ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE
ÇOCUK SAĞLIĞI VE HASTALIKLARI / PEDIATRICS

ATLJM 2025; 5 (13): 77-82
https://doi.org/10.54270/atljm.2025.83

PLASMA CARDIAC MYOSIN BINDING PROTEIN C AND SERUM NT PRO BNP LEVELS IN CHILDREN WITH CONGESTIVE HEART FAILURE

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ABSTRACT

Heart failure (HF) in children is a clinical syndrome defined as the inability of the heart to meet the metabolic needs of the body. Natriuretic peptides and cardiac troponins are the most used cardiovascular biomarkers for diagnosis and prognosis of HF. Many other biomarkers related to diagnosis, prognosis and risk classification in HF have also been identified.

In this study, we aimed to investigate whether the prognostic value of the cardiac myosin binding protein-C (cMyBP-C) is a possible new biomarker that can be used by the clinician while evaluating newly diagnosed HF in children. This is a prospective case-control study involving 24 children with congestive heart failure (CHF) and 30 healthy children. After taking a medical history and physical examination, patients were evaluated by electrocardiogram, telecardiography and echocardiography, and a modified Ross scoring was performed. Plasma cMyBP-C and other biomarker N-terminal pro-natriuretic peptide (NT-proBNP) values, routine blood tests, liver enzymes were measured during admission. The mean cMyBP-C (ng / ml) plasma level of the patient group was 1.55 ng / ml (0.1-9.4) and the control group, 0.1 ng / ml (0.3-1) ($p < 0.01$). After an evaluation of the etiological investigation, the mean plasma cMyBP-C level detected in the myocarditis group was 1.9 ng / ml (0.1-3.1). Accordingly, the mean value of cMyBP-C in the patient group was significantly higher than the control group and the highest in the acute myocarditis group ($p < 0.01$). CMyBP-C may be a new useful diagnostic and prognostic biomarker in children with acute HF.

Keywords: Heart failure, children, NT-proBNP, cardiac myosin binding protein C

KONJESTİF KALP YETMEZLİĞİ OLAN ÇOCUKLARDA PLAZMA KARDİYAK MİYOZİN BAĞLAYICI PROTEİN-C VE SERUM NT-PROBNP DÜZEYLERİ

ÖZET

Çocuklarda kalp yetmezliği (KY), kalbin vücudun metabolik ihtiyaçlarını karşılayamaması olarak tanımlanan klinik bir sendromdur. Natriüretik peptitler ve kardiyak troponinler, KY' nin tanısı ve prognozu için en çok kullanılan kardiyovasküler biyobelirteçlerdir. KY' de tanı, prognoz ve risk sınıflandırmasıyla ilgili birçok başka biyobelirteç de tanımlanmıştır.

Bu çalışmada, kardiyak miyozin bağlayıcı protein-C' nin (cMyBP-C) prognostik değerinin, klinisyen tarafından çocuklarda yeni teşhis edilen KY' yi değerlendirirken kullanılabilecek olası yeni bir biyobelirteç olup olmadığını araştırmayı amaçladık. Bu, konjestif kalp yetmezliği (KKY) olan 24 çocuk ve 30 sağlıklı çocuğu içeren prospektif bir vaka kontrol çalışmasıdır. Tıbbi öykü ve fizik muayene alındıktan sonra hastalar elektrokardiyografi, telekardiyografi ve ekokardiyografi ile değerlendirildi ve modifiye edilmiş bir Ross skorlaması yapıldı. Plazma cMyBP-C ve diğer biyobelirteç N-terminal pro-natriüretik peptid (NT-proBNP) değerleri, rutin kan testleri, karaciğer enzimleri başvuru sırasında ölçüldü. Hasta grubunun ortalama cMyBP-C (ng/ml) plazma düzeyi 1.55 ng/ml (0.1-9.4), kontrol grubunun ise 0.1 ng/ml (0.3-1) idi ($p<0.01$). Etiyolojik araştırmanın değerlendirilmesi sonrasında miyokardit grubunda saptanan ortalama plazma cMyBP-C düzeyi 1.9 ng/ml (0.1-3.1) idi. Buna göre hasta grubunda cMyBP-C'nin ortalama değeri kontrol grubundan anlamlı olarak yüksek olup akut miyokardit grubunda en yüksekti ($p<0.01$). CMyBP-C, akut KY' li çocuklarda yeni ve yararlı bir tanı ve prognoz biyobelirteci olabilir.

Anahtar kelimeler: Kalp yetmezliği, çocuk, NT-proBNP, kardiyak miyozin bağlayıcı protein C.

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ERDEN D, KARAKURT C, TAŞKAPAN MÇ, ELKIRAN Ö, GÖZÜKARA BAĞ H. PLASMA CARDIAC MYOSIN BINDING PROTEIN C AND SERUM NT PRO BNP LEVELS IN CHILDREN WITH CONGESTIVE HEART FAILURE. ATLJM. 2025;5(13):77-82.

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Gönderim Tarihi: 05 AĞUSTOS 2024
Kabul Tarihi: 16 NİSAN 2025

INTRODUCTION

Heart failure is a progressive clinical and pathophysiological syndrome brought on by cardiovascular or non-cardiovascular causes and accompanied by symptoms such as edema, respiratory distress, growth retardation, exercise intolerance, and circulatory, neurohormonal and molecular disorders (1).

Congestive heart failure is an important cause of morbidity and mortality it can be seen throughout childhood from birth onwards. Therefore, rapid diagnosis and management of heart failure is one of the most important components in heart failure. Natriuretic peptides and cardiac troponins are the most used cardiovascular biomarkers in the diagnosis and prognostic stratification of congestive heart failure (2).

Numerous other biomarkers have also been proposed for diagnosis, prognosis, and risk stratification of heart failure. The release mechanisms of these biomarkers are the ventricular remodeling, myocyte damage, and myocardial ischemia (3-4).

Myosin binding protein-C (MyBP-C) is a thick filament-associated protein localized to the crossbridge-containing C zones of striated muscle sarcomeres. MyBP-C contributes to thick filament structure via interactions at its C-terminus with the light meromyosin section of the myosin rod and with titin (5). MyBP-C also has a role in the regulation of contraction, due to the binding of its N-terminus to the subfragment-2 portion of myosin (5). cMyBP-C mutations have been identified as the underlying cause of hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy, left ventricular noncompaction, and other cardiomyopathies.

There are several in vitro studies which show that cMyBP-C is released after myocardial damage to myocardial tissue and its products appear in the circulation after myocardial infarction (MI) (6-7).

A study published in 2019, compared micro RNAs and protein biomarkers, and cMyBP-C was found to be the most sensitive cardiac biomarker for evaluation of myocardial damage (8).

However, there are few studies which investigate the diagnostic value of cMyBP-C in children with heart failure.

In this study, we aimed to investigate the prognostic value of cMyBP-C as a biomarker in children newly diagnosed with heart failure.

MATERIAL AND METHODS

In this study, 24 children who were diagnosed with acute congestive heart failure and 30 healthy age-matched children who were admitted to our Hospital, Pediatric Cardiology Clinic, were included.

After obtaining the permission of the ethics committee for the study (2018/99), medical histories were taken, physical examinations were performed, and patients were evaluated with electrocardiogram, telecardiography and echocardiography (Vivid 7 Pro, GE), and modified Ross scoring was performed (9). After obtaining written consent from the parents for each patient, the medical data of the patient and control groups were recorded, venous blood was collected in EDTA tubes and stored as frozen plasma at 80°C. Viral serological tests were requested from patients with suspected myocarditis.

Children with infections other than heart failure, autoimmune disease, malignancy, or genetic diseases were excluded from the study. Plasma cMyBP-C and other biomarker Pro-B type Natriuretic peptide (NT-proBNP) values, routine blood tests, liver and kidney function tests were measured at admission. The plasma concentrations of NT-proBNP were analyzed by the electrochemiluminescence method (Biotech brand sinergy H1 model biochemistry autoanalyzer, immunoturbidometric method; NT-proBNP, Siemens immulat-2000 model device and chemiluminescence method). Results are expressed in pg / mL.

Plasma cMyBP-C levels were analyzed with the Biotec synergy H1 model biochemistry autoanalyzer by ELISA method. Results are expressed in ng / mL.

Data were summarized with median, minimum and maximum values. The Mann Whitney U test was used to compare the Ross score of the two patient groups. The Kruskal-Wallis test followed by the Conover pairwise comparison methods were used for to compare the control group and the patient groups, The significance level was accepted as 0.05 in all tests.

RESULTS

In this study, 24 children (5 boys, 19 girls) who were diagnosed with acute congestive heart failure and 30 healthy (16 boys, 14 girls) age-matched children were included. The mean age of our patients was 3.1 years (3 days to 17 years), and the mean age of the control group was 9.8 years (3 to 17 years). The mean weight of the patient group was 12.9 (2.6-58) kg, and the average weight of the control group was 32 (14-62) kg. The average height of the patient group was 83 cm (49-168), and the average height of the control group was 128 cm (96-165). There was no statistically significance between the patient and control groups according to age, weight, height ($p>0.05$).

Medical history of patient group showed cyanosis in 7 patients, tachypnea in 8 patients, sweating during feeding in 4 patients, feeding difficulty in 11 patients, failure to gain weight in 11 patients, and fatigue during feeding or exercise in 18 patients. Six patients had prior viral infection history.

On physical examination, 19 patients have tachycardia, 15 patients have systolic ejection murmur, 13 patients have hepatomegaly and 14 of them have edema.

ECG findings were that 19 patients had sinus tachycardia, 10 patients had left ventricular hypertrophy, 1 patient had a right bundle branch block. Four patients had low voltage QRS on the EKG. ST segment elevation was observed in the ECG of the patient with myopericarditis.

Cardiomegaly was found in 16 patients (67%) on telecardiography. After echocardiographic evaluation, 6 patients were diagnosed with myocarditis, 6 patients had dilated cardiomyopathy, 2 patients noncompaction cardiomyopathy, 1 patient myopericarditis, 9 patients heart failure related to congenital heart disease (5 patients had VSD,1 patient complete AVSD, 1 patient double inlet left ventricle+ TGA, 1 patient single atrium+ VSD , and 1 patient had hypoplastic left heart syndrome) (Table 1).

The mean EF of the patient group was 50% (33-87), the control group was 70 (65-81), the mean SF of the patient group was 26% (15-41), and the control group was 40 (33-49).

The mean cMyBP-C (ng / ml) plasma level of the patient group was 1.55 ng / ml (0.1-9.4) and the control group was 0.1 ng / ml (0.3-1) ($p<0.01$). The mean plasma cMyBP-C level detected in the myocarditis group was 1.9 ng / ml (0.1-3.1).

Table 1: Demographic and clinical data of patient and control groups

	Patient group	Control group
Age (year)	3,1 (3 days- 17 years)	9.8 (3-17 years)
Gender (female/male)	19/5	14/16
Weight (kg)	12.9 (2.6-58)	32 (14-62)
Height (cm)	83 (49-168)	128 (96-165)
Diagnosis		
Myocarditis	6 (25%)	
Dilated cardiomyopathy	6 (20%)	
Noncompaction CMP	2 (8%)	
Myopericarditis	1 (4%)	
Congenital heart disease	9 (37 %)	
VSD	5	
Single atrium +VSD	1	
Complete AVSD	1	
Double inlet LV,TGA	1	
HLHS	1	
Modified Ross score		
Mild heart Failure	6 (%25)	
Moderate heart failure	10 (%42)	
Severe heart failure	8 (%33)	

DCM: Dilated cardiomyopathy, VSD: Ventricular septal defect, Noncompaction CMP: noncompaction cardiomyopathy, ASD: atrial septal defect, AVSD: atrioventricular septal defect, TGA: transposition of great arteries, HLHS: Hypoplastic left heart syndrome

Mean NT-proBNP levels were found to be 4250 pg / ml (195-35000) in the patient group, 30532.5 pg / ml (3935-35000) in myocarditis and 47.5 pg / ml (19-221) in the control group. ($p<0.01$). These values correlated with the cMyBP-C values (Table 2).

When the patients were evaluated according to the modified Ross scoring, there were 6 (25%) patients with mild CHF, 10 (42%) with moderate CHF and 8 (33%) with severe CHF. A significant increase was found in cMyBP-C and NT-proBNP values in relation to the severity of HF ($p<0.01$) (Table 3).

Table 2: Plasma cMyBP-C and NT-proBNP levels of patient and control groups

	Patient group	Myocarditis	Control group	p value
cMyBP-C (ng/ml)	1.55 (0.1-9.4)	1.9 (0.1-3.1)	0.1 (0.3-1)	<0.01
NT-proBNP (pg/ml)	4250 (195-35000)	30532 (3935-35000)	47.5 (19-221)	<0.01

cMyBP-C: Cardiac myosin binding protein-C , NT-proBNP: N terminal pro BNP

Table 3: cMyBP-C and NT Pro-BNP levels of patient group according to modified Ross score

Modified Ross score	cMyBP-C (ng/ml)	NT-proBNP (pg/ml)
Mild heart Failure	0.63 (0.4-1.43)	4320 (276-9097)
Moderate heart Failure	1.01 (0.075-2.96)	9052 (195-35000)
Severe heart Failure	3.1 (0.184-9.39)	28145 (3500-35000)
P value	p <0.01	p <0.01

DISCUSSION

Heart failure is a progressive clinical and pathophysiological syndrome brought on by cardiovascular or non-cardiovascular causes and accompanied by edema, respiratory distress, growth retardation, exercise intolerance, and circulatory, neurohormonal and molecular disorders (1).

Congestive heart failure is a condition that can be seen throughout childhood from birth onwards and it is an important cause of morbidity and mortality in childhood. Congestive heart failure is a condition such as congenital heart diseases, primary cardiomyopathy related to dilated, hypertrophic, arrhythmogenic right ventricular dysplasia and non-compaction cardiomyopathy and secondary cardiomyopathy related to ischemia, infections, arrhythmias with 60% of the cases in developing countries occurring due to cardiomyopathies (10).

Biomarkers are utilized in many clinical conditions, but in heart failure, as the processes involved in pathophysiology of the heart failure are becoming understood, biomarkers are also increasingly useful in diagnosis and risk stratification of heart failure.

Natriuretic peptides and cardiac enzymes are the most used biomarkers. Natriuretic peptides are a group of hormones providing sodium and fluid balances. B type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) primarily secreted by cardiac myocytes secondary myocardial lengthen by increased cardiovascular volume overload (2). C type natriuretic peptide (CNP) is also secreted by endothelial cells (2). BNP and N terminal pro BNP evolved to be most useful biomarkers in the diagnosis of heart failure as well as prognostic risk stratification (11-12).

Cardiac troponins are another useful cardiac biomarker and they are located within cardiac myocytes provides muscle cell contraction. Troponin I and T have been used in heart failure related to the assessment of cardiac myocyte damage (13).

Alternatively, other biomarkers such as mid-region pro ANP, mid region pro Adrenomedullin have been proposed instead of natriuretic peptides. Mechanical stress related biomarkers, such as sST2, fibrosis related biomarkers such as growth differentiation factor 15, inflammation related biomarkers such as CRP, TNF α and galectin 3 have been also studied in heart failure (14,15,16).

Myosin binding protein-C (MyBP-C) is a thick filament-associated protein localized to the crossbridge-containing C zones of striated muscle sarcomeres. MyBP-C contributes to thick filament structure via interactions at its C-terminus with the light meromyosin section of the myosin rod and with titin (3-4). The protein also has a role in the regulation of contraction, due to the binding of its N-terminus to the subfragment-2 portion of myosin (3-4).

There are several in vitro studies which show that cMyBP-C is released after myocardial damage to

myocardial tissue and its products appear in the circulation after myocardial infarction (MI) (6-7).

A study published in 2019, comparing micro RNAs and protein biomarkers, cMyBP-C was found to be the most sensitive cardiac biomarker for evaluation of myocardial damage (8).

However, there are few studies which investigate the diagnostic value of cMyBP-C in children with heart failure. It has been confirmed that cardiac stress can reduce the phosphorylation of cMyBP-C and trigger its cleavage, and that increased stress in the sick heart can trigger the release of the 40-kDa truncated fragment that competes for the actin and myosin binding site of cMyBP-C (17). This finding suggested that cMyBP-C level could be used for the evaluation of early diagnosis of HF. Govindan et al. found that the presence of elevated levels of cMyBP-C in the blood provides a promising novel biomarker able to accurately rule in MI, thus aiding in the further assessment of ischemic heart disease (7).

El Amrousy et al. found that there was a significant increase in plasma levels of cMyBP-C (ng/ml) in children with heart failure (122.44 ± 41.01) as compared to patients after treatment (71.38 ± 49.68) and to the control group (24.40 ± 9.83) (18). Chen et al. have confirmed that circulating cMyBP-C is a promising novel biomarker for evaluating cardiac surgical trauma in patients undergoing a cardiac operation (19). They found that released cMyBP-C peaked immediately after cardiac surgery (0 h), attaining a 3.8-fold higher than before the operation, then dropped abruptly within 24 hours, and stayed at a higher level until discharge. Postoperative cMyBP-C levels correlated positively with high-sensitivity cardiac troponin T (hs-cTnT), creatine kinase, myoglobin, and creatine kinase MB isoenzyme (19).

Contrary to the studies conducted on adult patients, there are few studies on this subject in children with heart failure. In our study, 24 patients with heart failure and 30 healthy children of similar age and sex as the control group were included. Myocarditis was considered as a separate group within the patient group. The mean cMyBP-C (ng / ml) plasma level of the patient group was 1.55 ng / ml (0.1-9.4) and the control group was 0.1 ng / ml (0.3-1) ($p < 0.01$). The mean plasma cMyBP-C level detected in the myocarditis group was 1.9 ng / ml (0.1-3.1). Accordingly, the mean value of cMyBP-C in the patient group was significantly higher than the control group and the highest in the acute myocarditis group. In one of the limited studies in this area, similar to our study, it was shown that there was a significant increase in cMyBP-C plasma levels at presentation in children with HF compared to patients and the control group after treatment (18). There was a significant decrease in cMyBP-C values in the healthy control group (mean 0.1 ng / dl (0.3-1)). When the patient group was evaluated within itself, a negative correlation was observed between the ejection fraction and that cMyBP-C values that patients with decreased EF have high cMyBP-C levels ($p < 0.01$).

When the patients were evaluated according to the modified Ross scoring, it was found that there was a significant increase in cMyBP-C values and as well as NT pro BNP values in relation to the severity of HF ($p < 0.01$). This was consistent with other studies (18-20).

CONCLUSION

According to the results of our current study, it is thought that cMyBP-C can be used as a new biomarker in pediatric patients with newly diagnosed heart failure and it may be more sensitive especially in patients with myocardial tissue damage related to myocarditis.

DECLARATIONS

Acknowledgements

None.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

The authors declare that they have no competing interests.

Ethical Standards

The study was approved by the local Independent Ethics Committee of the Inonu University Faculty of Medicine Hospital.

Review Identification No. EC: 2018/99.

All subjects participating in the study gave written informed consent.

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