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Original Article

Evaluation of troponin T levels and cardiac findings of the children in pediatric intensive care with high proBNP levels

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ABSTRACT

Objective: Pro-B type brain natriuretic peptide (proBNP) is released from cardiac ventricular myocytes as a result of increased volume and pressure. Troponin T plays a role in the contraction process. Both proteins may be elevated in many cardiac and non-cardiac conditions. Our aim is to evaluate troponin T values and cardiac findings of the patients in pediatric intensive care unit (PICU) with elevated proBNP levels.

Method: Patients with high proBNP values who were admitted to the PICU between January 2022 and January 2023 were included in the study. The clinical diagnoses, proBNP, and troponin T values were recorded. Information about the presence of heart disease and the status of systolic functions were obtained from echocardiographic examination reports.

Results: One hundred and ten patients were included in the study. Mean age of the patients was 2.48±3.41 years. Among the patients hospitalized in the pediatric intensive care unit, 41% had lower respiratory tract infections, and 20% had heart disease. The mean proBNP values were 11827.06±12652.82 ng/l, and troponin T was 201.41±737.74 ng/l. Ejection fraction (EF) was normal in 75% of the patients. The mean values of proBNP and troponin T in the patients with normal EF were 7284.74±8437.16 ng/l and 49.67±73.15 ng/l while the mean values of proBNP and troponin were 25129±13659.24 ng/l and 645.8±1380.74 ng/l in the patients with decreased EF ($p<0.05$, for both). ProBNP and troponin T values of the patients with decreased EF accompanied with or without heart disease were higher than those in the group with normal EF without existing heart disease ($p<0.0001$, for all). It was observed that decreased EF value was more common in cases who have proBNP>16314 ng/l and troponin T >114 ng/l ($p=0.0031$, $p<0.0001$, respectively).

Conclusion: ProBNP and troponin T values increase in many cardiac and non-cardiac diseases. However, quite high values of the parameters help to distinguish the patients with cardiac systolic dysfunction.

Keywords: Children, Pro-B type natriuretic peptide, systolic function, Troponin T

INTRODUCTION

NT-proBNP is an important marker in the diagnosis, evaluation, and treatment of heart failure.[1] NT-proBNP is a diuretic peptide released from ventricular myocytes as a result of increased volume and pressure load as a preprohormone (preproBNP). Then, it is converted to proBNP. ProBNP consists of N-terminal proBNP (NT-proBNP) which is biologically inactive, and biologically active form called BNP. Afterward, the N-terminal region separates from the prohormone and the active form which

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is called BNP stays in circulation. Both serum BNP and NT-proBNP levels are used to determine cardiac involvement and to evaluate the prognosis of the patients with congestive heart failure.[2-5] This peptide causes vasodilatation, natriuresis, inhibition of renin-angiotensin-aldosterone, and vasopressin release. The functions become apparent in target cells by receptors leading to the formation of cyclic guanosine monophosphate (cGMP). The receptors are present in the blood vessels, the kidney, the brain, the adrenal gland, the testis, the lung, and in ventricular myocytes in much lower concentrations.[6-9] They are inactivated by endopeptidase which is present in the lung and kidney.[1,10] BNP has a half-life of 22 minutes and can respond quickly to changes. The half-life of NT-proBNP is 2 hours, serum levels are relatively higher, and it is not disturbed in the serum sample. The concentrations of BNP and NT-proBNP are nearly similar in circulation. Therefore, NT-proBNP concentrations are used to evaluate pressure or volume overload to the ventricles. The clearance of NT-proBNP depends on renal function.[1,10]

Troponin T and troponin I called cardiac troponins were used for screening and detecting cardiac injury.[1,11] Troponin T is a protein involved in contraction by regulating the interaction of actin and myosin. Most of the troponins are present in the cardiac sarcomere, but 3-8% of troponin is present in the cytoplasmic form.[12] The plasma half-life of cardiac troponin is approximately 2 hours. Although the exact mechanism by which troponin is eliminated from the body is not fully known, it is hypothesized that renal reticulo-endothelial system plays role in the clearance of the protein.[12]

Both proteins may be elevated in some non-cardiac conditions besides cardiac conditions.[13] NT-proBNP increases in heart muscle diseases, arrhythmia, renal dysfunction, anemia, sepsis, burns, lung diseases, and pulmonary hypertension.[13] Troponin increases in coronary syndromes, inflammation, kidney failure, exercise, myocarditis, drugs, metabolic conditions, and sepsis.[2] Our aim is to evaluate troponin T values and cardiac findings in the patients with elevated NT-proBNP levels who were treated in ourpediatric intensive care unit.

MATERIAL AND METHODS

Patients with high NT-proBNP values who were admitted to the pediatric intensive care unit between January 2022 and January 2023 were included in the study. The clinical diagnoses, NT-proBNP, and troponin T values of the patients were examined retrospectively. Presence of heart disease and cardiac functions were recorded according to echocardiographic evaluations. M-mode and 2D measurements were made according to the recommendations of the American Society of Echocardiography.[14,15] The ejection fraction (EF) of the left ventricle was calculated with the modified Simpson method. Decreased EF was defined when it was<55%.[14,15]

The patients were also grouped according to the presence or absence of heart disease (HD) into four groups. Group 1- Decreased EF with the presence of HD: dilated cardiomyopathy (DCMP), noncompaction cardiomyopathy, hypertrophic cardiomyopathy (HCMP), operated complex congenital HD with significant hemodynamic residual cardiac findings; Group 2-Decreased EF with no HD: sepsis, renal pathologies, lower respiratory tract infection, asphyxia; Group 3- Normal EF with the presence of HD: complete atrioventricular septal defect (AVSD), pulmonary hypertension (PHT), large patent ductus arteriosus (PDA) and large ventricular septal defect (VSD), operated congenital HD with hemodynamically significant residual findings, functional single ventricle; Group 4- Normal EF with no HD: normal echocardiographic findings, mild valve insufficiency without hemodynamic significance, small atrial septal defect and ventricular septal defect.

Statistical analyses

Statistical analyses were performed using the SPSS software version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Categorical data are presented as numbers and percentages, and numerical data are presented with mean ± standard deviation if normally distributed, medium (minimum-maximum) if non-normally distributed. Kolmogorov-Smirnov test was used to determine the normal distribution of numerical variables. Kruskall-Wallis H test was used in the comparison of two independent groups. Bonferroni correction was used to determine the significance level of pairwise comparisons. Receiver operating characteristic (ROC) curve analysis was used to predict the presence of heart disease by troponin and proBNP measurements. The analysis of the ROC curve was performed using MedCalc version 20.0 software. The cut-off value was calculated and the sensitivity, and specificity values were determined. A p-value<0.05 was considered statistically significant.

Ethical approval

The study was approved by the Ethics Committee of the University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2023-04-12, date: 20.02.2023). Informed consent was obtained from all the patients and their parents.

RESULTS

The mean age of the patients was 2.48±3.41 years. 66 patients were male, and 44 patients were female (Table 1). 41% of the patients had lower respiratory tract infections and 20% had congenital heart disease (Table 2). Patients were grouped according to EF as the patients with decreased EF and the patients with normal EF. Patients with decreased EF included DCMP, non-compaction cardiomyopathy, and myocarditis and accounted for 25% of the patients. Patients with normal EF included left to right shunted diseases, pulmonary hypertension, single ventricle, and valvular insufficiencies (Table 3). NT-proBNP value was 7284.7± 8437.1 ng/l and troponin T value was 49.6 ± 73.1 ng/l in the patients with normal EF, while the mean NT-proBNP value of the patients with decreased EF was 25129 ± 13659.2 ng/l, and the mean troponin T value was 645.8 ± 1380.7 ng/l in the patients with decreased EF (p<0.001, for both) (Table 4). When we grouped the patients according to EF status and presence of HD, NT-proBNP and troponin T values were higher in the patients with low EF and presence of HD (group 1) and low EF without HD (group 2) than the group with normal EF without HD (group 4) (p<0.0001, for all). In addition, troponin T value was also higher in the patients with decreased EF accompanied by HD (group 1) than in the patients with normal EF accompanied by HD (Table 5).

Table 1. Demographic and laboratory findings of the patients

	PATIENTS n =110 (mean ± sd)
Age (year)	2.48 ± 3.41
Gender (M/F)	66/44
NT-proBNP (ng/l)	11827.06 ± 12652.82
Troponin T (ng/l)	201.41± 737.74

Table 2. Diagnoses of the patients

	(%)
Lower tract respiratory infections	41
Heart diseases	20
Renal diseases	12
Intracranial diseases	7
Sepsis	6
Dehydration	4
Ischemia	5
Metabolic disorder	5

Table 3. Distribution of cardiac diseases

DECREASED EF (%25)	NORMAL EF (%75)
Dilated cardiomyopathy	Left to right shunted diseases
Noncompaction cardiomyopathy	Pulmonary Hypertansion
Myocarditis	Single Ventricle
	Valvular insufficiencies

EF: Ejection fraction

Table 4. Laboratory parameters according to ejection fraction

	NORMAL EF (n=82) Mean ± sd	DECREASED EF (n=28) Mean ± sd	*p
NT-proBNP (ng/l)	7284.7± 8437.1	25129 ± 13659.2	<0.001
Troponin T (ng/l)	49.6 ± 73.1	645.8 ± 1380.7	<0.001

*Mann Whitney U test

Table 5. Laboratory parameters related with EF status and presence of HD

	Decreased EF, With HD (n=14) mean ± sd GROUP 1	Decreased EF , Without HD (n=14) mean ± sd GROUP 2	Normal EF, With HD (n=10) mean ± sd GROUP 3	Normal EF, Without HD (n=72) mean ± sd GROUP 4	*p
NT-proBNP (ng/l)	22454.7 ± 14834.4	27804.4 ± 12330.1	15713.8 ± 12768.8	6114.1 ± 7010.5	<0.0001
Troponin T (ng/l)	1042.2 ± 1890.1	249.4 ± 220.1	67.3 ± 64.8	47.2 ± 74.3	<0.0001

EF: Ejection fraction, HD: Heart disease.
*Kruskal Wallis H test

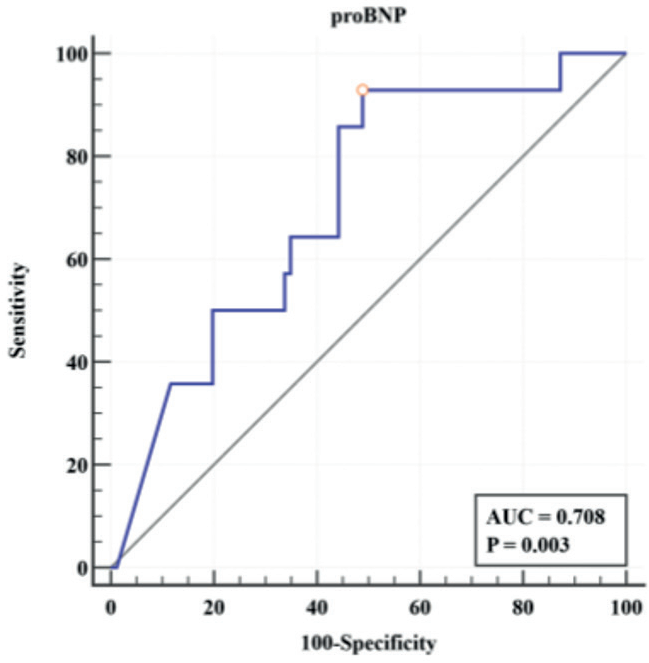

Figure 1. proBNP level in predicting left ventricular dysfunction

p=0.031 (sensitivity 71.4%, specifity 90.24%)

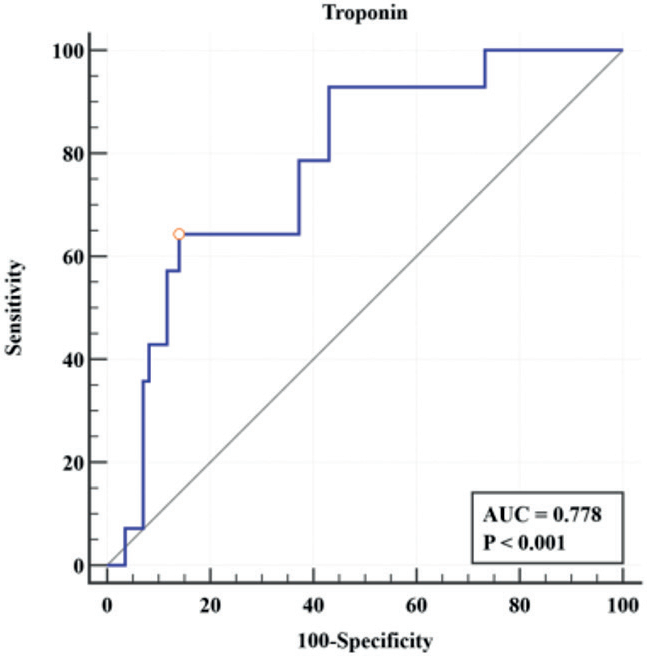

Figure 2. Troponin T level in predicting left ventricular dysfunction

p<0.001 (sensitivity 71.4%, specifity 93.9%)

The cut-off value for NT-proBNP was 16314 ng/l (p=0.0031, sensitivity 71.4%, specificity 90.24%), and for troponin T was 114 ng/l (p<0.0001, sensitivity 71.4%, specificity 93.9%) to predict decreased EF (Figure 1 and Figure 2).

DISCUSSION

In the literature, different reference intervals were defined for NT-proBNP and Troponin T levels.[2,13,16] These studies indicate that the reference values of these variables can differ according to age and sex. Most of the studies state that levels of these variables are at their maximum ranges at birth, afterward a prominent decline occurs during the first months of life with slight decreases during childhood.[2,13,16] Also, it was shown that the levels of NT-proBNP and troponin T showed a positive correlation with each other.[2] Studies have reported increased levels of these parameters in many cardiac pathologies, but also in many non-cardiac pathologies. The most prevalent causes of non-cardiac pathologies are lower respiratory tract infections, sepsis, renal diseases, and intracranial pathologies.[2] In our study, the patients with high NT-proBNP had lower respiratory tract infections, congenital heart diseases, renal pathologies, intracranial pathologies, sepsis, dehydration, ischemia, and metabolic diseases. Increases of the parameter in many non-cardiac conditions may be the result of the widespread presence of the receptors in the related tissues.

Yang et al.[17] performed a study on newborns and divided them into three groups: the first group comprised of patients with cardiovascular disease and sepsis, the second group consisted of patients with sepsis only, and the third group consisted of controls. The first group had the highest proBNP and troponin levels, followed by the second group and both groups had higher levels of these parameters than the controls. The study also declared a threshold of NT-proBNP of 12291.5 pg/ml (80% sensitivity and 79% specificity) to predict newborn sepsis. Favory et al.[18] stated that patients with sepsis accompanied by left ventricular dysfunction had higher NT-proBNP levels, but Klouche et al.[19] stated that patients without left ventricular dysfunction also had increased proBNP levels. Inflammation, endotoxins, endothelial damage, direct cardiac damage, excess volume in the ventricles, and low blood pressure cause an increase of this parameter. One of the other most prevalent cause of increased levels of these parameters is renal disease. Jones et al.[20] indicate that acute renal failure increases the levels of NT-proBNP and troponin. Nalcacioglu et al.[21], suggested that chronic renal failure also causes increased NT-proBNP levels as a result of volume excess, hypertension, left ventricular hypertrophy, and congestive heart failure.

There are many studies supporting that both parameters mostly increase in cardiac diseases.[2] Also, it was shown that different cardiac diseases act differently over NT-proBNP level. NT-proBNP is used to distinguish acute heart failure and chronic heart failure.[22] The increase is more prominent in acute left ventricular dysfunction. Congenital HD including pressure overload increases NT-proBNP levels more than volume overloading pathologies.[23] The patients in our study who were evaluated in the pediatric intensive care unit mostly had normal ejection fraction accompanied by left to right shunted diseases, pulmonary hypertension, single ventricle, and valvular insufficiencies. Patients with decreased ejection fraction include patients with dilated cardiomyopathy, non-compaction cardiomyopathy, and myocarditis. Lv et al.[24] conducted a study on patients with myocarditis and showed that the increase in NT-proBNP was apparent in 3-7 days of the disease and showed regression during the first month. Another study revealed that NT-proBNP values were significantly higher in children with myocarditis, predicting the early and late outcomes of the disease with similar troponin T levels. They also reported that NT-proBNP levels higher than 2000 pg/ml predict left ventricular dysfunction.[25] In our study, we found NT-proBNP level to be 7284.7 ± 8437.1 ng/l in the patients with normal EF, while it was 25129 ± 13659.2 ng/l in the patients with decreased EF. Consistent with these findings, the mean value of troponin T levels was 49.6 ± 73.1 ng/l, while it was 645.8 ± 1380.7 ng/l in the participants with decreased EF, supporting the idea that even though both groups had HD, the patients with decreased EF had the prominent increases in these parameters.

Soongswang et al.[26] stated that troponin values were found to be higher in the patients with acute myocarditis, compared to the patients with dilated cardiomyopathy and the group including large ventricular septal defect with congestion findings. This study also supported the importance of EF in determining the level of troponin. The threshold value for troponin T in acute myocarditis was found to be 0.052 ng/ml.[26] Dionne et al.[27] declared 0.045 ng/ml as a threshold value for troponin T in children <3 months, and 0.005 ng/ml for children ≥3 months for differentiating the diseases as cardiac and non-cardiac. When we evaluated the patients according to EF status and the presence of HD, we found that both the first and second groups had higher NT-proBNP levels and troponin T levels than the fourth group, supporting that having low EF demonstrates high serum parameters independent of the presence of HD. Higher troponin T levels in the first group, compared to the third group, also supported the idea that even though both groups had HD, the patients with decreased EF levels had higher levels of troponin T.

Sugimoto et al.[28] stated different cut-off values in the patients with heart failure according to heart failure stage and age. Lin et al.[29] stated the threshold values for NT-proBNP suggestive of heart failure according to age and it was 502 ng/l for 0-1 years old, 456 ng/l for 1-3 years old, 445 ng/l for 4-7 years old, 355 ng/l for 8-14 years old. NT-proBNP was 438.4 pg/ml in stage 2 while it was 7733.5 pg/ml in stage 4 under 3 years of age. The cut-off value was 295.2 pg/ml in stage 2 and 3617 pg/ml in stage 4 older than 3 years of age. El-Amrousy et al.[30] showed that values >10 pg/ml for troponin T indicate acute heart failure with 100% sensitivity and 85% specificity. This study also supported the increased mean values of troponin T according to heart failure stage which is 55.35±10.25 pg/ml in stage 2 and 92.35±14.52 pg/ml in stage 4. In our study, the threshold values for predicting decreased EF were >16314 ng/l for NT-proBNP (sensitivity 71.4%, specificity 91.24%) and >114 ng/l for troponin T (sensitivity 71.4%, specificity 93.9%). These increased values in our study also supported the studies in the literature.

CONCLUSION

NT-proBNP and troponin T values also increase in the presence of non-cardiac reasons besides cardiac causes. However, the values of NT-proBNP and troponin T levels were found to be quite high, especially in the patients with cardiac systolic dysfunction defined by low EF. Regardless of the diagnosis, patients with high NT-proBNP values and high troponin values should be evaluated for cardiac reasons.

Ethical approval

This study has been approved by the University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval date 20/02/2023, number 2023-04-12). Written informed consent was obtained from the participants.

Author contribution

Concept: AMM, EŞ; Design: AMM, EŞ; Data Collection or Processing: AMM, EŞ; Analysis or Interpretation: AMM, EŞ; Literature Search: AMM, EŞ; Writing: AMM. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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