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# HSPB7 and tetranectin levels are associated with severity of COVID-19

## *HSPB7 ve tetranektin düzeyleri COVID-19'un şiddeti ile ilişkilidir*

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**Abstract**

**Purpose:** COVID-19 may have acute and chronic adverse effects on the cardiovascular system. Heat shock protein beta-7 (HSPB7) is a cardiovascular heat-shock protein, and tetranectin is a type-C calcium (Ca)-binding lectin. The present study was conducted to investigate the relationship between HSPB7, tetranectin, disease severity and myocardial injury in COVID-19.

**Materials and methods:** This study included 26 COVID-19 patients and 26 age and sex-matched healthy controls. Demographic characteristics, routine hemograms, and biochemical parameters were recorded. COVID-19 patients were classified as having mild to moderate and severe COVID-19 using clinical and laboratory data. HSPB7 and tetranectin levels were measured using commercial ELISA kits.

**Results:** C-reactive protein, fasting glucose, ferritin, neutrophil-to-lymphocyte, monocyte-to-lymphocyte, and platelet-to-lymphocyte ratios were significantly elevated, whereas calcium, and albumin were decreased in COVID-19 patients ($p$<0.05). Respiratory rate, D-dimer, and ferritin were higher while SO2 and lymphocyte counts were lower in severe COVID-19 patients ($p$<0.05). Serum HSPB7 levels were higher in COVID-19 patients vs healthy controls ($p$<0.01), whereas tetranectin concentration was lower ($p$<0.001). When the cases were evaluated according to the severity of the disease it was observed that, HSPB7 level was increased in patients with severe COVID-19 and tetranectin was decreased parallel to the severity of the disease ($p$<0.001 and $p$<0.001, respectively). HSPB7 concentration was positively correlated with ferritin ($p$=0.002). Tetranectin was negatively correlated with HSPB7, ferritin and troponin ($p$=0.041, $p$<0.01, and $p$=0.005, respectively).

**Conclusion:** The consequence of the present study indicates tetranectin as a potential biomarker for an accurate and more comprehensive understanding severity of cardiac damage in COVID-19 patients.

**Keywords:** COVID-19, HSPB7, tetranectin, cardiac injury.

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**Öz**

**Amaç:** COVID-19'un kardiyovasküler sistem üzerinde akut ve kronik olumsuz etkileri olabilmektedir. Isı şoku proteini beta-7 (HSPB7), kardiyovasküler bir ısı şoku proteinidir ve tetranektin, tip-C kalsiyum (Ca) bağlayıcı bir lektindir. Bu çalışmanın amacı, COVID-19'da HSPB7, tetranektin, hastalık şiddeti ve miyokardiyal hasar arasındaki ilişkiyi tespit etmektir.

**Gereç ve yöntem:** Bu çalışmaya 26 COVID-19 hastası ve 26 yaşı ile cinsiyeti eşleştirilmiş sağlıklı kontrol dahil edildi. Demografik özellikler, rutin hemogramlar ve biyokimyasal parametreler kaydedildi. COVID-19 hastalarının klinik ve laboratuvar verileri kullanılarak hafif, orta ve şiddetli COVID-19 hastası olarak sınıflandırıldı. HSPB7 ve tetranektin seviyeleri ticari ELISA kitleri kullanılarak ölçüldü.

**Bulgular:** COVID-19 hastalarında C-reaktif protein, açlık glukozu, ferritin, nötrofil-lenfosit, monosit-lenfosit ve trombosit-lenfosit oranları anlamlı olarak artarken, kalsiyum ve albümin ise azaldı ($p$<0,05). Şiddetli COVID-19 hastalarında solunum sayısı, D-dimer ve ferritin daha yüksekken, SO2 ve lenfosit sayıları daha düşüktü ($p$<0,05). Serum HSPB7 düzeyleri COVID-19 hastalarında sağlıklı kontrollere göre daha yüksekti ($p$<0,01), tetranektin düzeyi ise daha düşüktü ($p$<0,001). Hastalığın şiddetine göre değerlendirildiğinde, HSPB7 düzeyinin şiddetli COVID-19 hastalarında arttığı, tetranektin düzeyinin ise hastalığın şiddetine paralel olarak azaldığı görüldü (sırasıyla $p$<0,001 ve $p$<0,001). HSPB7 konsantrasyonunun ferritin ile pozitif korelasyon gösterdiği görüldü ($p$=0,002). Tetranektin, HSPB7, ferritin ve troponin ile negatif korelasyon gösterdi (sırasıyla $p$=0,041, $p$<0,01 ve $p$=0,005).

**Sonuç:** Mevcut çalışmanın sonuçları, tetranektini COVID-19 hastalarında, kardiyak hasarın ciddiyetinin belirlenmesinde ve daha kapsamlı bir şekilde anlaşılması için potansiyel bir biyobelirteç olabileceğini göstermektedir.

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**Anahtar kelimeler:** COVID-19, HSPB7, tetranektin, kardiyak hasar.

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## Introduction

The World Health Organization (WHO) reported that the world faced a new coronavirus, a potential pandemic agent, in the early days of 2020. The etiological agent is SARS-CoV-2, which is an RNA virus from the Coronaviridae family [1]. It can affect the cardiovascular system directly or indirectly. Therefore, people with cardiac pathologies (acute coronary syndrome, myocardial damage, myocarditis, arrhythmia, pulmonary embolism, etc.) are accepted as a risky group [2]. Studies have shown that biomarkers of myocardial damage, especially cardiac troponin I and T, increase in infected patients. Although the mechanisms of COVID-19 causing myocardial injury are not fully understood yet, systemic inflammation, interferon-mediated immune response, cytokine storm induced by T helper cells, hypoxia, direct damage to cardiomyocytes, myocardial interstitial fibrosis and stabilization of coronary plaque are considered to be responsible [3].

Currently, studies on the use of serum proteins as biomarkers in the early diagnosis or in determining the prognosis of various diseases are widely carried out. Heat shock protein beta-7 (HSPB7), also known as the cardiovascular heat-shock protein, is a member of the small heat shock protein family [4]. HSPB7 is necessary for the maintenance of myofibril structure in skeletal muscle and mutations of this protein have been linked to dilated cardiomyopathy as well as heart failure in humans [5]. HSPB7 was demonstrated to release from the damaged cardiomyocytes to the blood and elevated serum HSPB7 level was proposed as an independent risk factor for myocardial injury [6].

Tetranectin, whose gene is known as CLEC3B, is a type C calcium (Ca)-binding lectin that increases plasminogen activation [7]. Tetranectin is known to take part in tissue remodeling and development due to its ability to bind extracellular matrix (ECM) components by regulating ECM proteolysis. In addition, it stimulates proteolytic activation of proteases and growth factors. Circulating tetranectin levels were shown to be downregulated in cardiac pathologies [8]. Hence, it is also used as a biomarker for risk of heart injury [9].

Despite many studies demonstrating the relationship between HSPB7, tetranectin and cardiovascular disease, there is no study evaluating these protein levels in COVID-19 infection, which may also cause cardiac injury [10]. Therefore, we aimed to demonstrate HSPB7 and tetranectin levels in serum samples from hospitalized COVID-19 patients and their association with disease prognosis. We consider that the results of the current study may lead to important information about the relationship between serum levels of these two proteins and the severity of COVID-19 disease as well as cardiac involvement in the future.

## Materials and methods

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study (permission date (03.08.2021), Number: E-60116787-020-90354 (NO: 14). Procedures were performed according to the Declaration of Helsinki. Written informed consent was obtained from the subjects before the study.

### Participants

26 adult patients with COVID-19 and 26 age- and sex-matched healthy controls from the same geographic area (the city of Denizli in the central southern part of Türkiye) participated in the study. The age range in both groups was 40-60 years. Patients were confirmed as SARS-CoV-2 positive by RT-PCR (Rotor GENE, Qiagen, USA) using oro and nasopharyngeal swab samples (Bioseepdy SARS CoV-2 Double Gene RT-qPCR Kit) and admitted to the COVID-19 Department of Pamukkale University Hospital. Moreover, COVID-19 participants were distributed into two subgroups, including a mild group (n=13) and a severe group

(n=13). Severe COVID-19 is characterised by features of severe pneumonia such as dyspnea, respiratory frequency ≥28 breaths per minute and blood oxygen saturation ≤93%, lower lymphocyte count and elevated D-dimer, ferritin and CRP levels [11].

**Patient exclusion criteria**

Patients with chronic diseases such as DM, chronic kidney disease, COPD, hypertension, and malignant disorders, and those who did not want to participate in the study were not included.

**Blood Collection and Processing**

Blood was drawn on the first day of admission with symptoms from the forearm veins of PCR-positive patients. Plasma was collected into tubes with spray-coated dipotassium EDTA (1.5 mg/ml) and serum was collected into plain tubes without any anticoagulant. After centrifugation at 3500 rpm for 20 minutes (room temperature), serum and plasma were stored at -80 °C until the experimental procedure was performed. Routine hemogram and biochemistry values [white blood cell (WBC), C-reactive protein (CRP), Neutrophil-to-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR), Monocyte-to-lymphocyte ratio (MLR), fasting blood glucose, Creatine kinase (CK), Ca, Albumin, Urea, Ferritin, troponin) were recorded.

**Measurements of HSPB7 and tetranectin levels**

Serum HSPB7 (BT Lab, E5380Hu, China) and tetranectin (BT Lab, E6262Hu, China) levels were determined by enzyme-linked immunosorbent assay (ELISA) kits.

**Statistical analysis**

Power analyses were performed by the G-power program (version 3.1.9.2. Heinrich-Heine-Universitat, Duesseldorf, Germany). The effect size obtained from the reference studies was quite strong (d=0.957). For a strong effect size (dz=0.8), when at least 52 people (at least 26 for each group) were included in the study, it was calculated that 80% power could be obtained at the 95% statistical confidence level.

The analysis of the data was carried out using the SPSS 25.0 package program and given as “mean ± standard deviation”. For statistical comparison of biomarker levels in serum, an independent samples t test was used. The relationship between HSPB7 and tetranectin and other laboratory parameters was evaluated by using Pearson’s correlation analysis. The statistical significance was accepted as $p<0.05$.

**Results**

26 patients with COVID-19 disease (43.8% men, mean age=45.76±1.38) and 26 age–sex matched healthy controls (56.3% men, mean age=50.88±1.93) were included in this study. The demographic features and laboratory parameters of the participants are given in Table 1. Age and gender of COVID-19 patients were not different from healthy controls ($p>0.05$). Mean CRP, fasting blood glucose, ferritin levels, and neutrophil count were significantly increased in COVID-19 patients compared to healthy controls ($p<0.001$). Mean Ca, albumin and lymphocyte count were significantly lower in COVID-19 patients than in healthy individuals ($p<0.001$). There were no significant differences in hemoglobin (Hgb), CK, urea levels, white blood cell (WBC), platelet count and monocyte count between COVID-19 patients and healthy controls ($p>0.05$). Mean neutrophil count, neutrophil-to-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR), and Monocyte-to-lymphocyte ratio (MLR) were significantly higher in COVID-19 patients compared to healthy controls ($p<0.001$).

When COVID-19 patients were evaluated according to the severity of the disease (Table 2), respiratory rate, D-Dimer and ferritin levels were higher in severe COVID-19 patients compared to subjects with mild-moderate COVID-19 ($p<0.001$). Oxygen saturation ($SO_2$) and mean lymphocyte count were significantly lower in severe COVID-19 patients compared to mild-moderate ($p=0.015$ and $p=0.007$, respectively), whereas no statistically significant alterations were observed in mean pulse, CRP and troponin levels.

**Table 1.** The demographic characteristics and laboratory parameters of COVID-19 patients and healthy controls

| | Healthy Controls n=26 | COVID-19 n=26 | *p* [a] |
|---|---|---|---|
| **Age (years)** | 45.76±1.38 | 50.88±1.93 | 0.105 (t=-1.652) |
| **Gender (men %)** | 43.8% | 56.3% | 0.254 |
| **CRP (mg/L)** | 1.23±0.17 | 79.11±11.06 | 0.000* (t=-7.035) |
| **Hgb (g/dl)** | 13.85±0.41 | 12.96±0.47 | 0.170 (t=1.393) |
| **Fasting Blood Glucose (mg/dl)** | 90.42±2.43 | 154.73±12.97 | 0.001* (t=-4.872) |
| **CK (U/L)** | 0.81±0.03 | 3.67±2.77 | 0.308 (t=-1.030) |
| **Ca (mg/dl)** | 9.35±0.09 | 8.34±0.14 | 0.001* (t=5.992) |
| **Albumin (g/dl)** | 46.72±0.62 | 32.83±1.68 | 0.001* (t=7.740) |
| **Urea (mmol/L)** | 24.57±1.52 | 34.88±4.89 | 0.050 (t=-2.012) |
| **Ferritin (ng/ml)** | 52.35±8.96 | 901.49±130.47 | 0.001* (t=-6.235) |
| **WBC ($mm^3$)** | 7.11±0.26 | 8.49±0.76 | 0.092 (t=-1.717) |
| **Platelet count (K/μL)** | 249.00±11.25 | 254.27±24.79 | 0.847 (t=-0.194) |
| **Neutrophil count (K/μL)** | 4.31±0.22 | 7.17±0.77 | 0.001* (t=-3.582) |
| **Lymphocyte count (K/μL)** | 2.23±0.10 | 0.89±0.13 | 0.001* (t=8.089) |
| **Monocyte count (K/μL)** | 0.42±0.02 | 0.44±0.06 | 0.815 (t=-0.235) |
| **NLR** | 1.99±0.12 | 11.02±1.73 | 0.001* (t=-5.190) |
| **MLR** | 0.20±0.01 | 0.56±0.06 | 0.001* (t=-5.671) |
| **PLR** | 114.69±5.97 | 353.15±39.43 | 0.001* (t=-5.979) |

Results are given in mean ± SD. [a]p-values were calculated using independent samples t test
CK: Creatin kinase, Ca: Calcium, PLR: Platelet-to-lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio
WBC: White blood cell, *: $p<0.05$ difference from healthy controls. CRP: C-reactive protein, Hgb: Hemoglobin

**Table 2.** Comparison of the clinical and laboratory parameters of mild-moderate and severe COVID-19 patients

| | Mild-Moderate COVID-19 n=11 | Severe COVID-19 n=15 | *p* [a] |
|---|---|---|---|
| **Age (years)** | 52.53±9.29 | 48.63±10.58 | 0.329 (t=0.996) |
| **Pulse (beats per minute)** | 82.86±15.85 | 91.72±10.56 | 0.121 (t=-1.606) |
| **Respiratory Rate (breaths per min)** | 20.46±2.32 | 28.90±4.67 | 0.001* (t=-6.070) |
| **$SO_2$ (%)** | 94.80±2.11 | 91.81±3.65 | 0.015* (t=2.628) |
| **D-Dimer (ng/ml)** | 559.53±526.96 | 2121.18±1474.89 | 0.001* (t=-3.727) |
| **CRP (mg/dL)** | 65.64±48.38 | 97.49±63.58 | 0.159 (t=-1.453) |
| **Ferritin (ng/ml)** | 250.59±195.15 | 1452.72±490.03 | 0.001* (t=-8.661) |
| **Troponin (ng/ml)** | 10.22±8.33 | 16.70±15.54 | 0.182 (t=-1.374) |
| **Lymphocyte count (K/μL)** | 1.18±0.76 | 0.49±0.17 | 0.007* (t=2.929) |

Results are given in mean ± SD. [a]p-values were calculated using independent samples t test, $SO_2$: Oxygen saturation, CRP: C -reactive protein
*: $p<0.05$ differences from mild-moderate COVID-19 group

Serum HSPB7 level was significantly higher in COVID-19 patients than in healthy controls (the HSPB7 levels of COVID-19 patients and healthy controls were 6.04±0.82 and 5.05±0.80 ng/mL, respectively, $p$=0.006) (Figure 1A), and serum tetranectin concentration was lower in COVID-19 patients compared to controls (the tetranectin values of patients with COVID-19 and healthy controls were 87.85±33.54 and 54.69±16.05 ng/mL, respectively, $p$=0.001) (Figure 1B).

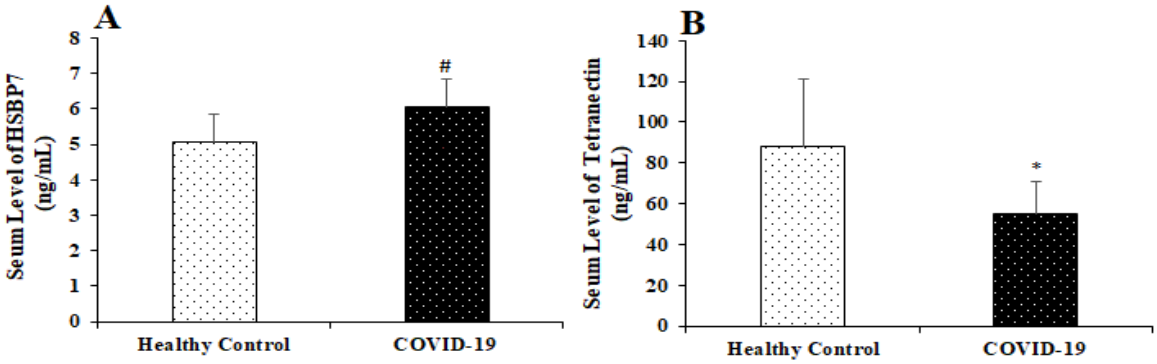


**Figure 1.** Serum levels of HSPB7

(A) and tetranectin, (B) in COVID-19 patients and healthy controls (Results are given in mean±SD
*: $p$<0.001 difference from healthy controls, #: $p$<0.01 difference from control)

When HSPB7 and tetranectin levels of COVID-19 patients were compared according to the severity of the disease, there were significant increases in HSPB7 (Figure 2A) and significant decreases in tetranectin levels (Figure 2B). Serum HSPB7 level was significantly higher in severe COVID-19 patients (7.76±1.6 ng/mL) compared to mild-moderate COVID-19 patients (5.18±0.59 ng/mL) and healthy controls (5.08±0.8 ng/mL) with $p$<0.001. However, serum HSPB7 levels of mild-moderate COVID-19 patients were not different from healthy controls. In addition, serum tetranectin levels were significantly lower in mild-moderate (65.06±16.92 ng/mL) and severe COVID-19 patients (45.86±2.98 ng/mL) compared to healthy controls (87.85±23.54 ng/mL) ($p$=0.035 and $p$=0.001, respectively). Serum tetranectin levels of mild-moderate COVID-19 patients were not different from patients with severe COVID-19.

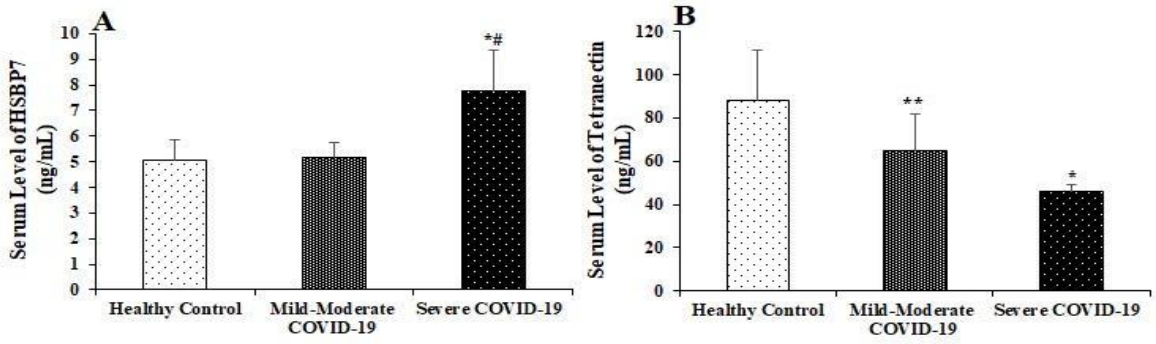


**Figure 2.** Serum HSPB7

(A) and tetranectin, (B) levels in healthy controls and COVID-19 patients according to severity of the disease (Results are given in mean±SD
*: $p$<0.001 difference from control, **: $p$<0.05 difference from control, #: $p$<0.001 difference from mild-moderate COVID-19

Figure 3 presents correlations of serum HSPB7, tetranectin, ferritin and troponin levels in COVID-19 patients. Serum HSPB7 level was positively correlated with ferritin (r=0.581, *p*=0.002) (Figure 3A), whereas tetranectin concentration was negatively correlated with ferritin (r=-0.529, *p*=0.005) in COVID-19 patients (Figure 3B). There was a statistically significant negative correlation between serum HSPB7 and tetranectin levels (r=-0.403, *p*=0.041) (Figure 3C). The positive correlation between serum HSPB7 and troponin levels was not statistically significant (r=0.364, *p*=0.068) (Figure 3D), while the negative correlation between serum tetranectin and troponin levels was found to be statistically significant (r=-0.605, *p*=0.001) in COVID-19 patients (Figure 3E).

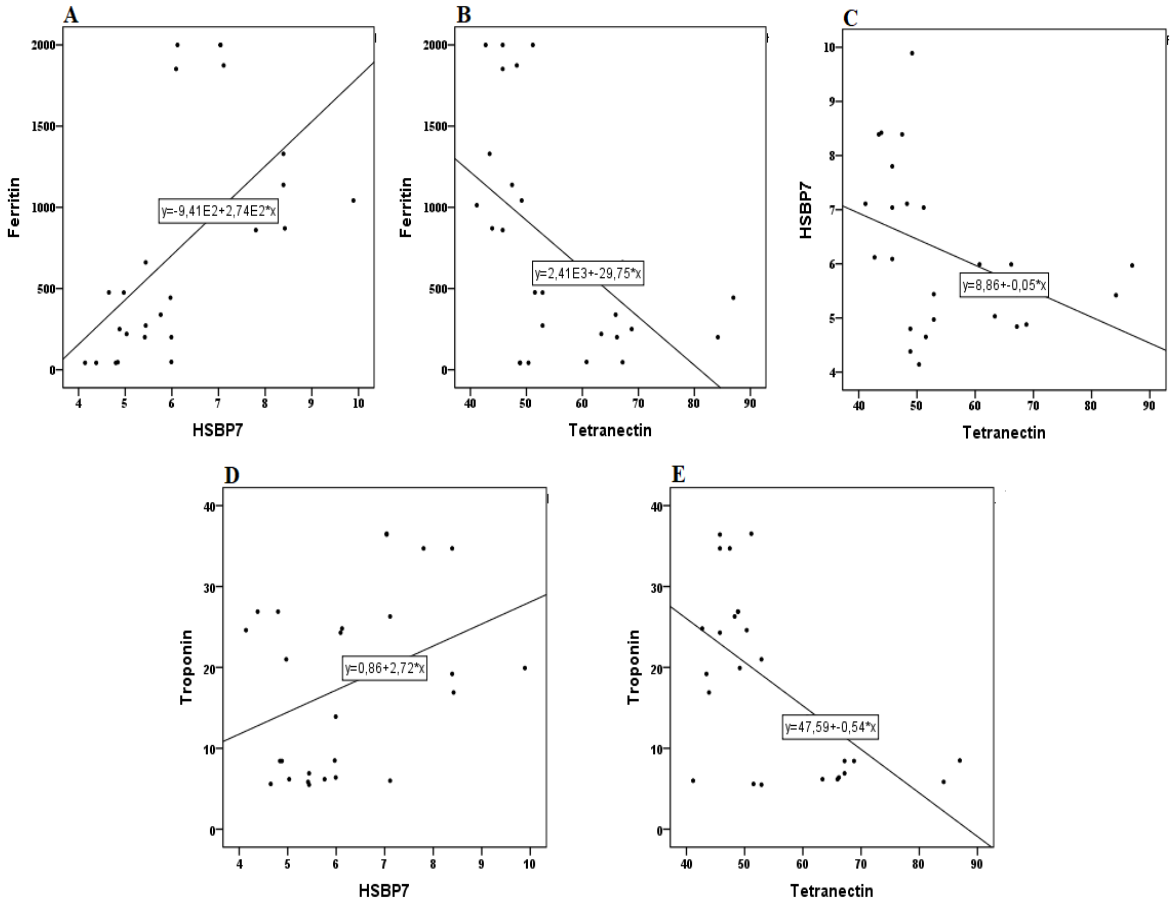


**Figure 3.** Pearson correlation scatter plot in COVID-19 patients

A: The correlation between circulating HSPB7 and ferritin levels (*p*=0.002)
B: The correlation between serum tetranectin and ferritin levels (*p*=0.005)
C: The correlation between circulating HSPB7 and tetranectin levels (*p*=0.041)
D: The correlation between serum HSPB7 and troponin levels (*p*=0.068)
E: The correlation between circulating tetranectin and troponin levels (*p*=0.001)

## Discussion

There is growing interest in identifying reliable diagnostic biomarkers to predict disease severity and cardiac involvement in COVID-19. In this context, our study focused on evaluating the potential roles of HSPB7 and tetranectin as prognostic markers. The key findings demonstrated that serum tetranectin levels were significantly reduced in both mild-moderate and severe COVID-19 patients, whereas elevated circulating HSPB7 levels were observed only in those with severe disease. To explore the potential association with myocardial injury, we performed correlation analyses between these biomarkers and serum troponin levels. Notably, tetranectin levels showed a significant

negative correlation with troponin, while the correlation between HSPB7 and troponin was not statistically significant. These results suggest that tetranectin may serve as a more consistent and sensitive biomarker for both disease severity and cardiac involvement in COVID-19.

In some COVID-19 patients, a cytokine storm occurs with the immune system being affected [12]. An often hallmark of the immune response to various invaders is characterized by increased neutrophil and decreased lymphocyte counts. Monocytes are also important components of the innate immune response, acting as a link to the adaptive immune system by antigen presentation to lymphocytes [13]. NLR, MLR, and PLR may be considered as markers of inflammation [14], representing cell activation associated with increased mortality in cardiovascular disease [15]. We found that patients' neutrophil count, NLR, MLR, and PLR data were higher and lymphocyte count was lower compared to healthy subjects. Activated neutrophils, which migrate from blood to the immune organ to release large amounts of reactive oxygen species, can cause DNA damage and free the virus from the cells. The high NLR values of COVID-19 patients in our study may indicate that these patients were exposed to tissue damage caused by oxidative damage. Increased PLR associated with lung injury and pulmonary endothelial cells activates platelets in the lungs, causing microthrombus formation and may increase platelet consumption [16]. Higher NLR and MLR levels in discriminating between different patient groups hospitalized for fever due to Sars-COV-2 infection and those without Sars-COV-2 infection were investigated [17, 18]. In addition, vascular permeability and capillary leakage increase due to systemic inflammation, causing an albumin shift toward the extravascular space. In this case, hypoalbuminemia may become more profound with the disruption of albumin synthesis. Albumin may also downregulate ACE2 receptors for modulating COVID-19 disease [19]. Low levels of albumin may result in upregulation of ACE2 receptors and a rise in COVID-19 disease. Consistent with these results, we have found lower albumin levels in COVID-19 disease.

In the case of cytokine storm respiratory failure, hypoxemia, hypotension or shock induced by COVID-19 can cause insufficient oxygen supply to myocardial tissue, leading to damage [10, 20, 21]. As an acute-phase inflammatory mediator, elevated CRP has been linked to unfavorable aspects of COVID-19 disease, such as myocardial injury and death [22]. Accordingly, we observed that CRP, ferritin and fasting blood glucose were increased in our patient group. Analysis in the literature revealed that inflammatory parameters including CRP and ferritin were higher in patients with elevated fasting blood glucose, in line with our results. Meanwhile, the counts of lymphocytes were lower and neutrophils were higher in the highest fasting glucose group compared to healthy individuals [23]. These data indicated that raised fasting glucose levels were associated with infection and immunity in COVID-19 patients. Higher serum ferritin level were related to the development of acute respiratory distress syndrome (ARDS) [24] and death [25]. In concordance with these findings, we demonstrated that ferritin levels were increased the severity of COVID-19. As expected, respiratory rate was elevated and $SO_2$ was decreased with severity of the disease and these consequences may result in an insufficient oxygen supply to the myocardium and cause muscle damage. D-dimers are produced when plasmin cleaves fibrin to break down clots. Elevation of D-Dimer is common in patients with COVID-19 and is associated with severity of the disease and mortality [26].

HSPB7, also known as cardiovascular heat-shock protein, is a member of the small heat-shock protein family sharing a conserved α-crystallin domain in the C-terminal region [4, 27, 28]. It was suggested to have the potential to be a diagnostic marker for myocardial damage, heart failure and an independent risk factor for acute coronary syndrome [6, 29]. Tetranectin, a protein located in the heart, was selected due to its association with cardiac metabolic pathways [9]. Prior literature has demonstrated an anti-thrombotic and an anti-proliferative role for tetranectin [7]. Higher plasma tetranectin levels were inversely associated with cardiovascular risk factors [8]. McDonald et al. [30] reported that a decrease in circulating tetranectin

may indicate cardiac uptake to help conflict myocardial interstitial fibrosis, or a decrease in circulating tetranectin may predispose to the development of heart failure.

The risk of in-hospital death in severe COVID-19 patients can be predicted via myocardial damage biomarkers and is linked to inflammatory response as well as cardiovascular comorbidities [3, 31, 32]. The exact mechanism of COVID-19 leading to myocardial damage remains not fully understood yet [33]. Elevated circulating HSPB7 levels in severe COVID-19 patients and reduced serum tetranectin concentrations, associated with the severity of the disease, were demonstrated in the current study. These two proteins were negatively correlated with each other. Furthermore, not HSPB7, but serum tetranectin levels were negatively correlated with troponin levels. When evaluated together, our results may indicate a more prominent role for tetranectin as a marker of cardiac involvement and severity of COVID-19.

Ferritin was also demonstrated to have an emerging role as a marker in the prognosis of COVID-19. Previous studies revealed the association between serum ferritin levels and clinical characteristics of COVID-19 patients including severity of the disease, as well as mortality and comorbidities [25]. Ferritin increases in the circulation during viral infections and is consistent with a highly inflammatory state [34]. Elevated levels of ferritin due to cytokine storm have also been reported in COVID-19 patients [35]. In line with above-mentioned reports, serum ferritin levels were increased in COVID-19 patients with disease severity in the current study. We also observed that ferritin was correlated positively with HSPB7 and negatively with tetranectin.

Recent studies have focused on the effects of COVID-19 on heart damage. Among the long-term complications following COVID-19 are ischemic heart disease, heart failure, arrhythmias, and myocarditis [36]. Studies have consistently shown that underlying cardiovascular disease in patients with COVID-19 and the development of acute cardiac injury due to COVID-19 illness are associated with significantly worse outcomes.

Numerous mechanisms have been suggested to explain cardiac injury: damage mediated by cytokines, microvascular thrombi, and/or direct cardiomyocyte injury due to viral invasion of the myocardium [37], although the precise effects on heart muscle remain unclear. Acute myocardial injury has been linked to persistent symptoms even 12 months after the initial COVID-19 infection, with an increased hospital readmission rate [38]. This is likely because myocardial dysfunction persists after the initial infection. Tobler et al. [38] reported that new-onset hypertension and heart failure were present in 2% of patients who were more than one year out from their acute COVID-19 infection. A high number of patients have ongoing myocardial inflammation after a COVID-19 infection; however, this is not diagnostic. Although they are primarily seen in patients with underlying cardiac conditions and/or advanced age, they may also be seen in those without preexisting cardiac disease. HSPB7 and tetranectin proteins are cardiac damage specific proteins and the levels changed with COVID-19, and may be it is a molecular reason for tissue damage after COVID-19 infection. Understanding the significance of these conditions in association with COVID-19 illness is of critical importance in ensuring an accurate diagnosis and timely management.

Despite the valuable findings presented in this study, several limitations should be acknowledged. First, the study was conducted in a single center with a relatively small sample size, which may reduce the generalizability of the results and prevent assessment of population heterogeneity among COVID-19 patients. Second, imaging data such as thoracic CT or echocardiographic evaluations were not available, which limited our ability to objectively differentiate between mild and severe disease or to assess myocardial injury directly. Finally, the cross-sectional design did not allow for longitudinal monitoring of biomarker fluctuations throughout the illness.

In summary, our findings suggest that, while both HSPB7 and tetranectin are associated with COVID-19-related cardiac involvement, tetranectin appears to be a more consistent and sensitive biomarker. HSPB7 levels were significantly elevated only in cases of

severe disease. In contrast, tetranectin levels decreased progressively with increasing disease severity and demonstrated a significant negative correlation with serum troponin levels, a well-established indicator of myocardial injury. These findings suggest a potential role for tetranectin as a biomarker reflecting the severity of COVID-19 and its associated cardiac involvement. Nevertheless, the potential utility of HSPB7 and tetranectin as markers of cardiac damage in COVID-19 warrants further investigation. Future studies with larger cohorts and mechanistic insights are needed to clarify their roles in the pathogenesis of COVID-19-related myocardial injury.

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