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ORIGINAL ARTICLE

Relationship between Serum Homocysteine Levels and Mortality in Vaccinated and Unvaccinated COVID-19 Patients

Aşılı ve Aşısız COVID-19 Hastalarında Serum Homosistein Düzeyleri ve Mortalite Arasındaki İlişki

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Abstract

Introduction: The aim of this study is to evaluate the difference in homocysteine levels between vaccinated and unvaccinated patients and determine the relationship between blood homocysteine levels and prognosis in hospitalized patients due to COVID-19.

Methods: This retrospective study was carried out in our hospital on 50 patients, 19 (38%) males and 31 (62%) females, who were hospitalized due to COVID-19. The patients were divided into two groups: vaccinated and unvaccinated. White blood cell count, lymphocyte count, C-reactive protein, D-dimer levels, and homocysteine levels taken at the time of hospitalization of the patients included in the study were evaluated.

Results: The mean age of all patients included in the study was 66.1±16.16 years. Of the included patients, 22 (44%) were vaccinated and 28 (56%) were unvaccinated. As a clinical prognosis, 32 patients (64%) were followed up in the ward. Twelve (24%) patients were intubated and discharged after treatment. However, 6 (12%) patients were intubated and unfortunately died. Six of the patients included in the study were mortal. Among these patients, 1 was vaccinated and 5 were not vaccinated. The mean D-dimer level of these patients was 965.16±544.39. All expired patients were hyperhomocysteinemic, and the mean homocysteine levels were 18.18±5.8 µmol/L in this group.

Discussion and Conclusion: Although D-dimer was found to be significantly higher at the time of admission to the hospital in unvaccinated individuals, there was no significant difference in blood homocysteine levels between vaccinated and unvaccinated COVID-19 patients.

Keywords: COVID-19; Homocysteine; Vaccine

COVID-19 is a pandemic that has resulted in high mortality and morbidity worldwide. Although it mostly causes lung damage and hospitalizations due to hypoxia, vascular damage and related serious complications are also frequently seen in the course of the disease. Unfortunately, an inexpensive and effective treatment has not yet been developed. For this reason, prevention of the disease has come to the fore and vaccines have been developed.[1,2]

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Since the beginning of the COVID-19 pandemic, biomarkers showing disease severity, mortality, and complications continue to be investigated. In this regard, laboratory data such as D-dimer, platelet count, and neutrophil–lymphocyte ratio were evaluated, but highly sufficient and reliable results could not be achieved.[3] To predict the severity and mortality of COVID-19, the level of biochemical parameters such as white blood cell (WBC) count, lymphocyte count, C-reactive protein (CRP) level, lactate dehydrogenase, creatine kinase, and troponin are to be closely monitored in treated patients.[4,5] Homocysteine, which is mainly followed in the course of cardiovascular diseases and known to be closely related to thrombosis, is one of the biomarkers that has been recently researched to show the severity of COVID-19 disease and to predict complications and mortality.[6]

If acute respiratory distress syndrome occurs in patients followed up for COVID-19, cytokine storm and oxidative stress may occur in the course of this disease.[7] Homocysteine is an intermediate in the trans-sulfuration pathway. Studies in chronic diseases showed that oxidative stress causes a decrease in S-adenosylmethionine and an increase in homocysteine levels.[8] In addition, rapid viral replication in RNA virus infections affects methyltransferase activity and may lead to impaired coordination between remethylation and trans-sulfuration reactions.[9] Hyperhomocysteinemia occurs by this mechanism in RNA virus infections.[10]

The aim of this study is to evaluate the difference in homocysteine levels between vaccinated and unvaccinated patients and determine the relationship between blood homocysteine levels and prognosis in hospitalized patients due to COVID-19.

Materials and Methods

This retrospective study was carried out by scanning the files of a total of 50 patients, 19 (38%) males and 31 (62%) females, who were hospitalized in our university hospital due to COVID-19 between August 2021 and February 2022. University ethics committee approval was obtained with serial number 2021017. This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practices guidelines.

The diagnosis of COVID-19 of each patient included in the study was performed by taking a nasopharyngeal swab with real-time PCR method. The patients were divided into two groups: vaccinated and unvaccinated. Patients in the vaccinated group received at least 2 doses of Pfizer-BioNTech vaccine, and at least 3 weeks had passed between the disease and the vaccine. The same treatment protocol approved by the scientific committee was applied to all hospitalized patients. WBC count, lymphocyte count, CRP, D-dimer levels, and homocysteine levels taken at the time of hospitalization of the patients included in the study were evaluated. Homocysteine levels and other biochemical parameters were studied by Roche Hitachi Cobas 601 (Switzerland) device. Homocysteine level > 15 µmol/L was considered as hyperhomocysteinemia. The patients' smoking history and the presence of chronic diseases such as hypertension, diabetes mellitus, and hyperlipidemia were recorded.

Each patient included in the study had a lung tomography and was graded according to the CO-RADS (A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19) classification system. In addition to radiological imaging, patients were divided into three groups according to their clinical prognosis. The first group consisted of patients with minimal oxygen need and followed up in the ward, the second group consisted of patients followed in the intensive care unit and intubated due to high oxygen demand, and the last group consisted of patients who died due to COVID-19.

Patients under the age of 18 years, patients with known hyperhomocysteinemia, patients taking antiagregan and/or anticoagulant treatments due to coagulation disorder, pregnant women, and patients with known malignancies were not included in the study. All patients diagnosed with COVID-19 and did not meet the exclusion criteria and had an indication for hospitalization were included in the study.

Statistical Analysis

All data were analyzed by the computer software program SPSS, version 20 (SPSS, Inc., Chicago, IL, USA, 2016). Results were reported as mean±standard deviation. Group analyses were made with Pearson's Chi-squared test. Within- and between-group differences were analyzed by Student's paired and unpaired t-tests. A value of $p<0.05$ was considered statistically significant.

Results

The mean age of all patients included in the study was 66.1±16.16 years. Of the included patients, 22 (44%) were vaccinated and 28 (56%) were unvaccinated. As a clinical prognosis, 32 patients (64%) were followed up in the ward. Twelve (24%) patients were intubated and discharged after treatment. However, 6 (12%) patients were intubated and unfortunately died. When the CO-RADS scores of the patients were compared according to their vaccination status, no significant difference was found ($p=0.139$). In addition, when the patients were divided into groups according to their CO-RADS scores, no significant difference was found

Table 1. Demographic data of the patients included in the study

Features	Vaccinated group (n=22)	Unvaccinated group (n=28)	p
Age (years)	66.54±13.85	65.75±18.01	0.275
Gender (F/M)	13/9	18/10	0.774
Coronary artery disease (present)	12	20	0.174
Smoking history	2	11	0.61

F: Female; M: Male.

Table 2. Laboratory and clinical characteristics of vaccinated and unvaccinated patients

Features	Vaccinated group (n=22)	Unvaccinated group (n = 28)	p
Lymphocyte count (10^3 μL^{-1})	1.28±0.67	1.36±0.68	0.603
Homocysteine (µmol/L)	14.99±7.19	15.03±6.22	0.120
Ferritin (ng/mL)	455.13±87.65	384.42±92.91	0.882
Platelet count (10^3 μL^{-1})	172±64	268±77	0.153
D-dimer level	475.40±393.19	1124.14±832.49	0.000
CRP (mg/L)	69.35±71.38	54.25±63.66	0.363
Number of intubated patients	5 (22.7%)	7 (25%)	0.440

CRP: C-reactive protein.

between groups regarding homocysteine and D-dimer levels (p=0.865 and p=0.550).

The demographic data of the patients included in the study are shown in Table 1.

Six of the patients included in the study were mortal. Among these patients, 1 was vaccinated and 5 were not vaccinated. All patients who died had comorbid diseases. While 1 patient died due to heart attack, the remaining 5 patients died due to respiratory failure. The mean age of the expired patients was 71.5±8.4 years. The mean D-dimer level of these patients was 965.16±544.39. All expired patients were hyperhomocysteinemic, and the mean homocysteine levels were 18.18±5.8 µmol/L in this group.

The laboratory and clinical characteristics of vaccinated and unvaccinated patients are shown in Table 2.

Discussion

This study was conducted to determine the importance of homocysteine in determining the prognosis and the effect of vaccines on homocysteine level in advanced age inpatients with severe COVID-19. We determined that the average D-dimer level was significantly higher in unvaccinated participants.

Like any other vaccines, vaccines used for the COVID-19 pandemic also have side effects. The most reported side effects related to the vaccine are known as local tenderness, fever, and headache.[11] D-dimer elevation and thromboembolic events may also occur due to the vaccine.[12] Generally, thromboembolic events, d-dimer elevation, and serious adverse reactions are seen in women, young people, and people who have had COVID-19 before, and they occur within an average of 2 weeks after vaccination. In our study, at least 3 weeks had passed between the COVID-19 vaccine and the hospital admission of the cases. In addition, elderly patients predominate in our study. Coronary artery disease was detected in only 1 unvaccinated patient, and this patient also died.

Studies have shown that high homocysteine levels cause damage to both small and large vessels.[13] In COVID-19 patients, blood D-dimer levels may be high due to both the destruction of the pulmonary vascular bed and the resulting hypoxic damage. However, its importance in determining the prognosis before this damage occurs in the early period is not clear. It has also been shown in a previous study that metabolic pathways, including homocysteine, activate the angiotensin 2 type 1 receptor.[14] Todua et al.[15] found a significant correlation between D-dimer levels and homocysteine levels in patients with pulmonary arterial thromboembolism. On the other hand, in our study, no significant correlation was found between D-dimer levels and homocysteine levels (r=0.076, p=0.602).

A recent study conducted in China showed that high blood homocysteine level may be an indicator of severe lung involvement.[16] In parallel with this, Ponti et al.[17] suggested that homocysteine may be a useful biomarker to predict mortality in hospitalized patients in a retrospective study. Similarly, Keskin et al.[18] suggested that homocysteine level is an important biomarker in the follow-up of COVID-19 patients. As it is known, methylene tetrahydrofolate reductase (MTHFR) polymorphism is accompanied by high homocysteine levels. In studies conducted in different populations, a positive correlation was found between MTHFR genetic polymorphism and the severity of COVID-19 infection. In addition, in these studies, it has been suggested that administering B12 and folic acid replacement to MTHFR mutant patients and administering treatments that reduce homocysteine levels may be beneficial for patients.[19] In our study, all 5 patients who died were having hyperhomocysteinemia. When the vaccinated and unvaccinated groups were compared, no statistically significant difference was found although homocysteine levels were higher in the unvaccinated group.

There are some limitations of the study. The main limitation is that the number of patients included in the study was low. Second, some other factors may also affect serum homocysteine levels.

As a result, although D-dimer was found to be significantly higher at the time of admission to the hospital in unvaccinated individuals, there was no significant difference in blood homocysteine levels between vaccinated or unvaccinated COVID-19 patients. Larger studies are needed to show the relationship between vaccine and homocysteine.

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