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Coronavirus Pandemic

Importance of evaluation of heart-type fatty acid binding protein (H-FABP) in COVID-19 Patients

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Abstract

Introduction: Recent studies have documented the cardiovascular consequences of acute coronavirus disease 2019 (COVID-19), although one of the early cardiac markers that can be used for diagnosis, the heart-type fatty acid-binding protein (H-FABP), has not been covered. Through the evaluation of H-FABP levels, we aim to contribute to the early diagnosis and treatment of cardiac problems in COVID-19 infection patients.
Methodology: Seventy-five patients who were admitted to the emergency department of Mehmet Akif Ersoy Hospital with a complaint of chest pain in the last 6 hours and whose corona PCR tests were positive, were included in our study as the case group and 60 healthy volunteers as the control group. The routine cardiac markers such as creatine kinase MB (CK-MB) cardiac troponin T (cTnT), and H-FABP levels were analyzed by routine laboratory methods.
Results: The mean age and gender distributions of the groups did not differ statistically ($p > 0.05$). CK-MB, cTnT, and H-FABP measurements were statistically different between the groups ($p = 0.001$; $p < 0.01$).
Conclusions: The relationship between AMI and COVID-19 with routine cardiac markers is already supported by recent studies. We also evaluated H-FABP levels in our study, as it affects the prognosis of the disease independent of the chronic disease history. At the same time, we showed that H-FABP levels increase earlier than routine cardiac markers, so it will be useful for COVID-19 patients with cardiac complaints.

Key words: COVID-19; acute cardiac injury; H-FABP.

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Introduction

During COVID-19, most patients have a diverse range of problems. The most common of these complications is acute respiratory distress syndrome (ARDS). Other COVID-19-related health damage issues have a cardiac background (including arrhythmias, acute cardiac damage, and shock), which are more common in critically ill patients receiving intensive care unit treatment [1,2]. Human H-FABP is a 132 amino acid acidic protein that is primarily responsible for transporting long-chain fatty acids. Because long-chain fatty acids are not very soluble in the intracellular environment, FABPs are required for their translocation. H-FABP can be thought of as plasma albumin's cytoplasmic counterpart. Ischemia disrupts oxygenation, causing an increase in anaerobic energy production mechanisms. Therefore, there will be an increase in fatty acid carrier molecules [3,4].

Methodology

Our study was planned between September and December 2020 with 75 patients who were admitted to the emergency department of Mehmet Akif Ersoy Hospital with a complaint of chest pain in the last 6 hours and whose corona PCR tests were positive, and 60 healthy volunteers without a history of chronic disease and no history of corona infection in the last 6 months. All the patients, patient relatives, and volunteers were informed about this study and their consent was obtained.

An extensive history and a thorough description of the symptoms must be obtained. We collected blood samples from these patients immediately after admission (within 15-20 minutes) of acute coronary syndrome signs and symptoms since the release of markers depends on the time of necrosis's initiation. Using an electro-chemiluminescence immune assay (ECLIA) based on electro-chemiluminescence technology's sandwich principle, cardiac markers

Table 1. Evaluation of demographic characteristics by groups.

	Total (n = 135)	Covid (+) group (n = 75)	Control group (n = 60)	*p*
Age (years)				
Mean ± SD	51.65±15.01	50.92±16.19	52.57±13.47	[a]0.529
Min-Max (Median)	20-84 (51)	20-84 (51)	23-814 (51)	
Gender n (%)				
Female	48 (35.6)	30 (40.0)	18 (30.0)	[b]0.228
Male	87 (64.4)	45 (60.0)	42 (70.0)	

[a]Independent Samples t Test; [b]Pearson Chi-Square Test; SD: Standard deviation.

Troponin T (cTnT) and mass CKMB were measured. (Cobas e411, Roche, Mannheim, Germany). The reference intervals for cTnT and CKMB were used as 0–14 ng/L and 0-6.22 ng/mL, respectively. The H-FABP concentrations are measured by using the H-FABP Kit (Catalog No:E1213Hu, Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's instructions; the assay is based on the method of quantitative sandwich enzyme immunoassay. Intra-assay and inter-assay coefficients of variation were 8% and 10%, respectively. For ELISA analysis, an ELx50 Microplate Strip Washer and an ELx800 Absorbance Microplate Reader (BioTek® Instruments, Inc., Winooski, Vermont, USA) were used. We didn't measure any hemolytic or lipemic samples for the assays. An electrogram (ECG) is recorded to allow differentiation of patients without or with ST-segment changes.

The IBM SPSS Statistics 23 (IBM SPSS, Turkey) program was used for statistical analysis in this study. When analyzing the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum, and quartiles) were used. Kolmogorov-Smirnov, Shapiro-Wilk, Skewness-Kurtosis, and graphical evaluations were used to determine whether the quantitative data conformed to the normal distribution. The Independent Samples t-test was used to compare normally distributed quantitative data between two groups, and the Mann-Whitney U test was used to compare data that did not have a normal distribution between the two groups. To compare qualitative data, the Pearson Chi-Square Test was used. To assess the fit of qualitative data, the McNemar test and Cohen's Kappa test were used. Diagnostic screening tests (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curve analysis were used to determine the cut-off for H-FABP levels. Significance was evaluated at least at $p < 0.05$.

This study was approved by the Ethics Committee of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital (date: 23-06-2020 decision no:2020/53)

Results

The mean admission time was 4.2 hours. In our study, 35.6% were female (n = 48) and 64.4% were male (n = 87). A total of 75 patients were chosen from those who had a positive Corona PCR test. A group of healthy volunteers were included in our study as the control group (n = 60). The mean age of the case group was 50.92 ± 16.19, and the mean age of the control group was 52.57 ± 13.47. As shown in Table 1, the mean age and gender distributions of the groups did not differ statistically ($p > 0.05$). As shown in Table 2, CK-MB, cTnT, and H-FABP measurements were statistically different between the groups. The measurements of the covid (+) group are higher than the

Figure 1. Distribution of CK-MB, cTnT, and H-FABP measurements by the groups.

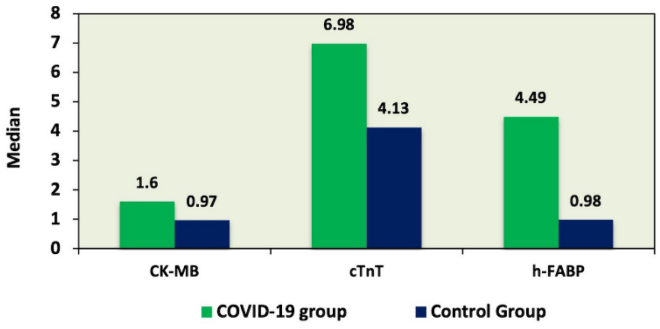


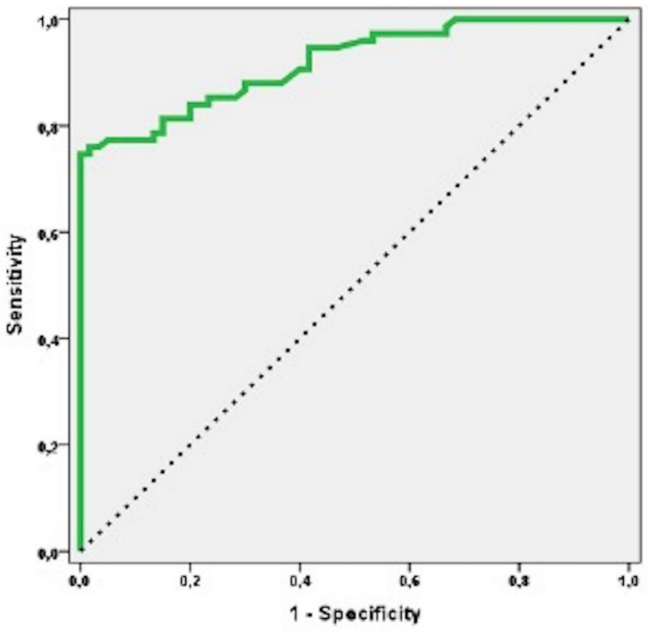
Table 2. Comparison of cardiac markers between groups.

		Covid-19 (+) group (n = 75)	Control group (n = 60)	*p*
CK-MB	Median (Q_1-Q_3)	1.6 (0.9-4.2)	0.97 (0.3-1.1)	0.001**
	Mean ± SD	2.79 ± 2.93	0.92 ± 0.69	
cTnT	Median (Q_1-Q_3)	6.98 (3.8-14.6)	4.13 (3-7.5)	0.001**
	Mean ± SD	15.25 ± 22.79	4.98 ± 2.76	
H-FABP	Median (Q_1-Q_3)	4.49 (2.1-12.1)	0.98 (0.7-1.2)	0.001**
	Mean ± SD	7.72 ± 8.01	1.00 ± 0.55	

Q_1: First quarter; Q_3: Third quarter; [c]Mann Whitney U Test; **$p < 0.01$; cTnT: Cardiac Troponin T; CK-MB: Creatine Kinase myocardial band; H-FABP: Heart-type fatty acid binding protein.

control group ($p = 0.001$; $p < 0.01$). CK-MB, Troponin T, and H-FABP measurements by the groups are shown in Figure 1. According to the COVID-19 and control groups, the cut-off point for H-FABP measurement was determined as 1.67 and above (≥ 1.67). For the 1.67 cut-off value of the H-FABP measurement, the sensitivity is 81.33%, the specificity is 85.25, the positive predictive value is 87.14%, the negative predictive value is 78.79%, and the accuracy is 83.09%. The standard error of the area under the ROC curve obtained was 91.9% and 2.2% (Table 3). The ROC curve analysis for H-FABP levels is shown in Figure 2.

Figure 2. The ROC curve analysis for H-FABP levels by the groups.



Discussion

According to recent studies, a reference high-sensitivity troponin I (hs-cTnI) value higher than the upper limit of the range (> 28 pg/mL) and cardiac troponin T (cTnT) (> 14 pg/mL (ng/L)) are defined as acute cardiac injury. In our study, we used cTnT and the reference value of > 14ng/L [3]. Acute myocardial injury develops due to infection-related myocarditis and/or ischemia. This situation has an important prognostic factor for COVID-19 [5,6]. In patients who have developed an acute cardiac injury, ARDS, malignant arrhythmia, acute renal injury, acute coagulopathy incidence, and mortality rates are higher than in patients without cardiac injury. ARDS and acute cardiac injury are statistically significant and related to COVID-19 mortality. Similarly, a recent study showed that the mortality rate of patients with a high troponin T level compared to patients with a normal troponin level was found to be significantly higher. It also has the highest mortality rate of patients with underlying cardiovascular disease who have developed troponin T elevation during an infection. Although the patient has cardiovascular disease, during the infection who has a normal troponin T level, the mortality risk didn't increase [6,7]. The initial symptoms of COVID-19 infection can include acute heart damage and even ventricular. In Italy, a patient who presented to the emergency room with chest pain underwent catheterization as a result of electrocardiographic changes. There was no evidence of occlusive coronary artery disease. Additional testing reveals that the patient has COVID-19 [8]. In a recent case published in Italy, the diagnosis of a mildly symptomatic COVID-19 patient with acute myopericarditis with systolic dysfunction without respiratory distress was confirmed by cardiac magnetic resonance imaging [9]. In conclusion, myocardial markers are useful for risk stratification in all COVID-19 patients [8,9].

In the literature, many cases with fulminant myocarditis associated with COVID-19 and glucocorticoids, human immunoglobulins, inotropic agents, and mechanical support are used for these patients' treatments [10]. Acute coronary syndrome can occur in COVID-19 patients. However, the incidence of this condition is uncertain. Endothelial and smooth muscle cell activation within the atheroma plaque due to inflammation, macrophage activation, and tissue factor expression, increased thrombotic tendency, and clinical laboratory biomarkers that increase the risk of developing acute coronary syndrome during COVID-19 are factors [7,11]. On the other hand, the transfer of COVID-19-infected patients to the angiography laboratory carries certain risks in terms of contagion. For this reason, many institutions changed their acute coronary syndrome treatment protocols in this period,

Table 3. According to the groups, diagnostic screening tests and ROC curve results for H-FABP measurement.

	Diagnostic Scan					ROC Curve		*p*
	Cut off	Sensitivite	Spesifisite	Positive Predictive Value	Negative Predictive Value	Area	95% CI	
H-FABP	≥ 1.67	81.33	85.25	87.14	78.79	0.919	0.875-0.963	0.001**

**$p < 0.01$.

and instead of using percutaneous treatment, they focused more on thrombolytic therapy [12].

Our knowledge of the pathophysiology of cardiac complications during COVID-19 is still very limited. Increased levels of cardiac markers during infection may even have a condition that reflects only systemic disease. On the other hand, various hypotheses related to the subject have been put forward. The first of these is that an individual who has underlying chronic cardiovascular disease has a limited cardiac reserve, and this condition is associated with the inability to meet the increased metabolic needs during infection [1]. It is also a known fact that viral infections can trigger acute coronary syndromes, arrhythmias, and heart failure. This condition is associated with a severe systemic inflammatory response and is caused by vascular inflammation localized at the level of arterial plaque. Myocardial damage is caused by the inability to meet increased metabolic needs and exaggerated inflammatory responses. During COVID-19, this may be the reason for cardiac complications [12-15].

H-FABP, a protein that binds to fatty acids, is released from cardiac myocytes after an ischemia episode. It is a cytoplasmic protein with a modest molecular weight (15 kDa). H-FABP is involved in the transport of fatty acids from the cell membrane to the mitochondria for oxidation, just like the other forms of FABPs. Compared to other cardiac biomarkers such as cardiac troponins (cTn) and CK-MB, which are often utilized in most hospitals, the heart-type fatty acid-binding protein (H-FABP) has greater specificity at an earlier stage (within 2 to 3 hours) in the assessment of the myocardial injury. A recent study has demonstrated that the increase in h-FABP values, particularly in individuals with non-ST elevation ACS (NSTE ACS), is significant for early detection in addition to other outcomes [5,16]. The relationship between COVID-19 and AMI was demonstrated in recent studies conducted in Italy and Israel using routine cardiac markers [8,9,17]. However, the time elapsed between myocardial damage and the attainment of measurable values, after these proteins are released into the blood, delays the detection of myocardial damage, and worsens the prognosis in a severe infection such as COVID-19. A biomarker, such as HFABP, whose levels increase more quickly can be evaluated alongside routine cardiac markers, as it will speed up the diagnosis and treatment process of assessing cardiac damage in COVID-19 patients. In our study, CK-MB, cTnT, and H-FABP measurements were statistically different between the groups. The measurements of the covid (+) group are higher than the control group ($p = 0.001$; $p < 0.01$). In previous research, it was stated that H-FABP levels rise in both renal and cardiac failure [18].

Conclusions

The relationship between AMI and COVID-19 with routine cardiac markers is already supported by recent studies. We also evaluated H-FABP levels in our study, as it affects the prognosis of the disease independent of the chronic disease history. At the same time, we showed that H-FABP levels increase earlier than routine cardiac markers, so it will be useful for COVID-19 patients with cardiac complaints.

Considering the intense inflammatory burden and multisystem involvement of COVID-19 disease and the possibility of AMI and many organ failures, we think that it will be important to evaluate H-FABP levels together with routine cardiac markers.

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