JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1279791
J Contemp Med 2023;13(3):549-554

Original Article / Orijinal Araştırma

Relationship of Pro-BNP Levels with Cardiovascular Events in Pediatric Cardiac and Non-cardiac Diseases

Pediyatrik Kardiyak ve Nonkardiyak Hastalıklarda Pro-BNP Düzeyi ile Kardiyovasküler Olayların İlişkisi

Ayse Sulu, Hikmet Kıztanır, Pelin Kosger, Birsen Ucar

Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatric Cardiology, Eskisehir, Turkey

Abstract

Aim: We aimed to determine the relationship of Pro-BNP levels, with the diagnosis, clinical, and laboratory parameters in children. In addition, the predictive power of the Pro-BNP levels in determining the cardiovascular events was evaluated.

Material and Method: This study comprised 829 patients whose levels of Pro-BNP were measured. The data were obtained retrospectively from the hospital records. The relationship of the Pro-BNP level of the patients with the clinical, laboratory, and echocardiographic data was determined. The predictive power of the Pro-BNP and Troponin T levels in determining the development of cardiovascular events was evaluated.

Results: Cardiovascular events developed in 143 patients during the follow-up period. The Pro-BNP levels were observed to be significantly higher ($p< 0.001$) in the group in which patients developed cardiovascular events. The Pro-BNP levels demonstrated a positive correlation with both Troponin T levels and procalcitonin levels and a strong negative correlation with the age, height, and weight of the patients. The most important predictive factors for determining the development of cardiovascular events were the presence of tachypnea, increased Pro-BNP levels, increased left ventricular end-diastolic diameter, and increased tricuspid regurgitation velocity.

Conclusion: The most important determinants of a cardiovascular event, as revealed in the present study, are the presence of tachypnea, Pro-BNP levels, TR velocity, and the LVEDD z-score of patients. Moreover, the Pro-BNP levels and Troponin levels demonstrate a strong positive correlation. Randomized prospective studies are warranted to improve the efficacy of using Pro-BNP in differentiating cardiac and non-cardiac diseases in children.

Keywords: Brain natriuretic peptide, congenital heart disease, sepsis, troponin T

Öz

Amaç: Bu çalışmada amacımız Pro- BNP düzeyi ile hastaların tanıları, klinik ve laboratuvar bulguları arasındaki ilişkiyi değerlendirmektir. Ayrıca pro-BNP düzeyinin kardiyovasküler olay belirlemedeki öngörü düzeyini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmada, Pro-BNP düzeyi bakılmış olan 829 hastanın verileri elektronik dosya kayıtlarından retrospektif olarak elde edildi. Pro-BNP düzeyi ile hastaların klinik, laboratuvar ve ekokardiyografik verileri rasındaki ilişki değerlendirildi. Ayrıca Pro-BNP ve troponin T düzeylerinin kardiyovasküler olayları belirleyiciliği değerlendirildi.

Bulgular: Takip süresi oyunca 143 hastada kardiyovasküler olay gelişti. Pro-BNP seviyesi bu hasta grubunda anlamlı yüksekti ($p< 0,001$). Pro-BNP düzeyi ile troponin T, prokalsitonin düzeyi ile pozitif, yaş, boy ve vücut ağırlığı ile güçlü negatif korelasyon mevcuttu. Kardiyovasküler olay belirlemede en güçlü prediktörler takipne, artmış Pro- BNP, artmış triküspit kapak velositesi ve artmış sol ventrikül end-diyastolik çapı idi.

Sonuç: Bu çalışmada kardiyovasküler olay belirlemede en güçlü belirleyiciler takipne, Pro-BNP düzeyi, triküspit yetersizlik velositesi ve sol ventrikül end-diyastolik çapı Z skoru idi. Ayrıca pro-BNP ve Troponin T düzeyleri arasında güçlü pozitif korelasyon mevcuttu. Çocuklarda kardiyak ve nonkardiyak hastalıkların ayırımında pro-BNP düzeyi belirleyiciliği düşük bulunmuş olup, randomize prospektif kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Beyin natriüretrik peptid, konjenital kalp hastalığı, sepsis, troponin T

Corresponding *(İletişim)*: Ayse Sulu, Eskisehir Osmangazi University Faculty of Medicine, Department of Pediatric Cardiology, Eskisehir, Turkey.
Address: Büyükdere mah. Prof Dr. Nabi AVCI bulvarı. No: 4 postal code: 26040.
E-mail *(E-posta)*: suluayse@windowslive.com
Received *(Geliş Tarihi)*: 10.04.2023 **Accepted *(Kabul Tarihi)*:** 15.05.2023

INTRODUCTION

B-type natriuretic peptide (BNP) is a peptide containing 32 amino acids and is secreted by the cells in the heart and the brain. The end-diastolic pressure and increased ventricular wall strain are the main triggers for BNP release.[1] The guidelines suggest a class 1 recommendation for the use of BNP in the diagnosis, differential diagnosis, and follow-up of adult patients.[2] Additionally, it is advised (class 2b) for pediatric heart disease diagnosis and follow-up.[3,4] Although the use of BNP in pediatric patients is growing nowadays because of its cost and convenience, there are still several restrictions on its use in children, such as the large variety of cardiac and non-cardiac disorders that can lead to heart failure.[5] The typical BNP range in children varies with age.[6] Numerous studies claim that the BNP levels, which are known to rise for a variety of causes, are inversely correlated with the clinical severity of pediatric heart failure.[7-11] BNP may also help distinguish between disorders that are cardiac and non-cardiac disease.[12]

Although there is evidence in support of the use of BNP in the diagnosis of heart failure in children, the differentiation of cardiac caused from the non-cardiac ones, the follow-up treatment, and prognosis determination, no consensus has been reached so far on the situations in which the use of BNP is recommended.[5] However, several studies have been conducted to compare specific diagnostic groups with healthy controls. A few of these studies also compared the factors underlying Pro-BNP elevation and Pro-BNP data among different diagnostic groups. The main goal of the current study was to determine whether there were any significant differences in the illness groups based on the Pro-BNP levels. In addition, the relationship of the Pro-BNP levels with the clinical and other laboratory data of the patients and the predictive power of these levels in determining the development of cardiovascular event (CVE) were evaluated.

MATERIAL AND METHOD

The current study included all patients who were less than 18 years old and who had Pro-BNP testing done in our institution between March 2014, and March 2020. Patients who were newborns and had heart surgery were excluded. The patient's age, height, weight, symptoms, physical examination findings, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, serum albumin, troponin T, procalcitonin level, C-reactive protein (CRP), culture results, electrocardiography, echocardiography, and chest X-ray. Data on the final diagnosis, CVE, history, mortality, and length of hospital stay were obtained from hospital records. We investigated the correlations between pro-BNP levels and CVE (surgery, arrhythmia, severe heart failure, interventional cardiac procedure, repeated hospitalization, and mortality). Eskişehir Osmangazi University non-interventional researches ethics committee approval was obtained (2020-181, 25403353-050.99-E.52038).

Statistical Analysis

The IBM SPSS package software was used to statistically analysis. The homogeneity of the quantitative variables to the normal distribution according to the groups was evaluated using the Shapiro–Wilk test. The t-test was used to compare the two groups for variables with normally distributed data, and the Mann-Whitney U test was used for variables with non-normally distributed data. The Kruskal- Wallis test was used to compare groups of three or more. By using Spearman's correlation analysis, the factors' associations with the CVE were established. Multivariate logistic regression analysis was adopted to evaluate independent risk factors related to cardiovascular event. The specificity and sensitivity values for Pro-BNP utilized at the levels were assessed using the ROC analysis. Pro-BNP was utilized at levels of 350pg/mL and 1701pg/mL and Troponin T was used at normal threshold values (0-0.014 ng/ml) in the Ross clinical scoring for assessing the CVE were evaluated using the ROC analysis to determine their specificity and sensitivity values.

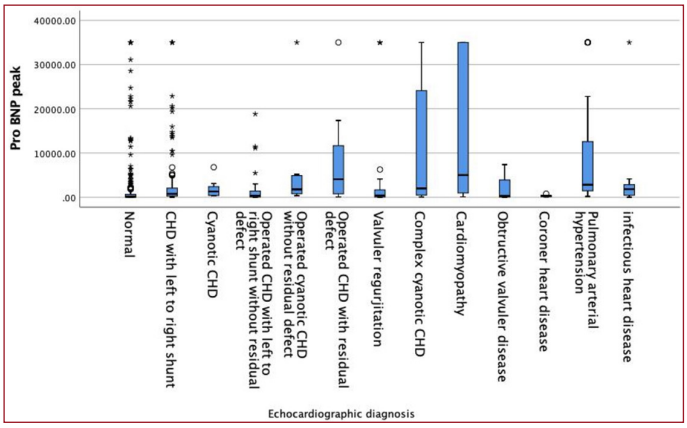
RESULTS

A total of 829 patients who had undergone pro-BNP examination between March 2014 and March 2020 were included in the present study, 397 (47.9%) of them were male. The median age was 84.72 months (1-251), median height was 110.64 cm (44-184), mean weight was 27.42 kg (1.32-112), and median duration of stay in the hospital was 6.19 days (0–76). The mean follow-up was 26± 18 months. In the 629 (75.2%) patients for whom the echocardiographic data were available, the left ventricular end-diastolic diameter (LVEDd) z score was 0.79 (-3.02 to +9.56) and the median tricuspid valve regurgitation velocity was 2.14 m/s (1- 5.4). The median peak Pro-BNP level was 3205.7 pg/mL (1.98–35000), while the minimum level was 4330.34 pg/mL (6.45–35000) in the patients with repeated measurements; the time interval between the minimum and maximum levels was 6.29 days (0.25–40). The median levels for troponin T, CRP, procalcitonin, hemoglobin, hematocrit, ALT, AST, serum creatinine, and serum albumin were 0.069 ng/mL (0.00-3.3), 4.28 mg/L (0-134.2), 3.33ng/mL(0-100), 12.08 gr/mL(5.7-19.9), 12.08% (5.7%–19.9%), 27.8 IU/L (2–1207), 46.5 IU/L (8–5582), 0.61 mg/dL (0.04–13.11), and 3.97 gr/dL (0.53–5.7), respectively.

A total of 338 (40.7%) of the patients were hospitalized; of these, 99 (11.9%) were admitted to the pediatric intensive care unit, 157 (18.9%) to the pediatric emergency service, 143 (17.2%) to the pediatric cardiology outpatient clinic, and 11.3% to other outpatient clinics for follow-up. Inpatient units were shown to have higher pro-BNP levels than outpatient units (inpatient units median= 665.45 pg/mL (min-max: 5- 35000); outpatient unit median: 78.84 pg/mL (min-max: 1.98- 35000; p< 0.0001).

The most common causes of pro-BNP detection were underlying congenital heart disease in 23.2% of patients and

other cardiac conditions in 40% of patients. The additional symptoms included respiratory distress, illnesses including acute and chronic renal failure that can lead to volume overload. Twenty three percent of patients had tachypnea, 20% had tachycardia, and 14% had fever, as determined by the physical exam. There were 629 individuals who had transthoracic echocardiography, and 290 of them had normal echocardiographic findings. **Graph 1** shows the pro-BNP levels and echocardiographic abnormalities. When the pro-BNP levels of the patients with volume and pressure load were compared according to their echocardiographic diagnosis, no significant difference was found (median, min-max 827 (6.48-36000), 1369 (11.17-35000) pg/ml, respectively).



Graph 1. Pro-BNP levels according to echocardiographic diagnosis groups
CHD: Congenital heart disease

Electrocardiographic pathology was detected in 39 of 652 patients (5.9%) with available electrocardiographic records, tachyarrhythmia was detected in 20 patients, sinus tachycardia was detected in six patients, right ventricular hypertrophy in nine patients, the atrioventricular block in two patients, Wolf Parkinson White (WPW) in one patient, and tachyarrhythmia in one patient. and frequent ventricular extrasystoles in one patient.

The highest pro-BNP levels were found in the sepsis group when the patients were divided into six groups: cardiac, respiratory, sepsis, nephrological, neurological, and hematological (Pro-BNP median levels QR 25-75: 355 pg/mL (62-3147), 375 pg/mL (69-3822), 1213 pg/mL (65-19386), 365 pg/mL (36-9644), 850 pg/mL (64-35000), and 104 pg/mL (29-1283), respectively). In comparison to the cardiac, nephrological, and hematological groups, the pro-BNP levels in the sepsis group were significantly higher (p= 0.03, 0.044, and 0.001, respectively). The hematological group's pro-BNP levels were significantly lower than those of the other groups' (p= 0.001, 0.001, 0.001, 0.019, and 0.015, respectively). The median troponin T levels in the cardiac group were 0.006 (0.004-0.019) ng/mL and in the respiratory group, they were 0.009 (0.005-0.048) ng/mL. The troponin T in the respiratory group were significantly higher than cardiac group (p= 0.018). In the sepsis group, the median troponin T levels were 0.008 (0.006- 0.088) ng/mL, while in the hematological group, it was 0.006 (0.004-0.011) ng/ml. The median troponin T in the sepsis group were significantly higher (p= 0.048) compared to the hematological group and significantly lower (p= 0.013) compared to the respiratory group. **Table 1** shows the correlations of the pro-BNP levels and other parameters.

Table 1. Correlation of Pro-BNP level with clinical and laboratory data

	Correlation Coefficient	p
Length of stay in hospital	0.496	<0.0001
Years	-0.512	<0.0001
Height	-0.531	<0.0001
Weight	-0.534	<0.0001
Troponin	0.568	<0.0001
C-reactive protein	0.164	<0.0001
Procalcitonin	0.550	<0.0001
Hemoglobin	-0.493	<0.0001
Hematocrit	-0.454	<0.0001
ALT	0.280	<0.0001
AST	0.388	<0.0001
Creatinine	-0.159	<0.0001
Albumin	-0.459	<0.0001
TR velocity	0.357	<0.0001
LVEDD z score	0.205	<0.0001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TR:Tricuspit regurgitation, LVEDD: left ventricul end-diastolic diameter

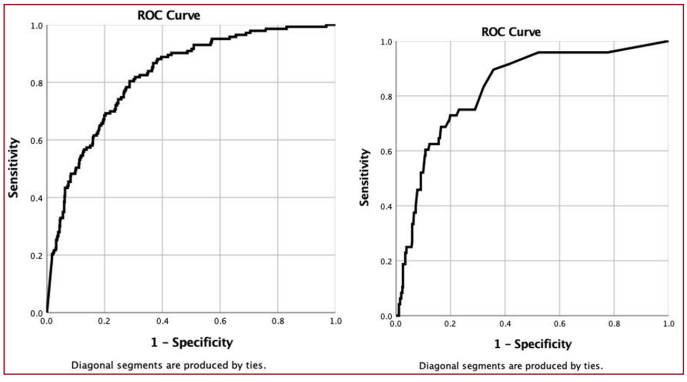
In the 143 patients who had one or more events had developed follow-up. Cardiac surgery was required in 71, interventional angiography in 8, tachyarrhythmia requiring ablation in one, uncontrolled congestive heart failure in one, arrhythmia in 4, and repeated hospitalizations in 12 patients. Among these 143 patients, 46 had died. In 13 cases, the second event had gone further. **Table 2** shows comparison of the data of the group with and without CVE.

The presence of fever and tachycardia did not show a significant correlation with the CVE, but tachypnea (p 0.0001 Exp(B): 0.106, B: -2.243, lower: 0.067, upper: 0.168) and blood culture positive (p< 0.0001 Exp(B): 0.171, B:–1.763, 95% CI lower:0.065, upper:0.451) had positive correlations. The pro-BNP level (p< 0.0001 Exp(B):1, B: 0.95% CI lower:1, upper:1), the LVEDD z score (p=0.008 Exp(B):0.837, B:–0.178, 95% CI lower:0.733, upper:0.955), and the TR velocity (p<0.0001 Exp(B):0.444, B:–0.812, 95% CI lower:0.305, upper:0.647) were revealed as the significant positive predictors of the CVE. In terms of the development of CVE, 84% sensitivity and 65% specificity were revealed when using 350pg/mL pro-BNP and Ross scoring for the ROC analysis, while 58% sensitivity and 85% specificity were revealed for 1701pg/mL Pro-BNP (13). When using troponin T at 0.0014ng/mL for event detection, 73% sensitivity and 79% specificity were revealed (**Graph 2A** and **2B**).

Table 2. Comparison of the data of the group with and without cardiovascular event

	With cardiovascular event	Without cardiovascular event	p
	Median (min- max)	Median(min-max)	
Ages (month)	9 (1-210)	95.5 (1-251)	<0.001
Height (cm)	66 (45-182)	124.0 (44-184)	<0.001
Weight (kg)	6.34 (1.32- 100)	25 (2.25-112)	<0.001
TR Velocity (m/s)	2.5 (1.1-5)	2 (1-5.4)	<0.001
LVEDD z score	1.4 (-3.02- 9.56)	0.42 (-2- 6.84)	<0.001
Peak Pro-BNP (pg/ml)	3013 (6.69- 35000)	144 (1.98- 35000)	<0.001
Troponin (ng/ml)	0.052 (0.003-1.56)	0.006 (0.003- 3.35)	<0.001
C- reactive protein (mg/L)	0.5 (0.001-119.8)	0.6 (0- 134.2)	
Procalcitonin (ng/ml)	0.378 (0.2-100)	0.1050 (0.0001-100)	<0.001
Hemoglobin (g/dl)	10.8 (5.7-19.9)	12.6 (5.7-19)	<0.001
Hematocrit (%)	32.7 (18- 64.6)	37 (14.4-52)	<0.001
ALT (IU/L)	23.5 (4-1207)	14 (2- 253)	<0.001
AST (IU/L)	40 (15- 5582)	27 (8- 337)	<0.001
Creatinine (mg/dl)	0.33 (0.04- 4.08)	0.44(0.05- 13.11)	<0.001
Albumin (g/dl)	3.9 (1.1- 5.2)	4.2 (0.53- 5.7)	<0.001
Sex (Female %)	46.9	48.2	0.762
Fever (%)	21.7	12.4	0.004
Tachypnea (%)	61.5	15.1	<0.001
Tachycardia (%)	47.6	14.3	<0.001
ECG pathology (%)	9.7	4.9	<0.001
Positive hemoculture (%)	12.7	2	<0.001
Angiography (%)	21.7	2	<0.001
Cardiomegaly (%)	48.3	5.8	<0.001
Length of stay in hospital (days)	7 (0-73)	0 (0-76)	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TR:Tricuspit regurgitation, LVEDD: left ventricul end-diastolic diameter, ECG: electrocardiography



Graph 2 A: ROC analysis for cardiovascular event predictor of Pro BNP, **2B**: ROC analysis for troponin T predictive of cardiovascular events

DISCUSSION

In the present study, pro-BNP, LVEDD z score, and TR velocity were shown to be the most significant predictors for CVE. Pro-BNP levels were strongly correlated with patient age, height, and weight negatively, but troponin T and procalcitonin levels were strongly correlated positively. The sepsis group had the highest pro-BNP level. The patients with complex CHD, pulmonary hypertension, and cardiomyopathy in the cardiac group had the highest pro-BNP values. There is not much research in the literature that compares several diagnostic groups, similar to the present study. Kim et al.[10] divided into cardiac, infectious, non-cardiac, and non-infectious groups and assessed the levels of pro-BNP in each group. The pro-BNP value was significantly higher in the cardiac group, and there was a positive correlation between pro-BNP levels and the requirement for mechanical ventilation, oxygen treatment, inotrope use, changed mental status, and death. Contrarily, even though the total number of patients in each group was significantly larger in our study, the pro-BNP levels were not higher in the cardiac group than the others. However, the group with major CVE in our study had higher pro-BNP levels, and the regression analysis found to be an independent predictor for CVE. In addition, unlike the earlier study, the association between troponin T level and the pro-BNP levels was also examined in the present study, demonstrating a significant positive correlation. Pro-BNP elevation can also be seen in noncardiac diseases due to secondary cardiac effects. There is no consensus on the distinction, especially in the childhood age group, and it is given as a class 2b recommendation in the guidelines.

Sepsis is strongly correlated with pro-BNP levels, which are higher in severe sepsis. Additionally, it has been previously shown that an increase in pro-BNP levels is associated with left ventricular dysfunction, mechanical ventilation support, oxygen therapy, the need for inotropic therapy, and a change in mental status, but not with systemic inflammatory response syndrome or mortality.[12,14,15] Pro-BNP and procalcitonin levels

were shown to be strongly correlated in our research, as has been noted in the literature.[9] Additionally, the sepsis group had the highest levels of pro-BNP. This may be explained by the fact that the majority of these patients were treated in the critical care unit for their severe sepsis. The pro-BNP levels in the group with severe sepsis were high, which is consistent with the literature. The pro-BNP levels showed no association with mortality in the sepsis group, according to the literature.[12] While no mortality assessment was conducted for the sepsis group in our study, when the whole group was examined, the pro-BNP value was revealed as an independent positive predictor for CVE.

Pro-BNP levels were found to help separate the respiratory reasons from the cardiac causes in research involving 49 kids.[16] The levels of pro-BNP may also help identify cardiac disease from non-cardiac diseases, according to several research.[7,16-20] However, there was no difference between the respiratory group and the cardiac group's pro-BNP levels also found higher troponin T level in the current investigation. This may be due to the tendency to test pro-BNP levels in patients with more severe respiratory symptoms. At the same time, most of the patients in the cardiac group have hemodynamically significant congenital heart disease, however, no significant difference was found in our patient group. It may be associated with cardiac involvement secondary to hypoxia due to severe respiratory disease.

In an metaanalysis in which cardiotoxicity is evaluated in pediatric cancer patients, increased pro-BNP levels were shown to be correlated with the degree of left ventricular but it has been reported that the sensitivity was low and not predictive.[21] According to reports, although this value helps validate exclusions, there is no established pro-BNP value for assessing left ventricular dysfunction in cancer patients.[15] Although there were no cancer patients with substantial left ventricular dysfunction in our research, there was a favorable association between the pro-BNP and the hemoglobin and hematocrit levels. Additionally, the hematological group's significance of this correlation was discovered to be lower than that of the other groups, which might be explained by the lack of a patient with significant left ventricular failure.

Pro-BNP levels have been shown to rise in renal failure patients in correlation with the degree of kidney failure and the results of echocardiography, with a positive predictive value for cardiac strain.[22] The levels of pro-BNP and creatinine showed only a minor correlation in our study. However, in the case of volume overload leading to ventricular dilatation or an increase in the right ventricular pressure, positive predictive power in predicting the development of CVE was detected, in line with previous research.

In comparison to children with simple congenital heart diseases, children with complex congenital heart problems were shown to have greater levels of pro-BNP.[5,23] In similar to previous research, individuals with complex heart disease and cardiomyopathy had the highest levels of pro-BNP.[7] Patients with volume overload and systolic ventricular dysfunction in particular had higher levels of Pro BNP.[8] Pro-BNP levels were found to be higher in complex cyanotic patients, such as a single ventricle in our study. Other research with similar findings has shown that individuals with complex cardiac disease have greater BNP levels.[17,24,25] There is enough data to support the BNP level's utility in diagnosis and follow-up, although it has not yet been confirmed that it might serve as a sufficient diagnostic marker for pediatric pulmonary hypertension. In the present study as well, a significant increase in the BNP levels was observed in the group of patients with left-right shunt and inoperable pulmonary hypertension.

Additionally, compared to individuals with congenital heart disease, people with volume and pressure load had greater BNP values.[4] Consistent with this, in the present study, patients with pulmonary arterial hypertension and high LVEDD scores presented higher BNP levels. Additionally, a positive correlation between BNP levels and the TR velocity and LVEDD z-score was noted.

The New York Heart Association (NHYA) classification and the pro-BNP levels were found to be positively correlated by Sahin et al.[5] Ross classification-based relationships have not yet been the subject of any studies.[13] Although the NHYA or Ross classification could not be used in the current investigation since it was retrospective in nature, there was a strong association between the presence of tachypnea, tachycardia, and cardiomegaly.

The current study has some limitations, retrospective design, the non-homogeneous patient population. Additionally, some patient information, such as electrocardiography data were unavailable, and some patients' follow-up information was not available either because hospital staff failed to follow-up.

CONCLUSION

The development of CVE was shown to be independently related to the Pro-BNP level. In addition, the presence of tachypnea, the Pro-BNP level, the TR velocity, and the LVEDD z-score were the most significant predictors of CVE. Moreover, unlike the findings obtained for adults, the benefit of using the Pro-BNP levels for determining cardiac diseases in children could not be demonstrated in the present study. Therefore, it is advised that randomized prospective studies be carried out to show the value of Pro-BNP in separating cardiac disorders from non-cardiac diseases in children.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskisehir Osmangazi University non-interventional researches Ethics Committee (Decision No: 2020-181, 25403353-050.99-E.52038).

Informed Consent: The data were obtained retrospectively from electronic medical records.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Hauser JA, Demyanets S, Rusai K, et al. Diagnostic performance and reference values of novel biomarkers of pediatric heart failure. Heart. 2016(15);102(20):1633-9.
2. Caselli C, Ragusa R, Prontera C, et al. Distribution of circulating cardiac biomarkers in healthy children: from birth through adulthood. Biomark Med. 2016;10(4):357-65.
3. Iacob D, Butnariu A, Leucuţa DC, et al. Romanian Journal of Internal Medicine Evaluation of NT-proBNP in children with heart failure younger than 3 years old. Rom J Intern Med. 2017;1;55(2):69-74.
4. Davis GK, Bamforth F, Sarpal A, et al. B-type natriuretic peptide in pediatrics. Clin Biochem. 2005;39(6):600-5.
5. Cantinotti M, Walters HL, Crocetti M, et al. BNP in children with congenital cardiac disease is there now sufficient evidence for its routine use. Cardiol Young .2015;25(3):424-37.
6. Şahin M, Portakal O, Karagöz T,et al. Diagnostic performance of BNP and NT-ProBNP measurements in children with heart failure based on congenital heart defects and cardiomyopathies. Clin Biochem. 2010;43(16-17):1278-81.
7. Cantinotti M, Law Y, Vittorini S, et al. The potential and limitations of plasma BNP measurement in the diagnosis, prognosis, and management of children. Heart Fail Rev. 2014;19(6):727-42.
8. Gangnus T, Burckhardt BB. Potential and limitations of atrial natriuretic peptide as biomarker in pediatric heart failure- a comparative review. Front Pediatr. 2019;29;6:420.
9. Lin CW, Tang W, Wen F, et al. Diagnostic accuracy of NT-ProBNP for heart failure with sepsis in patients younger than 18 years. PLoS One. 2016;26;11(1):e0147930.
10. Kim HS, Choi HJ. N-terminal pro-B-type natriuretic peptide levels in children:comparison in cardiac and non-cardiac diseases. Cardiol Young. 2020;30(4):500-4.
11. Sugimoto M, Kuwata S, Kurishima C, et al. Cardiac biomarkers in children with congenital heart disease. World J Pediatr. 2015;11(4):309-15.
12. Li J, Ning B, Wang Y, et al. The prognostic value of left ventricular systolic function and cardiac biomarkers in pediatric severe sepsis. Medicine (Baltimore) 2018;98(13):e15070.
13. Ross RD. The Ross classification for heart failure in children after 25 years:a review and an age-stratified revision. Pediatr Cardiol.2012;33(8):1295-300.
14. Cirer-Sastre R, Legaz-Arrese A, Corbi F, et al. Cardiac Biomarker Release After Exercise in Healthy Children and Adolescents:A Systematic Review and Meta-Analysis. Pediatr Exerc Sci. 2019;1;31(1):28-36.
15. Leerink JM, Verkleij SJ, Feijen EAM, et al. Biomarkers to diagnose ventricular dysfunction in childhood cancer survivors a systematic review. Heart. 2019;105(3):210-216.
16. Koulouri S, Acherman RJ, Wong PC, et al. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. Pediatr Cardiol 2004;25:341–6.
17. Cantinotti M, Giovannini S, Murzi B, et al. Diagnostic, prognostic and therapeutic relevance of B-type natriuretic peptide assay in children with congenital heart diseases. Clin Chem Lab Med. 2011;49:567–580.
18. Eindhoven JA, van den Bosch AE, Jansen PR, et al. The usefulness of brain natriuretic peptide in complex congenital heart disease:a systematic review. J Am Coll Cardiol 2012;60:2140–2149.
19. Maher KO, Reed H, Cuadrado A, et al. B-type natriuretic peptide in the emergency diagnosis of critical heart disease in children. Pediatrics. 2008;121:e1484–e1488.
20. Law YM, Hoyer AW, Reller MD, et al. Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children:the better not pout children! Study. J Am Coll Cardiol 2009;54:1467–1475.
21. Desjardins L, Dionne A, Meloche-Dumas L, et al. Echocardiographic parameters during and beyond onset of Kawasaki disease correlate with onset serum N-Terminal pro-Brain Natriuretic. Pediatr Cardiol.2020;41(5):947-54.
22. Michel L, Mincu RI, Mrotzek SM, et al. Cardiac biomarkers for the detection of cardiotoxicity in childhood cancer a meta-analysis. ESC Heart Fail. 2020;7(2):423-433.
23. Butnariu A, Iancu M, Samaşca G,et al. Changes in NT-proBNP in young children with congenital heart malformations. Lab Med. 2014;45(1):43-7.
24. Cantinotti M, Storti S, Parri MS, et al. Reference intervals for brain natriuretic peptide in healthy newborns and infants measured with an automated immunoassay platform. Clin Chem Lab Med. 2010;48:697–700.
25. Holmgren D, Westerlind A, Berggren H, et al. Increased natriuretic peptide type B level after the second palliative step in children with univentricular hearts with right ventricular morphology but not left ventricular morphology. Pediatr Cardiol.2008;29:786–792.