation of D-dimer Levels In The Post-Covid-19 Period

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Abstract

Aim: D-dimer elevation is observed during acute Coronavirus disease-2019 (COVID-19) and the post- COVID-19 period. It is not known how long the D-dimer remains elevated in the post-COVID-19 period. The aim of the study was to determine how long the D-dimer level remained elevated in the post-COVID-19 period.

Methods: This study was conducted as a cross-sectional study, a type of observational study, at the University of Health Sciences Turkey, Darica Farabi Training and Research Hospital Cardiology Outpatient Clinic between March 1, 2022, and December 1, 2022. Past medical histories, examination notes, and laboratory results were extracted from standard electronic medical records. Patients were also categorized as those over 50 years old and those under 50 years old. Age-adjusted D-dimer levels were used when analyzing the D-dimer values of patients over 50 years old.

Results: Three hundred twenty two patients were included in this study. Two hundred nineteen (68%) patients were women. Two hundred twenty-three (69%) patients were under the age of 50. Elevated D-dimer levels were present in 77 (23.91%) patients, and age-adjusted elevated D-dimer levels were present in 22 (6.80%) patients. The median duration from the time the patient's reverse transcription-polymerase chain reaction (RT-PCR) test resulted in a positive result to the time of admission was 6 (1-24) months. The highest number of patient admissions to the cardiology outpatient clinic occurred in the 12th month after the RT-PCR test resulted in a positive.

Conclusion: We investigated how long the D-dimer remained elevated in the post-COVID-19 period. We examined the time distribution of D-dimer elevation and calculated age-adjusted D-dimer values. The highest number of patients whose D-dimer level was elevated on admission occurred in the 3rd-4th month after the RT-PCR test resulted positively.

Keywords: COVID-19, D-dimer, age-adjusted D-dimer level

Introduction

The World Health Organization declared Coronavirus disease-2019 (COVID-19) a pandemic on March 11, 2020 (1). Among the complaints of patients with COVID-19 are chest pain, palpitations, and shortness of breath. These cardiac complications occur both during COVID-19 treatment and after the treatment is completed. COVID-19 can directly cause cardiac and vascular injuries. These conditions are arrhythmias, heart failure, myocarditis, pericarditis, myocardial infarction, and thromboembolic events (2). Several previous studies have shown that patients with acute COVID-19 are in a hypercoagulable state and therefore have an increased risk of adverse thromboembolic events (3-5). Elevated D-dimer levels are associated with worse clinical outcomes, such as deep vein thrombosis and pulmonary embolism (6,7). D-dimer levels increase during COVID-19.

How long the D-dimer level remains elevated in these patients after the initial diagnosis is unknown. There is no consensus on how long anticoagulant therapy should be administered to patients. In this study, our aim was to determine when patients apply to the cardiology outpatient clinic after an initial diagnosis of COVID-19 and how long the D-dimer level stays elevated in the post COVID-19 period.

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Methods

Compliance with Ethical Standards

Permission for the research was obtained from the Ministry of Health of the Republic of Turkey. Approval was obtained from the Clinical Studies Ethics Committee of Kocaeli Derince Training and Research Hospital (approval number: 2022/6; approval date: February 24, 2022). This study was conducted at the University of Health Sciences Turkey, Darica Farabi Training and Research Hospital Cardiology Outpatient Clinic. The study was conducted between March 1, 2022, and December 1, 2022. The study was conducted in accordance with the rules of the Declaration of Helsinki.

Study Design

This study was conducted as a cross-sectional study, a type of observational study. Past medical histories, examination notes, and laboratory results were extracted from standard electronic medical records. Demographic features of the patients age, gender, chronic diseases [diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), documented coronary artery disease (CAD)], impaired fasting glucose, atrial fibrillation, mitral valve prolapse, bicuspid aorta, rheumatic valve disease, hypothyroidism, hyperthyroidism, and metallic valve prosthesis were recorded. Laboratory findings, i.e., D-dimer, C-reactive protein (CRP), high-sensitive cardiac troponin T, hemoglobin, white blood cells, creatinine, alanine aminotransferase, thyroid stimulating hormone, thyroxine, low-density lipoprotein, triglyceride, N terminal pro B type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR) were recorded on admission, and they were evaluated as normal or abnormal according to the reference range of the laboratory assays. Estimated glomerular filtration rate was assessed by the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). The CKD-EPI was calculated electronically using age, gender, and race parameters. An eGFR under 60 mL/min/1.73 m^2 was defined as chronic renal failure. Anemia was defined as a hemoglobin level below 12.0 g/dL in women and <13.0 g/dL in men. If the plasma fasting glucose was between 100 and 126 mg/dL, it was defined as impaired plasma fasting glucose. Patients were also categorized as those over 50 years old and those under 50 years old. To discuss the D-dimer elevation in patients over 50 years of age, we used age-adjusted D-dimer levels. The patients whose D-dimer level was above the cut-off value according to age-adjusted D-dimer level at the time of admission were determined.

Electrocardiography (ECG) was performed by cardiology outpatient clinic nurses. Normal sinus rhythm and atrial fibrillation were recorded on the ECGs of the patients. Transthoracic echocardiography was conducted by the cardiologists at the Cardiology Outpatient Clinic. The left ventricular ejection fraction (LVEF) was recorded. LVEF below 50% was defined as systolic heart failure.

A chest contrast-enhanced computed tomography (CT) angiography scan was performed in the pulmonary phase in patients with severe dyspnea, tachycardia, and high D-dimer levels. The reports were interpreted by the radiology department.

Inclusion Criteria

Patients over the age of 18, who applied to the cardiology outpatient clinic between January 3, 2021, and December 31, 2021, had a positive RT-PCR test, completed COVID-19 treatment, wanted to have a heart control, or had heart complaints such as chest pain, shortness of breath, palpitations, backache, and fatigue, were included in the study. The patients were consecutively included in the study.

Exclusion Criteria

Patients under 18 years of age, hospitalized patients, patients with systolic heart failure, acute renal failure, chronic kidney disease, patients on hemodialysis or peritoneal dialysis, pregnant women, patients with acute deep vein thrombosis, chronic deep vein thrombosis, acute pulmonary embolism, chronic pulmonary embolism, patients with known coagulation disorders, pneumonia, urinary tract infections, and other system infections were excluded from the study.

Statistical Analysis

The statistical analyses were performed using SPSS software (version 26.0, SPSS Inc., Chicago, IL, USA). The normality of the parameters was assessed by the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median [interquartile range (IQR)] where appropriate. Categorical variables were expressed as numbers and percentages.

Results

Consecutively, 322 adult patients diagnosed with COVID-19 with RT-PCR positivity and admitted to the Cardiology Outpatient Clinic after completion of COVID-19 treatment were included in the study. Of the patients, 219 (68%) were women and 103 (32%) were men. Of the patients, 223 (69%) were under 50 years old, and 99 (31%) were over 50 years old. Of the patients over 50 years of age, 59 (59.6%) were women and 40 (40.4%) were men. The median age was 44 (18-92) years. The accompanying comorbidities of all the patients were as follows: DM 48 (14.90%), HT 65 (20.2%), HL 62 (19.30%), CAD 31 (9.60%), impaired

fasting plasma glucose 79 (24.50%), atrial fibrillation 11 (3.40%), metallic valve prosthesis 1 (0.003%), bicuspid aorta 2 (0.006%), rheumatic valve disease 1 (0.003%), hypothyroidism 3 (0.009%), hyperthyroidism 3 (0.009%) (Table 1).

Table 1. Basic clinical characteristics of the patients	
The total number of patients	322
>50-year patients (n) (%)	99 (30)
Gender (female/male) (n) (%)	219/103 (68/32)
Age (median) (IQR) years	44 (18-92)
>50 years (female/male) (n) (%)	59/40 (59.60/40.40)
Follow-up (median) (IQR) months	6 (1-24)
Hypertension (n) (%)	65 (20.2)
Diabetes mellitus (n) (%)	48 (14.90)
Hyperlipidemia (n) (%)	62 (19.30)
Coronary artery disease (n) (%)	31 (9.60)
Impaired fasting glucose (n) (%)	79 (24.50)
Atrial fibrillation (n) (%)	11 (3.40)
Mitral valve prolapse (n) (%)	1 (0.003)
Bicuspid aorta (n) (%)	2 (0.006)
Rheumatic valve disease (n) (%)	1 (0.003)
Hypothyroidism (n) (%)	3 (0.009)
Hyperthyroidism (n) (%)	3 (0.009)
Metallic valve prosthesis n (%)	4 (1.20)
n: Number, IQR: Interquartile range	

Laboratory findings of the patients on admission are shown in Table 2. Elevated hs-cTn was present in 3 (0.90%) patients; elevated NT-proBNP was present in 11 (3.40) patients; elevated D-dimer was present in 77 (23.90%) patients; and age-adjusted elevated D-dimer was present in 22 (6.80%). A chest contrast-enhanced CT angiography scan was performed in 12 patients. A pulmonary embolism was not found in any patient.

Figure 1 shows the frequency of application and the months after the initial diagnosis. Figure 2 shows the distribution of patients by month, and Figure 3 shows the distribution of patients by month.

Discussion

In this study, we included adult patients diagnosed with COVID-19 with RT-PCR positivity and admitted to the cardiology outpatient clinic after completion of COVID-19 treatment for cardiac control or due to cardiac complaints. The majority of patients were female and under 50 years of age.

When the literature is reviewed, it is seen that HT and DM are the leading chronic diseases accompanying COVID-19. However, in our study, the most common co-morbidity was impaired fasting plasma glucose, seen in

Table 2. Laboratory findings of the patients on admission		
Glucose (mg/dL) median (IQR)	97.00 (73.00-495.00)	74-106 mg/dL
Creatinine (mg/dL) median (IQR)	0.70 (0.17-1.26)	0.5-0.9 mg/dL
Glomerular filtration rate (mL/min/1.73 m²) median (IQR)	106 (61-157)	-
Alanine aminotransferase (U/L) median (IQR)	17.50 (6-95)	0-33 U/L
CRP (mg/L) median (IQR)	2.60 (0.14-39.30)	0-5 mg/L
Thyroid stimulating hormone (mIU/L) median (IQR)	1.57 (0.07-34.91)	0.35-4.94 mIU/L
Thyroxine (T4) (ng/dL) median (IQR)	0.96 (0.61-1.92)	0.70-1.48 ng/dL
White blood count (10^3/mL) median (IQR)	6.69 (0.32-14.30)	3.98-10.04 10^3/mL
Hemoglobin (g/dL) means SD	13.18 1.66	11.7-16.0 g/dL
High sensitive cardiac troponin T (ng/L) median (IQR)	1.00 (1.00-66.00)	0-14 ng/L
D-dimer (mg/mL) median (IQR)	0.31 (0.10-4.51)	0-0.5 µg/mL
Age-adjusted D-dimer (mg/mL) median (IQR)	1.24 (0.55-3.40)	>0.50
NT-proBNP (pg/mL) median (IQR)	14.50 (5.00-2176.00)	0-125 pg/mL
Low-density lipoprotein mg/dl means SD	124±35.97	0-130 mg/dL
Triglyceride mg/dl median (IQR)	123 (33-729)	0-150 mg/dL
Ejection fraction percentage median (IQR)	60 (50-65)	50-72
Anemia n (%)	23 (17.40)	
Elevated D-dimer n (%)	77 (23.90)	
Age-adjusted elevated D-dimer n (%)	22 (6.80)	
Elevated high sensitive cardiac troponin T n (%)	3 (0.90)	
Elevated NT-ProBNP n (%)	11 (3.40)	
bpm: Beats per minute, IQR: Interquartile range, n: Number, SD: Standard deviation, mg/dL: Milligram/deciliter, pg/mL: Picogram/milliliter, NT-proBNP: N terminal Pro B type natriuretic peptide, CRP: C-reactive protein, ng/L: Nanogram/liter, U/L: Unit/liter		

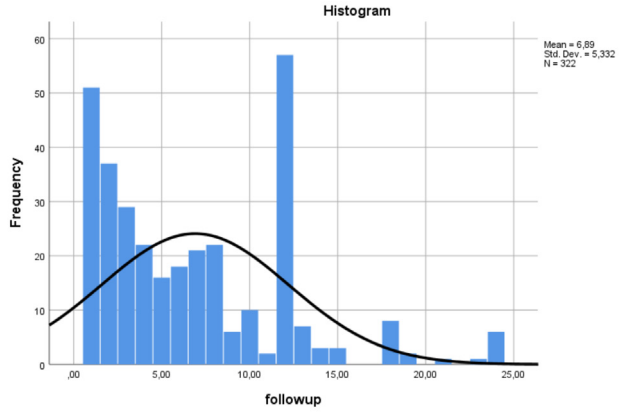

Figure 1. Distribution of all patients by month

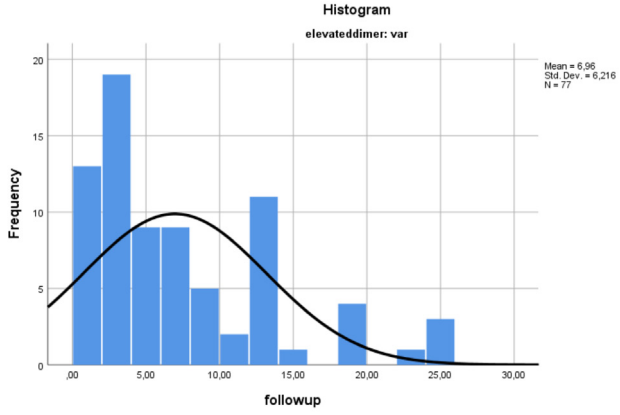

Figure 2. Distribution of all patients with elevated D-dimer values by months

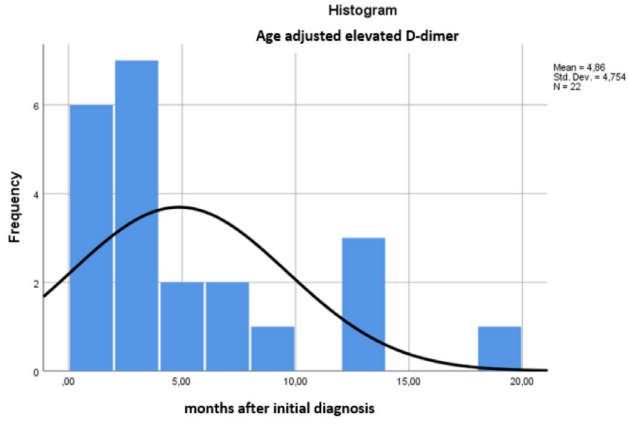

Figure 3. Distribution of patients over 50 years of age with elevated D-dimer values by months

79 (24.50%) patients. In the literature, few articles have examined the relationship between COVID-19 and plasma glucose. Huang et al. (8) found a relationship between plasma fasting glucose and mortality in a study they conducted on non-diabetic patients. Cai et al. (9) found that patients with DM with COVID-19 had a worse prognosis. Alahmad et al. (10) found a correlation between the increase in fasting plasma glucose and follow-up in the intensive care unit.

Anticoagulants are used in the treatment because there is a predisposition to coagulopathy in this disease (11-14). Elevated D-dimer as an independent predictor for mortality and complications (15). There are many articles showing the relationship between D-dimer level and morbidity. However, there are very few studies studying how long the D-dimer level stays high. Townsend et al. (16) conducted a study involving 150 patients. They followed the patients for a median of 80 days. Elevated D-dimer levels were observed in 25.30% of patients up to four months after the initial diagnosis. Compared to this study, the number of patients in our study was higher, and the proportion of women participating was higher (56.7% vs. 68%). The elevated D-dimer ratio was similar (25.30% vs. 23.90%), and the mean age of the study participants was similar (47.3 vs. 44 years), but the age-adjusted D-dimer was not mentioned in this study either.

Meisinger et al. (17) conducted a study with similar issues. A total of 411 participants (178 males, or 43.3%) were included in the study, with a mean age of 46.8 years. Sixty-one patients (15%) showed increased plasma D-dimer concentrations (≥500 µg/L) after a median of 255 days after the acute infection; of these, 17 individuals had even higher D-dimer values ≥1000 µg/L. Compared to this study, the number of patients was higher, the proportion of men participating was higher (43.3% vs. 32%), and the elevated D-dimer ratio was lower (15% vs. 23.90%). The mean age of the study participants was similar (46.8 vs. 44 years). Age-adjusted D-dimer was not mentioned in this study either.

Lehmann et al. (18) measured D-dimer values 3 months after hospitalization in patients recovering from COVID-19. They included 129 patients (median age 48.8 years; range 19-91 years) in this study. They evaluated D-dimer levels after a median (IQR) of 94 days (64-130) following COVID-19. D-dimer elevation was found in 15% (19/129) and was significantly more common in patients who had experienced a severe severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection that required hospitalization compared with patients with mild disease (p=0.049). The number of patients in this study was less than in our study (129

vs. 322), and the elevated D-dimer ratio was lower than in our study (15% vs. 23.90%). However, this study was a prospective study. They detected acute pulmonary embolism in one patient and chronic thromboembolic pulmonary HT in another.

In our study, the highest number of patients admitted to the cardiology outpatient clinic occurred in the 12th month after the post-SARS-CoV-2 infection. We attributed this result to the continuation of the pandemic and increased knowledge about the cardiac effects of COVID-19. Television, the media, and the internet contributed positively to the increase in awareness of pandemics. When Figures 2 and 3 are examined, it is observed that the D-dimer level decreases after the 3rd and 4th months. It is noteworthy that there was an increase again in the 12th month. The reasons for this increase are: 1) The highest number of applications was made in the 12th month; 2) Patients may be infected with SARS-CoV-2 again one year later, but they are not aware of the situation because RT-PCR testing is not done; 3) Most of the patients are vaccinated; they remain asymptomatic in case of re-infection, but the inflammatory process continues in the body.

In our study, we examined both the time distribution of patients on admission and the time distribution of D-dimer elevation. When similar studies in the literature were examined, there was no study that made a detailed examination like ours. It is unclear in which month the patients applied for these studies. On the other hand, in our study, we determined how many patients applied in which month and in which month the D-dimer of the patients was high. When other studies in the literature were examined, figurative scatter plots were not found.

In addition, we calculated age-adjusted D-dimer values in our study. When other studies in the literature were examined, it was seen that the age-adjusted D-dimer level was not calculated. While D-dimer elevation was detected in 77 (23.9%) of the patients included in our study, only 22 (6.80%) patients had age-adjusted D-dimer elevation. Thanks to this corrected calculation, unnecessary coagulopathy research was avoided. In addition, unnecessary anticoagulant treatment was prevented.

Patients who apply to the hospital with complaints such as weakness, malaise, and shortness of breath in the post-COVID-19 period should be evaluated for long-term COVID. Discussions continue about the duration of thromboprophylaxis after discharge in long-term COVID cases. Anticoagulant therapy should be given to patients with high D-dimer values (19).

We detected elevated hs-cTn levels in 3 (0.90%) patients. None of the patients with high troponin levels had an acute coronary syndrome. Troponin-level increases may occur in conditions other than acute coronary syndrome (20). The common feature of the three patients with high troponin in this study was that they were hypertensive.

We detected elevated NT-proBNP levels in 11 (3.40%) patients. N terminal pro B type natriuretic peptide levels increase in heart failure (21), chronic kidney disease (22), and cirrhosis (23). We did not include patients with these diseases in our study. Therefore, elevated NT-proBNP levels cannot be attributed to these diseases.

Study Limitations

This study has several limitations. First, our study might have had selection bias because it was a single-center and retrospective study. Second, inpatients and outpatients were not compared. Despite these weaknesses, we examined how many months after the positive RT-PCR test patients came to the control and in which months the D-dimer value was high. We used age-adjusted D-dimer levels when analyzing the D-dimer values of patients over 50 years old. There was no study in the literature that was designed in this way before.

Conclusion

In our study, we found that the highest rate of D-dimer elevation was in the 3rd and 4th months of the post-COVID-19 period. The D-dimer level should be studied in patients who have experienced COVID-19 and applied to the Cardiology Outpatient Clinic with chest pain, shortness of breath, palpitation, fatigue, and weakness. Individuals over the age of 50 should be evaluated separately. Patients may have a long-term COVID-19 status as well as the possibility of re-infection. Reverse transcription-polymerase chain reaction can be performed in these patients, and a chest contrast-enhanced CT angiography scan can be performed in patients with severe symptoms. Anticoagulant therapy should be given to patients with elevated D-dimer levels.

Ethics

Ethics Committee Approval: Permission for the research was obtained from the Ministry of Health of the Republic of Turkey. Approval was obtained from the Clinical Studies Ethics Committee of Kocaeli Derince Training and Research Hospital (approval number: 2022/6; approval date: February 24, 2022).

Informed Consent: Informed consent from was not obtained because it was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A., E.G., Design: G.A., E.G., Data Collection or Processing: G.A., E.G., Analysis or Interpretation: G.A., E.G., Literature Search: G.A., E.G., Writing: G.A., E.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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