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ORIGINAL ARTICLE

Blood prestin levels in COVID-19 patients

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Abstract

Background: Many studies have found that viral infections affect different tissues, including the inner ear. Coronavirus disease 2019 (COVID-19), a viral infection, is a significant health problem worldwide. Prestin is a motor protein with important functions both in the outer hair cells of the inner ear and in cardiac tissue. In addition, prestin is promising as an early biomarker in the detection of ototoxicity. To determine the severity of infection in COVID-19 patients and to determine whether other tissues are affected by the infection, lactate dehydrogenase (LDH), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase MB (CK-MB), biochemical markers such as ferritin and D-dimer are used. This study aimed to compare prestin levels in patients with COVID-19 and healthy volunteers.

Methods: In blood samples taken from 45 patients diagnosed with COVID-19 and 40 healthy volunteers, prestin levels were determined with the kit that used an enzyme-linked immunosorbent assay method and was commercially available. At the same time, LDH, CRP, ALT, AST, CK-MB, ferritin, and D-dimer levels were also detected in both patients and healthy control groups and correlations with prestin levels were examined.

Results: The main result of our study is that serum prestin levels in COVID-19 patients are significantly higher than in healthy controls ($p < 0.001$). In addition, a statistically significant strong positive correlation was found between prestin-LDL ($r = 0.537$, $p = 0.001$), prestin-CRP ($r = 0.654$, $p = 0.001$), and prestin-D-dimer ($r = 0.659$, $p = 0.001$).

Conclusion: The levels of prestin, a motor protein in inner ear outer hair cells and cardiac myocytes, were found to be higher in COVID-19 patients than in healthy volunteers. It also showed a positive correlation with CRP and D-dimer. This may be associated with systemic dysfunction.

Keywords: Cardiac myocytes; Cochlear outer hair cells; COVID-19; Prestin

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a severe infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After the first case was reported in Wuhan, China, in December 2019, cases began to be seen worldwide, and a few months later, COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[1] From the first case to the present day, more than 5.5 million people have died due to COVID-19.[2] COVID-19 is characterized by an abnormal host immune response that causes an extreme inflammatory response or cytokine storm.[3] It has been reported to cause multiple-organ failure, especially in the respiratory system.[4] Effective vaccines have been developed for COVID-19, but variants have emerged over time due to mutations, so its virulence continues.

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Although COVID-19 is a respiratory infection, it has been reported to affect many different tissues, such as the liver, kidney, central nervous system, gastrointestinal system, and ear.[5,6] For example, it has been reported to induce myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism.[7] Cases of COVID-19 with sudden hearing loss (SHL) have been reported.[8,9] After these reports, it was thought that infection caused by SARS-CoV-2 might have an effect on hearing function. In addition to SHL, tinnitus, gingivitis, Bell's palsy and hoarseness have been seen in COVID-19 patients.[10] Viral infections of the inner ear often cause outer hair cell (OHC) damage and related disorders. In addition, it has been reported that in experimental animal models infected with the virus, OHCs are damaged and lost, and fibrosis occurs in the tympani and vestibule, which can cause hearing loss.[11]

Prestin (SLC26A5) is a volta-sensitive membrane protein with a molecular range of 81 kDa produced in OHCs.[12] Prestin is located on the lateral wall of OHCs and is responsible for the electromethylity of these cells.[13] Previous studies presented evidence that prestin is a protein associated with OHC function.[14,15] Although the expression of the gene responsible for the synthesis of prestin was investigated in most of the studies, prestin can also be observed in the blood circulation of humans and animals.[16,17] Prestin levels in the blood can be determined by the enzyme-linked immunosorbent assay (ELISA) method, and with this method, changes in the concentration of prestin that occur, even with less than 1% OHC loss, can be detected.[18] In

later studies, it was hypothesized that prestin levels in the blood could be a serum biomarker that can be used for the evaluation OHC function, but a recent study reported that prestin increases actin-myosin force production in mouse and human cardiac myocytes.[19–21] In addition, the role of prestin as an early biomarker of ototoxicity was suggested by different researchers.[16,22,23] Therefore, it may be possible to relate changes in the blood prestin level to its function in OHCs and cardiomyocytes.

Some biochemical blood biomarkers are used in the follow-up and determination of the severity of COVID-19 disease.[24] Among these is C-reactive protein (CRP), a nonspecific marker of inflammation.[25] In COVID-19 patients, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are important biochemical markers used to evaluate liver function, and creatinine kinase MB (CK-MB) and lactate dehydrogenase (LDH) are used to evaluate cardiac function.[26,27] D-dimer is also one of the important biomarkers for determination of the coagulation status of COVID-19 patients.[28] Lung involvement is one of the most important indicators of COVID-19 infection severity; however, CRP and D-dimer have also been shown in previous studies to be important markers of COVID-19 infection severity.[29,30]

In this study, prestin levels were determined and compared in COVID-19 patients and a healthy control group. In addition, the levels of LDH, CRP, ALT, AST, CK-MB, ferritin, and D-dimer analytes, which are used in the evaluation of infection status, as well as liver and heart function, were examined in our study.

2. METHODS

2.1. Study population

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Van Yuzuncu Yil (protocol number: 31.03.2021-10). We obtained an informed consent form from all patients and healthy volunteers. Patients were diagnosed by reverse transcription-polymerase chain reaction (RT-PCR) from oral or nasopharyngeal swab samples taken using the correct technique.

Individuals who did not have any chronic or acute diseases such as diabetes, kidney failure, cardiovascular diseases, etc, who had not been hospitalized for any reason in the last six months, and who did not have hearing loss or any diseases related to the ear, such as acute and chronic otitis media, otosclerosis, etc, were included in the healthy control group. Individuals in the age range mentioned above who did not have comorbidities such as diabetes, COPD, cancer, kidney failure, etc, and who did not have a hearing loss complaint nor ear-related disease were included in the COVID-19 patient group.

2.2. Measurement of prestin levels

Following the diagnosis of COVID-19 patients, 3-mL blood samples were taken in dry serum tubes before initiation of treatment. Blood samples of the same volume were also taken from healthy volunteers. Serum samples were obtained by centrifugation at 3500*g* for 15 minutes. All serum samples were stored at –80°C until further processing.

Prestin levels were determined with commercially available kits using the ELISA method (Human Prestin ELISA kit from BT Lab, Zhejiang, China) (Cat. No: E4170hu). Prestin concentrations were determined in accordance with the protocol specified by the manufacturer in the kit manual. First, 40 µL of serum samples were added to the wells, and then 10 µL of anti-PRES antibody was added to the sample wells. To the sample and standard wells was added 50 µL of Streptavidin-horseradish peroxidase (HRP). After the mixture was incubated at 37°C for 1 hour, the wells were washed with the washing solution. To all wells were added 50 µL of solution A and 50 µL of solution B, and the plates were incubated at 37°C for 10 minutes. After incubation, 50 µL of stop solution was added, and the absorbance of the final mixture at 450 nm was determined. Results were expressed as pg/mL. The limit of detection was 100 to 1600 pg/mL, and the sensitivity was 4.87 pg/mL.

2.3. Measurement of routine biochemical parameters

The serum LDH, ferritin, AST, ALT, and CK-MB levels were detected with an Abbott architect c16000 autoanalyzer (Abbott Diagnostics Inc, Park City, IL, USA). The CRP levels were determined by the turbidimetric method in the same autoanalyzer.

2.4. Statistical analysis

The G-Power 3.1 package program was used to calculate the sample size. The sample size of each group was calculated as 40 for an effect size of 0.6, power of 0.85 and type 1 error value 0.05. All statistical analyses were performed using Analyze-it software (Analyse-it Software, Ltd., Leeds, United Kingdom) and the IBM-SPPS 23 package statistical program (IBM Corp., Armonk, NY, USA). It was determined via the Kolmogorov-Smirnov test that the data were not normally distributed. Data that did not show a normal distribution were expressed as median and interquartile range (IQR), while data with a normal distribution were expressed as mean ± SD. The chi-square test was used in the analyses of categorical data. An independent-sample *t* test was used for comparisons between groups for data showing a normal distribution. The Mann–Whitney *U* test was used for group comparison for data not showing a normal distribution. Correlations were determined by Spearman correlation analyses. A $p < 0.05$ was considered statistically significant.

3. RESULTS

A total of 45 COVID-19 patients, 20 males and 25 females, aged between 21 and 65 years, who applied to the COVID-19 outpatient clinic between June and December 2021, and apparently healthy volunteers (18 male and 22 female), whose age range was similar to that of the patients, were included in the study. When we investigated age and gender results, there was no statistically significant difference between COVID-19 patients and healthy control groups in terms of gender and age (Table 1) ($p = 0.321$ and $p = 0.841$, respectively).

The levels of LDH, CRP, ferritin, and D-dimer in the COVID-19 patient group were statistically significantly higher than those in the healthy control group. There was no statistically significant difference between the COVID-19 patient and healthy control groups regarding ALT, AST, and CK-MB levels. The level of prestin in the COVID-19 patient group was statistically significantly higher than those in the healthy control group (Fig. 1). All results are summarized in Table 1.

In the correlation analyses, we determined significant positive correlations among prestin-LDH (Fig. 2), prestin-CRP (Fig. 3), and prestin-D-dimer (Fig. 4) levels. The correlation analyses are summarized in Table 2.

4. DISCUSSION

Our investigation determined significantly higher prestin levels in the COVID-19 patient group than in healthy controls. Zhang et al[21] reported on the presence of prestin expression in heart tissue and also noted significant changes in cardiac contractility in prestin knockout mice. The results of their study show that while prestin was previously considered specific to the OHCs of the inner ear, prestin serves a broader cellular motor function.[21] There are studies showing that cardiac function is impaired in patients with COVID-19. Bailey et al[31] reported cardiomyocyte

Table 1

The result of biochemical parameters and prestin in both groups

	COVID-19 patient group (n = 45) (median [IQR])	Healthy control group (n = 40) (median [IQR])	Difference of median	*p*
F/M	20/25	18/22	-	0.841
Age	52 (33–63)	50 (32–64)	–2	0.321
LDH (U/L)	434,9 (340.3–519.9)	160.1 (145.7–198.6)	–274.8	0.001
CRP (mg/mL)	63.6 (31.7–137)	3 (2.42–3.7)	–60.6	0.001
ALT (U/L)	33 (16–43)	28.4 (21.9–32.8)	–4.6	0.402
AST (U/L)	35.9 (26.3–54.8)	34.7 (29.1–46.1)	–1.2	0.799
CK-MB (U/L)	14.6 (11.9–23.2)	14.5 (12.1–16.4)	–0.1	0.305
Ferritin (ng/mL)	396.7 (240.8–975.3)	179.9 (134.9–205.4)	–216.8	0.001
D-Dimer (μg/mL)	1.65 (0.84–2.72)	0.17 (0.12–0.25)	–1.48	0.001
Prestin (pg/mL)	520.4 (479.8–577.5)	269.3 (168.1–341.7)	–251.1	0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK-MB = creatinine kinase MB; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; IQR = interquartile range; LDH = lactate dehydrogenase.

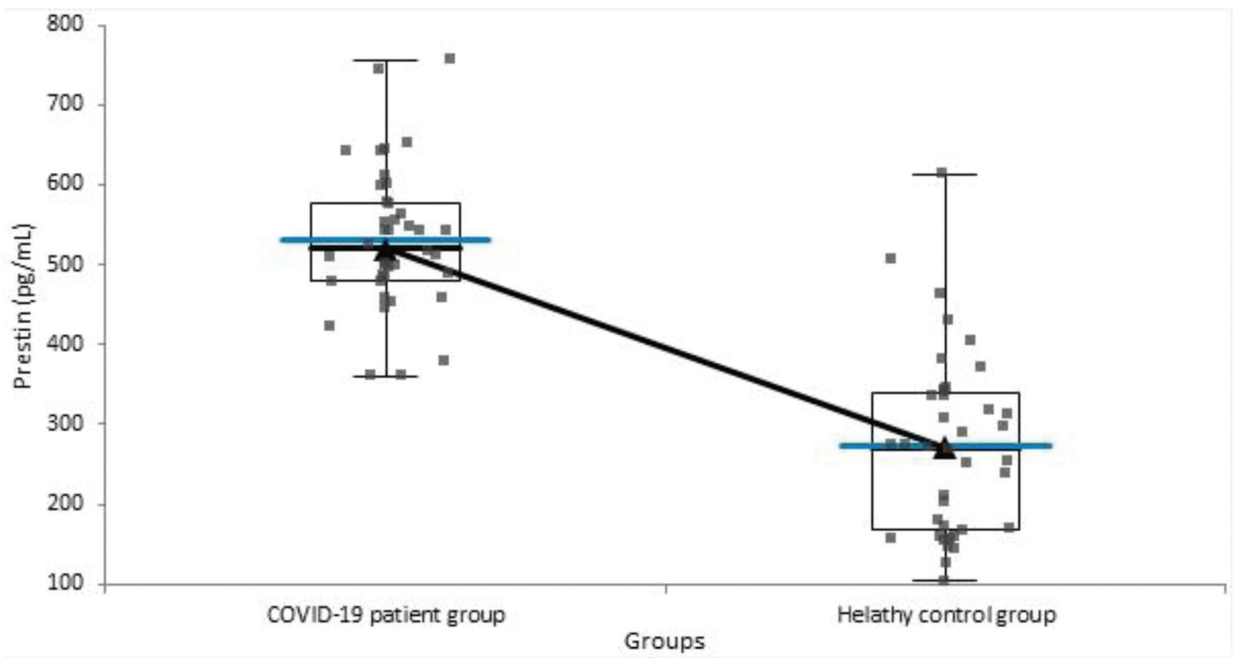

Fig. 1 The prestin levels in healthy control group and COVID-19 patient group. A box plot presentation. COVID-19 = coronavirus disease 2019.

cell death and impaired cardiac contraction in COVID-19 patients. Therefore, high prestin levels in COVID-19 patients may be associated with cardiac function, but patients with cardiovascular comorbidities were not included in our study. In addition, there are studies reporting that serum prestin levels are closely related to the inner ear and are a promising marker for early diagnosis.[15,32] Sun et al[20] compared serum prestin levels audiometrically in 42 cases and found that pre-treatment prestin levels were higher in the patient group than in the healthy control group. Hana and Bawi[33] compared a noise-exposed group with a healthy control group and reported that prestin levels increased significantly immediately after exposure to noise. One month after the treatment in the noise-exposed group, the prestin level was found to be 55% lower than the baseline level.[33] In addition, Parker et al[34] reported that serological assessment of prestin levels could be used to differentiate those at risk of cochlear injury from those at less risk and to provide new insights into inner ear dysfunction. Dogan et al,[16] on the other hand, conducted an experimental animal study in which they examined the predictive value of prestin in the early diagnosis of ototoxicity. In their study, they applied low and high doses of amikacin to two groups and cisplatin at low and high doses to two groups and compared serum prestin levels with those of the control group. As a result of their studies, they reported that the prestin levels of the groups to which they applied amikacin and cisplatin were significantly higher than those of the control group.[16] In our study, a hearing test could not be performed due to pandemic conditions and the high risk of contamination. However, we showed that prestin levels were high in the COVID-19 patient group, and we propose this as a key finding for future studies.

Interestingly, we determined a positive correlation between prestin and CRP levels. There is no study in the literature examining the relationship between prestin and CRP levels. However, there are studies examining CRP levels in inner ear function. Göde et al[35] investigated prolactin and highly sensitive CRP levels in patients with sudden sensorineural hearing loss. They

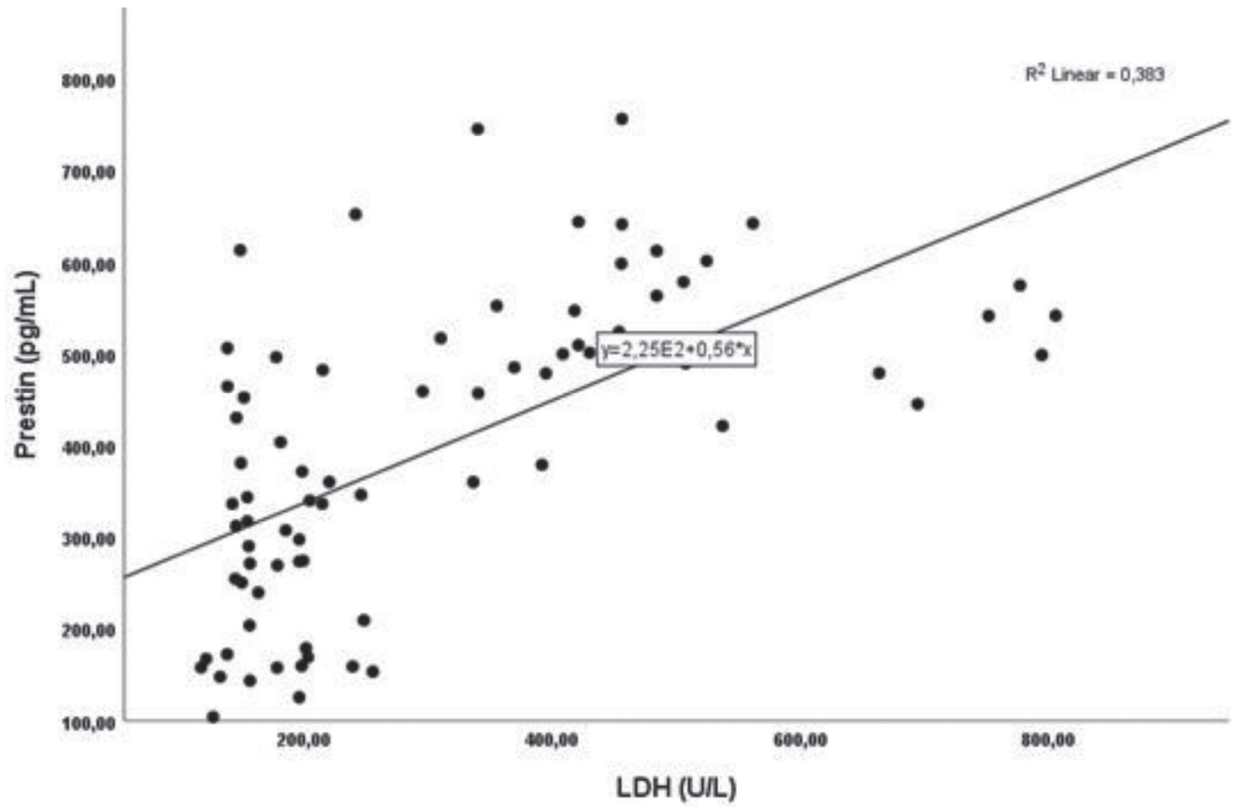

Fig. 2 The correlation between prestin and LDH levels. Scotter dot presentation. LDH = lactate dehydrogenase.

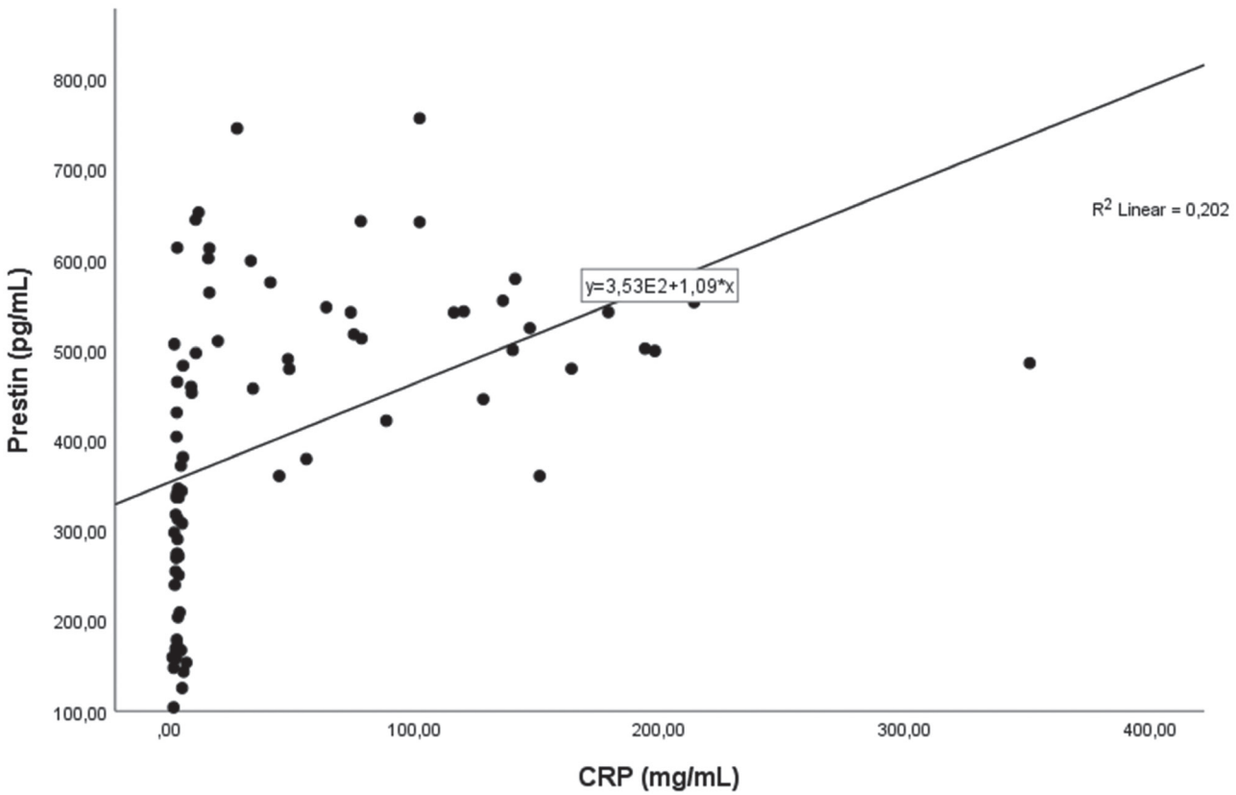

Fig. 3 The correlation between prestin and CRP levels. Scotter dot presentation. CRP = C-reactive protein.

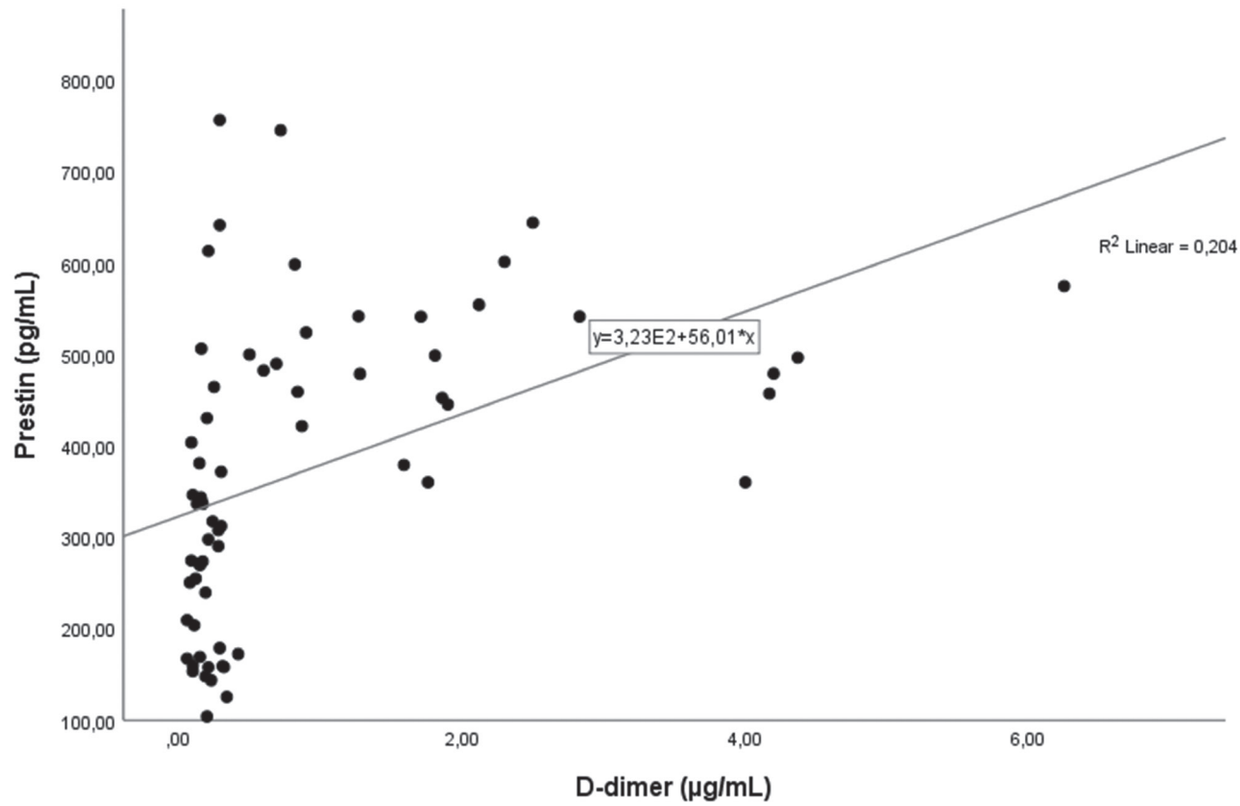

Fig. 4 The correlation between prestin and D-dimer levels. Scotter dot presentation.

reported that errors with sudden sensorineural hearing loss had increased hsCRP levels, but this increase was not statistically significant.[35] Guo et al[36] evaluated the CRP levels of patients with sudden sensorineural hearing loss retrospectively and reported that there was no relationship between sensorineural hearing loss and CRP. However, in this study, it should be emphasized that the cause of hearing loss in patients is not viral infection.[36] As a result of our findings, a strong positive correlation was revealed between CRP, which is an indicator of the severity of infection, and prestin. Therefore, it may be said that the damage to OHCs will increase with the increase in the severity of viral infection.

We also determined a strong positive correlation between prestin and D-dimer levels. D-dimer is a biomarker used to examine coagulation status. There is no study in the literature examining the relationship between D-dimer and prestin levels, but coagulation parameters in the inner ear microcirculation have been examined. Bao et al[37] compared the coagulation parameters of 424 patients with SHL and 244 patients with vocal cord polyps and reported that prothrombin, thrombin time measurement, fibrinogen, D-dimer, and neutrophil incidence are risk factors associated with SHL. Our findings show that the coagulation disorder caused by SARS-CoV-2 may be related to prestin levels.

One of the most important limitations of our study is the inability to perform a hearing test on COVID-19 patients due to pandemic conditions. The SARS-CoV-2 variant that caused the COVID-19 disease could not be detected either. It will be useful to examine the effects of different SARS-CoV-2 variants on prestin levels with further vertical studies.

In conclusion, we determined that prestin levels were increased in COVID-19 patients, and we also found that prestin levels were positively correlated with CRP and D-dimer. According to our findings, it can be said that prestin levels in COVID-19 patients may be associated with a systemic dysfunction. However, we cannot say that the increase in prestin levels alone is a result of inner ear and heart damage in COVID-19 patients. Future longitudinal studies are needed to determine if prestin elevation is a result of inner ear or heart damage or both in COVID-19 patients.

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Table 2

The correlation analysis of all parameters

Groups	Prestin (*r* value)
LDH (U/L)	
Total (n = 85)	0.537[a]
COVID-19 patient (n = 45)	0.161
Healthy control (n = 40)	0.044
CRP (mg/mL)	
Total (n = 85)	0.654[a]
COVID-19 patient (n = 45)	0.539[b]
Healthy control (n = 40)	0.135
ALT (U/L)	
Total (n = 85)	0.062
COVID-19 patient (n = 45)	0.457
Healthy control (n = 40)	−0.046
AST (U/L)	
Total (n = 85)	0.166
COVID-19 patient (n = 45)	0.338
Healthy control (n = 40)	0.156
CK-MB (U/L)	
Total (n = 85)	0.118
COVID-19 patient (n = 45)	0.049
Healthy control (n = 40)	−0.098
Ferritin (ng/mL)	
Total (n = 85)	0.390[a]
COVID-19 patient (n = 45)	0.029
Healthy control (n = 40)	−0.285
D-dimer (μg/mL)	
Total (n = 85)	0.659[a]
COVID-19 patient (n = 45)	0.610
Healthy control (n = 40)	−0.098

r = correlation coefficient.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK-MB = creatinine kinase MB; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; LDH = lactate dehydrogenase.

[a]Correlation is significant at the 0.01 level (2-tailed).

[b]Correlation is significant at the 0.05 level (2-tailed).

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