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Assessment of Cardiac Myosin-binding Protein C Levels in Coronavirus Disease 2019

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ABSTRACT

Objective: This study aimed to evaluate cardiac myosin-binding protein C (cMyBP-C) levels in patients with COVID-19.

Materials and Methods: Overall, 187 patients were enrolled in the study. Patients with mild–moderate and severe–critical illness constituted groups 0 and 1, respectively.

Results: Admission to the intensive care unit and hospitalization period were significantly higher in group 1. Hemoglobin levels, lymphocyte count, and albumin levels were significantly lower, and lactate dehydrogenase, C-reactive protein (CRP), D-dimer, cardiac troponin I (cTnI), and procalcitonin levels, prothrombin time (PT), and CRP/lymphocyte ratio were higher in group 1 patients compared to group 0 patients. cTnI and CRP/lymphocyte ratio were higher, and ferritin/procalcitonin and albumin/CRP ratios were lower in deceased patients than in surviving patients, while MyBP-C levels were similar in the two groups. Multivariate regression analysis revealed that lymphocyte count and urea levels were independent predictors of mortality. Receiver Operating Characteristic (ROC) curve analysis showed that cTnI level and ferritin/procalcitonin, CRP/lymphocyte, and albumin/CRP ratios were valuable biochemical parameters for predicting mortality in patients with COVID-19.

Conclusion: cMyBP-C level may not be a valuable tool for predicting the severity or prognosis of COVID-19.

Keywords: Cardiac myosin-binding protein C, Coronavirus disease 2019, infection

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a subgroup of coronavirus initially identified in Wuhan, China, in December 2019. After the diagnosis of coronavirus disease 2019 (COVID-19), the infection rapidly spread into various countries, and it was declared a pandemic on March 11, 2020. The infection is highly contagious, and its mortality is higher than that of seasonal influenza (1). The severity of COVID-19 varies widely in the population, ranging from an asymptomatic state to multi-organ failure and death. Hyper-activation of the immune system, inflammatory response, and cytokine storm are responsible for the pathogenesis and clinical symptoms of the disease (2). Cardiac involvement is relatively common among patients who are hospitalized during the course

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of the infection. Multiple mechanisms have been proposed to clarify the mechanism of cardiac injury in patients with COVID-19. Direct invasion of the myocardial tissue through angiotensin-converting enzyme-2 (ACE-2) receptor binding and release of inflammatory cytokines, coronary plaque destabilization, and hypoxia may contribute to cardiac dysfunction (3, 4). It is now well demonstrated that cardiac involvement is associated with high mortality (5). Myocardial injury in the acute phase of the infection has been reported in up to 15.8% of patients with COVID-19 who are more likely to be older, require intensive care unit (ICU) admission, and have preexisting heart disease (6). Furthermore, cardiovascular morbidities, including hypertension, atrial fibrillation, and coronary artery disease, are linked with the severity of the illness (7). Cardiovascular manifestations of COVID-19 include myocardial injury, myocarditis, arrhythmia, congestive heart failure, and cardiac arrest (8). Several biomarkers have been studied to diagnose cardiac involvement and assess prognosis.

The contraction and relaxation of heart muscles depend on cross-bridge formation between actin and myosin filaments. Cardiac myosin-binding protein C (cMyBP-C) regulates cardiac contraction by controlling the actin–myosin interaction (9). In its dephosphorylated form, cMyBP-C inhibits the interaction between actin and myosin (10). Notably, the phosphorylated form of cMyBP-C decreases in patients with congestive heart failure, ischemic heart disease, and atrial fibrillation (11-14). Furthermore, cMyBP-C mutations are among the most common causes of hypertrophic cardiomyopathy. cMyBP-C is a novel biomarker that may be more useful than cardiac troponin I (cTnI) in clinical practice (15). Thus, this study aimed to evaluate cMyBP-C levels and their prognostic value with respect to in-hospital mortality in patients with COVID-19.

MATERIALS AND METHODS

This study was conducted between April and June 2020 with the inclusion of 187 patients with COVID-19 who were admitted to an infectious disease clinic and ICU in a tertiary hospital in Turkiye. The local ethics committee approved the study, and informed consent from patients or their legal representatives was obtained. The study was conducted in accordance with the Declaration of Helsinki. Demographic and clinical characteristics of the patients were recorded during hospitalization. COVID-19 infection was identified by obtaining viral RNA in nasopharyngeal swabs using real-time polymerase chain reaction. The patients' clinical status was categorized as mild, moderate, severe, and critical according to the China Diagnosis and Treatment of COVID-19 (16). Patients with the absence and presence of pneumonia were described as mild and moderate cases, respectively. Patients who had a respiratory rate of >30 breaths/min, resting oxygen saturation level < 93%, and partial oxygen saturation to fraction of inspired oxygen ratio < 300 mmHg were classified as severe cases. Patients with respiratory failure, shock, or other organ failure that required ICU admission were categorized as critical cases. Patients were classified into two groups according to their clinical situation: patients with mild–moderate disease and severe–critical disease constituted groups 0 and 1, respectively.

Blood samples of the patients were drawn by venipuncture in either a sitting or supine position. Blood parameters, including haemogram; liver and kidney function tests; albumin, ferritin, triglyceride, fibrinogen, and coagulation tests; and D-dimer, cTnI ,and procalcitonin tests, were assessed. Serum cMyBP-C levels were determined using enzyme-linked immunosorbent assay (ELISA) (Allsheng APW-200 microplate washer, Hangzhou Allsheng Instruments Co., China).

Statistical Analyses

All analyses were performed using Number Cruncher Statistical System (NCSS) Statistical Software (Utah, USA). Data with Gaussian and non-Gaussian distributions were expressed as mean ± SD and median (minimum–maximum), respectively. Categorical data were expressed as numbers and percentages. For the comparison of groups, Mann–Whitney U and independent sample t tests were used. Receiver Operating Characteristic (ROC) curve analysis was performed to predict mortality, ICU admission, and severity of the disease. The binomial exact test was used for binary comparison of the variables. For the current study with an alpha level of 0.05 and effect size of 0.38, the estimated power was 80%. p -value < 0.05 was considered significant.

RESULTS

The mean age of the study population was 60.89 ± 16.90 years. A total of 64 patients (34.2%) had severe disease, 54 (28.9%) had diabetes, 97 (51.9%) had hypertension, and 9 (7.0%) were admitted to the ICU, and the in-hospital mortality was 5.3%.

No differences were noted between the two groups with regard to age, sex, prevalence of diabetes mellitus, chronic renal failure, coronary artery disease, hypertension, and chronic obstructive pulmonary disease. As expected, admission to the ICU and hospitalization period were significantly higher in group 1. Hemoglobin (Hgb) level, lymphocyte count, and albumin level were significantly lower, and lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, cTnI, and procalcitonin levels; prothrombin time (PT); and CRP/lymphocyte ratio were higher in group 1 than those in group 0. A comparison of the clinical and biochemical parameters of the two groups is presented in Table 1.

cTnI levels and CRP/lymphocyte ratio were substantially higher, and ferritin/procalcitonin and albumin/CRP ratios were substantially lower in deceased patients than in surviving patients. However, cMYBP-C levels did not differ between the two groups (Table 2).

Logistic regression was used to assess the prognosticators of mortality. According to univariate analysis, Hgb, aspartate aminotransferase (AST), urea, creatinine, albumin, and CRP levels; PT; activated partial thromboplastin time (aPTT); D-dimer

Table 1. Comparison of clinical and biochemical parameters of two groups.

	Patients with mild-moderate disease (Group 0)	Patients with severe-critical disease (Group 1)	p
Age (years)	59.49±16.89	63.58±16.72	0.117
Gender n (%)			0.578
Female	61 (49.6)	29 (45.3)	
Male	62 (50.4)	35 (54.7)	
Diabetes mellitus n (%)	33 (26.8)	31 (32.8)	0.392
Hypertension (n, %)	65 (52.8)	32 (50.0)	0.712
Coronary artery disease n (%)	37 (30.1)	17 (26.6)	0.614
COPD n (%)	19 (15.4)	9 (14.1)	0.800
Chronic renal failure	5 (4.1)	4 (6.3)	0.495
Intensive care unit	0 (0)	13 (20.3)	0.000
Mortality	1 (0.8)	9 (14.1)	<0.001
Hospitalization period (days)	8.00 (3.0-31.0)	13.00 (4.0-49.0)	<0.001
Hemoglobin (g/dL)	12.5 (5.3-16.1)	11.45(7.1-1.5)	0.042
Hematocrit (%)	38.00 (14.8-47.7)	34.75 (22.6-51.6)	0.093
White blood cell (10^9/L)	7.37 (2.47-26.48)	7.6 (1.78-26.81)	0.775
Lymphocyte count (10^9/L)	1.51 (0.45-17.70)	1.20 (0.35-2.75)	0.002
Neutrophil count (10^9/L)	5.00 (1.29-73.10)	5.45 (0.71-22.64)	0.609
Platelet count (10^9/L)	223.00 (113.0-830.0)	229 (29.0-567.0)	0.559
Aspartate aminotransferase (IU/L)	26.00 (10.0-133.0)	29.0 (9.0-227.0)	0.251
Alanine aminotransferase (IU/L)	21.00 (3.0-191.0)	24.00 (5.0-170.0)	0.501
Urea (mg/dL)	32.20(5.0-147.0)	37.00(10.0-249.0)	0.017
Creatinine (mg/dL)	0.78 (0.37-6.71)	0.91 (0.37-8.48)	0.057
Lactate dehydrogenase (IU/L)	264.00 (118.0-968.0)	299.50 (160.0-620.0)	0.005
Albumin (g/dL)	36.71±5.30	33.21±5.16	<0.001
Ferritin (mg/L)	151.00 (5.7-4816.0)	154.40 (11.4-3428.0)	0.340
Triglyceride (mg/dL)	116.00 (31.0-582.0)	108.0 (36.0-401.0)	0.621
Creatine kinase (U/L)	74.00 (14.0-1383.0)	90.0 (10.0-1677.0)	0.445
Procalcitonin (ng/mL)	0.07 (0.01-31.51)	0.13 (0.03-77.26)	0.000
CRP (mg/dL)	21.00 (0.58-358.00)	85.50(4.00-328.97)	<0.001
Fibrinogen (mg/dL)	468.924±120.28	505.37±118.41	0.067
Prothrombin time (s)	12.80(0.0-62.4)	14.00 (0.0-29.2)	0.001
aPTT (s)	34.90 (21.7-65.0)	36.3(24.6-73.1)	0.272
D-dimer (mg/L)	0.42 (0.04-7.8)	0.55 (0.00-7.24)	0.041
cTnI (ng/mL)	5.00 (1.0-836.0)	9.00 (1.0-576.0)	<0.001
cMYBPC (ng/L)	1.64 (0.07-10.48)	1.27 (0.16-10.48)	0.717
Ferritin/Procalcitonin ratio	1682.00 (1.89-96320.00)	892.50 (1.08-26743.33)	0.163
CRP/lymphocyte ratio	16.39 (0.49-344.23)	78.94 (2.47-939)	<0.001
Albumin/CRP ratio	1.55 (0.11-67.24)	0.40 (0.10-9.90)	<0.001

aPTT: Activated partial thromboplastin time, COPD: Chronic obstructive pulmonary disease, cTnI: Cardiac troponin I; cMYBPC: Cardiac myosin-binding protein C; CRP: C-reactive protein. Data were expressed as n(%), mean ± SD or median (minimum–maximum).

Table 2. Comparison of parameters between deceased and survived patients.

	Deceased	Survived	p
cTnI (ng/mL)	16.5 (5-31)	6 (1-836)	0.002
cMyBPC (ng/L)	0.7 (0.3-8.7)	1.5 (0.1-10.5)	0.534
Ferritin/Procalcitonin	255 (14.8-4555)	1680 (1.1-96320)	0.019
CRP/Lymphocyte	113.5 (14-558.7)	35.4 (0.5-939.9)	0.004
Albumin/CRP	0.3 (0.1-2.6)	0.8 (0.1-67.2)	0.011

cTnI: Cardiac troponin I; cMYBPC: Cardiac myosin-binding protein C; CRP: C-reactive protein. Data were expressed as median (minimum–maximum).

Table 3. Univariate and multivariate logistic regression for predictors of mortality.

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	OR	p	95% CI	OR	p	95% CI
Hgb	0.725	0.021	0.551 – 0.954			
AST	1.013	0.028	1.001 -1.024			
Urea	1.028	0.001	1.012 – 1.043	1.020	0.035	1.001-1.038
Creatinine	1.473	0.016	1.073 -2.020			
Albumin	0.811	0.001	0.714 – 0.921			
CRP	1.007	0.070	0.999 -1.014			
PT	1.070	0.028	1.007 – 1.137			
aPTT	1.080	0.030	1.007-1.157			
D-dimer	1.386	0.047	1.004-1.911			
Lymphocyte	0.145	0.002	0.023-0.876	0.174	0.039	0.033-0.919
CRP/lymphocyte	1.004	0.043	1.000-1.008			

Hgb: Hemoglobin, AST: Aspartate aminotransferase, CRP: C-reactive protein, PT: Prothrombin time, aPTT: activated partial thromboplastin time, OR: odds ratio, 95% CI : 95% confidence interval.

Table 4. ROC curve analysis results for predicting mortality.

				95% CI	
	AUC	Standard Error	p	Lower	Upper
cTnI	0.795	0.062	0.008	0.673	0.918
MYBPC3	0.429	0.116	0.523	0.201	0.656
Ferritin/Procalcitonin	0.831	0.073	0.003	0.764	0.886
CRP/lymphocyte	0.852	0.051	0.002	0.751	0.952
Albumin/CRP	0.823	0.076	0.004	0.755	0.878

cTnI: Cardiac troponin I; cMYBPC: Cardiac myosin-binding protein C; CRP: C-reactive protein.

level; and CRP/lymphocyte count were independent predictors of mortality. Multivariate regression analysis revealed that lymphocyte count and urea level were independent predictors of mortality (Table 3).

ROC curve analysis showed that cTnI level and ferritin/procalcitonin, CRP/lymphocyte, and albumin/CRP ratios were valuable biochemical parameters for predicting mortality in patients with COVID-19 (Table 4).

DISCUSSION

This study showed that patients with severe COVID-19 had longer hospital stays and higher mortality rate; higher urea, LDH, procalcitonin, CRP, D-dimer, and cTnI levels; and higher prothrombin times but had lower Hgb and albumin levels and lymphocyte counts. No significant difference was observed in cMyBP-C levels between patients who had mild–moderate and severe disease. Lymphocyte count and urea concentration were the two parameters that independently predicted mortality.

Cardiac involvement during the course of infection may be mediated through the interaction of the virus with ACE-2 receptor, found in lung and cardiac tissue. Virus can initiate cardiac myocyte damage by entering the cell using the ACE-2 receptor and initiating an inflammatory response (17). Conversely, a dysfunctional immune response with an associated cytokine storm may result in acute respiratory distress syndrome and multiorgan failure, including heart, liver, and kidney failure. A study has shown that myocarditis and virus-induced myocardial injury are among the major causes of death (18).

Identification of myocardial injury during COVID-19 infection is of paramount importance as its prognostic significance has already been demonstrated (18). An ideal biomarker should have high sensitivity and specificity for detecting the extent of myocardial damage. Several biomarkers have been used in clinical practice; however, each of them has certain drawbacks. For example, creatine kinase-MB fraction and myoglobin are present in cardiac and skeletal muscles, which limit their usefulness in diagnosis and management. The most specific and sensitive biomarkers used thus far have been cardiac troponins. cTnI and C are only expressed in cardiac muscles and have both cytosolic and structurally bound molecule release kinetics that result in their continuous release to the circulation (19). Elevation of cardiac troponin levels has been reported in 5%–25% of hospitalized patients with COVID-19 (20, 21). Usually, increased troponin levels have been considered a myocardial infarction equivalent. However, inflammatory response, sepsis, and thromboembolic events are other pathophysiological mechanisms underlying high troponin levels in patients with COVID-19. Moreover, troponin levels elevate together with other acute phase reactants, including procalcitonin, ferritin, CRP, and interleukin-6, suggesting common causation (22). As such, the American College of Cardiology stated that, for the diagnosis of myocardial infarction, troponin can only be used with clinical evaluation (22). Several studies and meta-analyses have shown that increased troponin concentrations have prognostic value in patients with COVID-19 (23-25). Based on this information, the measurement of troponin levels in hospitalized patients has been recommended for prognostic purposes (26). In addition to cardiac troponins, elevation of creatine kinase-MB and N-terminal pro-brain natriuretic peptide levels have been found as indicators of cardiac damage (27).

cMyBP-C, a novel biomarker for several cardiac conditions, has gained interest over the past few years. It plays an important role in sarcomere organization and the regulation of cardiac contraction and relaxation. It has a better diagnostic power than high-sensitivity cardiac troponin T (hs-cTnT) Troponin T for the diagnosis of acute myocardial infarction (28). Values < 10 ng/L had 100% sensitivity for ruling out myocardial infarction in patients with chest pain for 2 h (28). Studies have shown that serum cMyBP-C levels begin to increase within 30 min and significantly decline after 12 h of coronary obstruction (29). Hence, it could be used for the early diagnosis of myocardial infarction (30). While there is no doubt that troponins are reliable indicators of myocardial damage, slow release of the troponin complex may obscure repetitive episodes of injury. Accordingly, this study aimed to analyze cMyBP-C molecule levels, which are cardiac specific and have a short half-life, in COVID-19 victims.

Higher cMyBP-C levels were expected in severe disease, but any significant differences were not found between patients who had severe and mild–moderate disease. Moreover, according to regression analysis, cMyBP-C was not a predictor of mortality in COVID-19. In the present study, serum cMyBP-C levels were measured within 24 h of hospital admission. Since our hospital was a tertiary referral hospital, patients from different hospitals were transferred to our COVID-19 ward. This might cause discrepancies in the timing of blood specimen collection among patients. The hospitalization period of the patients who had been transferred from other institutions was unknown. Hence, blood samples might be collected from these patients during the fall phase. When we looked closely at the data, creatine kinase levels also did not differ between the two groups, which also show rapid rise and fall kinetics. Most studies conducted on cMyBP-C has mainly focused on its diagnostic power to detect myocardial infarction and its role in the pathogenesis of hypertrophic and dilated cardiomyopathies. To the best of our knowledge, no study has been conducted to determine cMyBP-C levels in infectious diseases, including COVID-19. According to our results, cMyBP-C has limited use in the prognostification of COVID-19.

The present study did not assess the function of the left and right ventricules in patients with COVID-19. Previous studies have shown that either left or right ventricular dysfunction predicted mortality in this group of subjects (31). Moreover, there are some datas suggesting that COVID-19 predominantly affect the right ventricle (32). D'alto et al. showed that COVID-19-induced acute respiratory distress syndrome was associated with uncoupling of right ventricular function from pulmonary

function (33). Moody et al. demonstrated that patients with severe COVID-19 pneumonia had reduced right ventricular systolic function without abnormalities of left ventricular function (34). In that study, reduced right ventricular function was found to be an independent predictor of all-cause mortality.

Our study findings were in line with those of previous studies. Further research has already been conducted to determine the best diagnostic/prognostic parameter in patients with COVID-19. Several circulatory biomarkers have been found to be valuable during the course of infection, including procalcitonin, CRP, and Interleukin-6 (35-38). Considering that the early recognition of severe cases is of utmost importance, finding a reliable marker for the management of the disease to improve outcomes is essential. The present study showed that renal function, CRP, procalcitonin, cTnI, and D-dimer tests can be used for the clinical classification of COVID-19. Moreover, lymphocyte count and urea levels should be closely monitored until full recovery, as these levels were associated with increased mortality.

This study has several limitations: (1) It was a single-center and observational study. (2) The sample size was relatively small. (3) Levels of cMyBP-C were measured only once; thus, individual variation in cMyBP-C during the hospital stay stay remain unknown. (4) As the number of deaths in the study population was small, accurate estimation of mortality could not be performed. (5) Echocardiographic examinations of the patients were not performed.

In conclusion, cMyBP-C has limited use in determining the severity and predicting the prognosis of COVID-19. Multicenter and large-scale studies are required to evaluate the role of cMyBP-C in patients with COVID-19.

Ethics Committee Approval: The Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee agreed to the study protocol (Date: October 16, 2020/No:20208181).

Informed Consent: Informed consent from patients or their legal representatives was obtained.

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