Original Article

N-terminal pro B-type Natriuretic Peptide Levels and Dilated Cardiomyopathy: A Tissue Doppler Echocardiographic Study in Children

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ABSTRACT

Background: The N-terminal segment of the pro-brain natriuretic peptide (NT-proBNP) has emerged as a marker for heart failure. Dilated cardiomyopathy (DCM) as a major cause of congestive heart failure in children leads to a low cardiac output. However, only a few studies have shown the role of tissue Doppler imaging (TDI) in children with DCM. We sought to explore the associations between TDI parameters and NT-proBNP among DCM patients.

Methods: The present cross-sectional study consecutively enrolled 28 children with DCM. All the patients were on medical therapies in a stable condition upon entrance into the study. All the children were examined by 2D transthoracic echocardiography. TDI imaging was taken from lateral and septal mitral valve areas, and myocardial velocity was calculated by TDI. All the children gave blood samples for the measurement of the NT-proBNP level.

Results: Seventeen patients (60.7%) were female, and the patients' median age was 10 ($IQR_{25\%-75\%}$: 1 to 13) years. The NT-proBNP median was 8614 ($IQR_{25\%-75\%}$, 2592 to 20909) pg/mL. There were statistically significant linear relationships between the NT-proBNP level and the lateral myocardial performance index (MPI) (ρ=0.416), the septal MPI (ρ=0.740), the septal E/e´ (ρ=0.533), and the lateral E/e´ (ρ=0.448). The strongest correlation coefficients were observed between the NT-proBNP level and the left ventricular ejection fraction (ρ= −0.754; *P*=0.001) and the septal MPI (ρ=0.740; *P*=0.001), even after indexing by body surface area.

Conclusions: NT-proBNP levels correlated strongly with the left ventricular function measured by TDI parameters. Noninvasive echocardiographic evaluations can be implemented to assess children with DCM. ***(Iranian Heart Journal 2022; 23(1): 54-64)***

KEYWORDS: Dilated cardiomyopathy, Brain natriuretic peptides, Tissue Doppler imaging, Echocardiography

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The brain natriuretic peptide (BNP), secreted mainly by ventricular myocytes, is involved in the regulation of extracellular volume and blood pressure. [1,2] During past years, BNP has emerged as an important biomarker for cardiac dysfunction. [3] A measurable prohormone was developed as the N-terminal segment of proBNP (NT-proBNP), which is secreted concomitantly with BNP from cardiac myocytes. [4] BNP and NT-proBNP, as an equivalent to BNP, are used for the diagnostic and prognostic evaluation of cardiovascular disease in neonates and children. [5,6]

Congestive heart failure (CHF) is a major cause of morbidity and mortality and is deemed a multiple hormonal deficiency syndrome. [7,8] Dilated cardiomyopathy (DCM) is characterized by dilated ventricles, along with systolic and diastolic dysfunction, leading to a low cardiac output. [9] DCM is the most common type of cardiomyopathy and contributes to cardiac transplantation in adults and children. [10] Numerous studies have suggested that the serum level of BNP is of paramount importance in excluding heart failure in patients presenting with dyspnea or fluid retention. [1,3] Increased BNP levels are associated with increased worse outcomes in children with symptomatic heart failure. [11-13] Furthermore, several reports have found that NT-proBNP is a good indicator of the diagnosis and prognosis of patients with heart failure, particularly in the 3-month outcome of pediatric DCM, [14] the severity of the functional class in adult patients with idiopathic DCM, [15] and the severity of heart failure due to DCM or congenital heart diseases in children older than 3 years. [16]

Tissue Doppler imaging (TDI) is used to assess myocardial velocities. The contraction of the left ventricle (LV) along its longitudinal axis leads to the motion of the mitral valve annulus. The early diastolic and systolic velocities of the mitral annulus, which are measured by TDI, are associated with the diastolic and systolic functions of the LV. [17,18] Only a few studies have shown the role of TDI parameters in children with cardiomyopathies. [19,20] In this study, we sought to determine the relationship between TDI parameters and the NT-proBNP level in children with idiopathic DCM in our teaching hospital-based pediatric cardiology clinic.

METHODS

Study Protocol and Patients

The current cross-sectional study consecutively enrolled 28 children with idiopathic DCM. All the children underwent transthoracic echocardiography (TTE) by the implementation of the TDI modality. All the patients were stable and on medication before examination in our echocardiographic laboratory. Patients visited our laboratory in Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, between December 2017 and June 2018. The exclusion criteria included patients without cooperation to maintain accurate echocardiographic parameters, any cardiac arrhythmias, renal failure, and the secondary cases of DCM. The study was approved by the institutional review board and the local ethics committee (identification number: IR.IUMS.FMD.REC.1396.9411169001).

Echocardiographic and Laboratory Evaluations

All the children were examined and evaluated by TTE to measure the TDI parameters of the cardiac function (iE33 echo machine, Philips Ultrasound, WA, USA). DCM was diagnosed in our cohort when the participants exhibited a reduced left ventricular ejection fraction ([LVEF], <40%), concomitant with an LV end-diastolic diameter of greater than 2 standard deviations (SDs) from the normal value (Z

scores >2 SD) corrected by body surface area and age or sex. All the patients with secondary DCM were also excluded. [21] For the diagnosis of idiopathic DCM, after an echocardiographic examination, all the patients underwent cardiac magnetic resonance imaging and computed tomographic angiography to explore any anatomic anomalies, coronary lesions, or myocarditis that could justify failure. The metabolic causes of DCM were also assessed by using a metabolic panel.

TDI was taken from lateral and septal mitral valve areas. All the measurements were averaged over 3 to 5 consecutive beats. Myocardial velocity was calculated directly via TDI, which helps to measure the myocardial area function. This method is less affected by the volume load of the heart. The examination of myocardial velocity at the level of the mitral valve represents the longitudinal function of the heart. Notably, "s′" is a sign of the myocardial systole; "e′" indicates the beginning of the diastole; and "a′" is a sign of myocardial velocity at the end of the diastole. The myocardial performance index (MPI), a time-based index of global myocardial performance, is another measure that is useful for measuring the systolic and diastolic functions of both ventricles. MPI can be calculated in 2 ways by using pulsed Doppler and TDI. All the other aspects of the protocols used in TDI imaging were similar to those specified in a study by Tekten et al. [22] In addition, the previously reported reference values for TDI parameters in children were drawn upon to interpret findings. [23]

All the children gave 5 mL of blood samples via venipuncture to measure the serum level of NT-proBNP. The blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA). The NT-proBNP was measured by electrochemiluminescence immunoassay with the Elecsys system (Roche, Mannheim, Germany). The Elecsys proBNP contains polyclonal antibodies that recognize epitopes located in the N-terminal part of proBNP.

Statistical Analysis

All variables are presented as the mean ± the SD or the median (the interquartile range $_{25\text{-}75\%}$), as appropriate. For the comparison of the variables between groups, the Mann–Whitney *U* rank-sum test or the *t* test was employed. For the comparison of categorical variables, the χ^2 test was implemented. Correlations between 2 continuous variables were calculated with the Spearman rank correlation coefficient test. It has been demonstrated that among children aged between 10 and 14 years, the level of NT-proBNP is different. [24] Therefore, we performed a subgroup analysis among children aged between 10 and 14 years. In addition, we indexed all TDI parameters by body surface area to adjust them for the patients' age. Receiver operating characteristics (ROC) curve analysis was conducted to find the best cutoff points for NT-proBNP and indexed and non-indexed TDI parameters to detect patients with a low LVEF (≤20%, the median value in our population). The statistical analyses were performed by using STATA software (College Station, TX, USA). Two-sided *P*-values were calculated.

RESULTS

Twenty-eight patients with idiopathic DCM were studied. Seventeen patients (60.7%) were female, and 11 patients (39.3%) were male. The median of NT-proBNP was 8614 ($IQR_{25\%\text{-}75\%}$, 2592 to 20909) pg/mL. The patients' median age was 10 years (from 90 days to 16 years of age; $IQR_{25\%\text{-}75\%}$, 1 to 13). The mean LVEF was 21.6±8.4, and other echocardiographic parameters are summarized in Table 1.

Table 1. Baseline characteristics and echocardiographic parameters of the left ventricle in the study patients

Variables	Values (N=28)
Sex	
Male, n (%)	11 (39.3%)
Female, n (%)	17 (60.7%)
Height, mean (SD) cm	124.6 ± 38.3
Weight, mean (SD) kg	27.3 ± 18.2
Age, median ($IQR_{25\%-75\%}$), y	10 (1 - 13)
NT-proBNP, median ($IQR_{25\%-75\%}$) (pg/mL)	8614 (2592 - 20909)
Lateral MPI, mean (SD)	0.9 ± 0.3
Septal MPI, mean (SD)	0.8 ± 0.3
e´ septal, mean (SD) cm/s	9.8 ± 4.4
a´ septal, mean (SD) cm/s	5.9 ± 2.5
s´ septal, mean (SD) cm/s	5.9 ± 2.6
e´ lateral, mean (SD) cm/s	13.8 ± 6.4
a´ lateral ,mean (SD)cm/s	5.4 ± 2.4
s´ lateral, mean (SD) cm/s	6 ± 2.9
Left ventricular ejection fraction, mean (SD) %	21.6 ± 8.4

NT-proBNP, N-terminal segment of the pro-brain natriuretic peptides; Lateral MPI, Myocardial performance index assessed by tissue Doppler imaging from the lateral corners of the mitral annulus; Septal MPI, Myocardial performance index assessed by tissue Doppler imaging from the medial corners of the mitral annulus; e´, Early diastolic velocity; a´, Late phase of diastolic velocity; s´ septal, Systolic velocity; E, Transmitral early filling velocity; E/e´, Transmitral early filling velocity/early diastolic velocity

Correlation analysis showed a statistically significant linear relationship between the NT-proBNP level and the lateral MPI (ρ=0.416; *P*=0.031), the septal MPI (ρ=0.740; *P*<0.001), the septal E/e´ (ρ=0.533; *P*=0.003), and the lateral E/e´ (ρ=0.448; *P*=0.019). Other correlations are summarized in Table 2. The strongest correlation coefficients were observed between the NT-proBNP level and the LVEF (ρ= −0.754; *P*<0.001) and the septal MPI (ρ=0.740; *P*<0.001) (Fig. 1). Other values are presented in Table 2. After the indexing of TDI parameters by body surface area, the most powerful correlations were again observed for the LVEF (ρ= −0.754; *P*<0.001) and the septal MPI (ρ=0.788; *P*<0.001). Other correlations for indexed TDI parameters are presented in Supplementary Table 1.

Supplementary Table 1. Correlation coefficients between NT-proBNP and the TDI parameters of the left ventricle indexed by BSA

TDI Parameters Indexed by BSA	Correlation Coefficient, ρ	*P*-value
Lateral MPI	0.608	0.001
Septal MPI	0.788	<0.001
e´ septal (cm/s)	0.413	0.029
a´ septal (cm/s)	0.247	0.214
s´ septal (cm/s)	0.117	0.554
E (cm/s)	0.572	0.001
Septal E/e´	0.706	<0.001
Lateral E/e´	0.575	0.002
e´ lateral (cm/s)	0.460	0.16
a´ lateral (cm/s)	0.335	0.088
s´ lateral (cm/s)	0.248	0.214
Left ventricular ejection fraction (%)	-0.754	<0.001

TDI, Tissue Doppler imaging; BSA, Body surface area; Lateral MPI, Myocardial performance index assessed by tissue Doppler imaging from the lateral corners of the mitral annulus; Septal MPI, Myocardial performance index assessed by tissue Doppler imaging from the medial corners of the mitral annulus; e´, Early diastolic velocity; a´, Late phase of diastolic velocity; s´ septal, Systolic velocity; E, Transmitral early filling velocity; E/e´, Transmitral early filling velocity/early diastolic velocity

All the patients were divided into 2 groups based on the median value of NT-proBNP (ie, 8614 pg/mL) (low <8614 pg/mL and high ≥8614 pg/mL NT-proBNP; 14 patients in each group). All baseline and echocardiographic parameters were compared between the groups as well (Table 3).

In addition, ROC curve analysis was performed, in which the cutoff points of each echocardiographic parameter and NT-proBNP were calculated to detect patients with LVEF values of 20% or lower. The highest area under the curve (AUC) was observed for NT-proBNP (AUC, 0.985, 95% confidence interval [CI], 0.945 to 1.024) and the septal MPI (AUC, 0.888, 95% CI, 0.757 to 1.020). Other values are presented in Supplementary Table 2.

One child, who was older than 14 years, was excluded. Consequently, a subgroup analysis based on sex was performed among the patients aged older than 10 years. The NT-proBNP level was comparable between the boys and girls in children aged at least 10 years (5983 [$IQR_{25-75\%}$, 2922 to 9660] in boys vs 4094 [$IQR_{25-75\%}$, 35.5 to 12562] in girls; *P*=0.663). Further, similar to all the patients together, among the children between 10 and 14 years old, the strongest correlations were observed between the NT-proBNP level and the LVEF (ρ= −0.763; *P*=0.001) and the septal MPI (ρ=0.600; *P*=0.041).

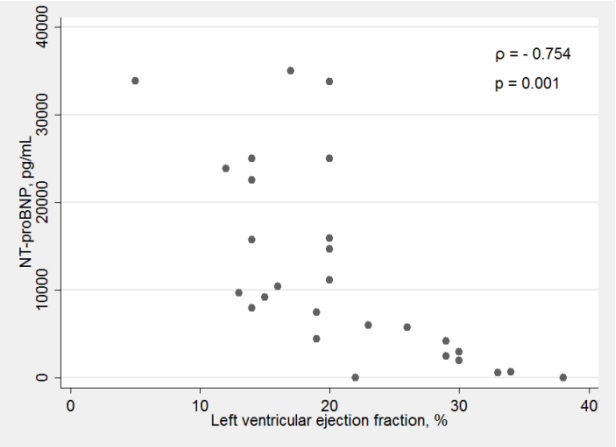

Figure 1-(A)

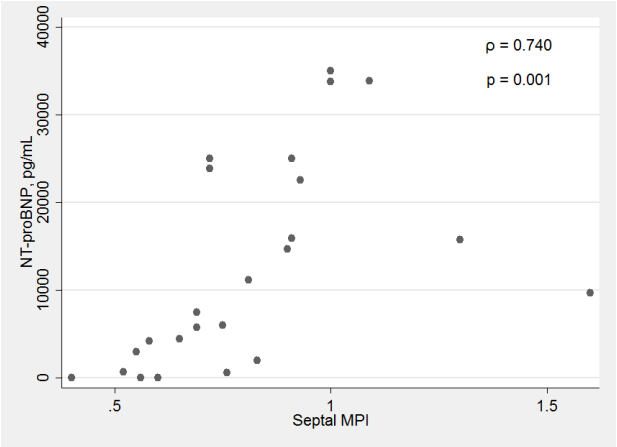

Figure 1-(B)

Figure 1. The images depict the correlation between NT-proBNP and echocardiographic parameters: (A) left ventricular ejection fraction and (B) septal myocardial performance index.

MPI, Myocardial performance index

Table 2. Correlation coefficient between NT-proBNP and TDI parameters of the left ventricle

Variables	Correlation Coefficient, ρ	*P*-value
Lateral MPI	0.416	0.031
Septal MPI	0.740	<0.001
e´ septal (cm/s)	-0.373	0.051
a´ septal (cm/s)	-0.538	0.004
s´ septal (cm/s)	-0.688	<0.001
E (cm/s)	0.064	0.747
Septal E/e´	0.533	0.003
Lateral E/e´	0.448	0.019
e´ lateral (cm/s)	-0.485	0.010
a´ lateral (cm/s)	-0.535	0.004
s´ lateral (cm/s)	-0.591	0.001
Left ventricular ejection fraction (%)	-0.754	<0.001

TDI, Tissue Doppler imaging; Lateral MPI, Myocardial performance index assessed by tissue Doppler imaging from the lateral corners of the mitral annulus; Septal MPI, Myocardial performance index assessed by tissue Doppler imaging from the medial corners of the mitral annulus; e´, Early diastolic velocity; a´, Late phase of diastolic velocity; s´ septal, Systolic velocity; E, Transmitral early filling velocity; E/e´, Transmitral early filling velocity/early diastolic velocity

Supplementary Table 2. ROC curve analysis showing the diagnostic ability of the variables to detect LVEF ≤20%

TDI Parameters	AUC	95% CI	*P*-value
NT-proBNP pg/mL	0.985	0.945-1.024	<0.001
Lateral MPI	0.742	0.537-0.948	0.051
Septal MPI	0.888	0.757-1.020	0.002
e´ septal (cm/s)	0.697	0.444-0.950	0.092
a´ septal (cm/s)	0.821	0.638-1.004	0.006
s´ septal (cm/s)	0.858	0.712-1.003	0.002
E (cm/s)	0.546	0.298-0.795	0.710
Septal E/e´	0.754	0.508-1	0.041
Lateral E/e´	0.800	0.609-0.991	0.016
e´ lateral (cm/s)	0.794	0.614-0.974	0.012
a´ lateral (cm/s)	0.845	0.691-1	0.003
s´ lateral (cm/s)	0.836	0.672-1.001	0.004

TDI, Tissue Doppler imaging; ROC, Receiver operating characteristic; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal segment of the pro brain natriuretic peptides; BSA, Body surface area; Lateral MPI, Myocardial performance index assessed by tissue Doppler imaging from the lateral corners of the mitral annulus; Septal MPI, Myocardial performance index assessed by tissue Doppler imaging from the medial corners of the mitral annulus; e´, Early diastolic velocity; a´, Late phase of diastolic velocity; s´ septal, Systolic velocity; E, Transmitral early filling velocity; E/e´, Transmitral early filling velocity/early diastolic velocity

Table 3. Comparison of baseline characteristics and echocardiographic parameters of the left ventricle between the groups based on the median of NT-proBNP

Variables	Low Group (n=14)	High Group (n=14)	*P*-value
Male, n (%)	11 (78.6%)	4 (28.6%)	0.246
Female, n (%)	3 (21.4%)	10 (71.4%)	0.156
Age, median ($IQR_{25\%-75\%}$) y	12 (5 - 13.5)	3.5 (0.3 - 10)	0.016
Weight mean (SD) kg	35.4 ± 15.7	19.1 ± 17	0.008
Height, mean (SD) cm	148.9 ± 22.1	100.3 ± 35.9	0.001
NT-proBNP, median ($IQR_{25\%-75\%}$) pg/mL	2701 (576 - 5758)	19238 (11192 - 25000)	<0.001
Lateral MPI, mean (SD)	0.8 ± 0.4	0.9 ± 0.2	0.094
Septal MPI, mean (SD)	0.6 ± 0.1	1 ± 0.2	<0.001
e´ septal, mean (SD) cm/s	11.9 ± 5.2	7.8 ± 1.8	0.043
a´ septal, mean (SD) cm/s	7.5 ± 2.5	4.3 ± 1.2	0.001
s´ septal, mean (SD) cm/s	7.5 ± 2.4	4.2 ± 1.6	<0.001
E mean (SD) cm/s	85.2 ± 21.2	91.9 ± 20.2	0.491
Septal E/e´, mean (SD)	8.5 ± 4.1	12.1 ± 3	0.002
Lateral E/e´, mean (SD)	5.6 ± 1.7	10 ± 4.1	0.008
e´ lateral, mean (SD) cm/s	16.3 ± 5.6	11.1 ± 6.3	0.006
a´ lateral ,mean (SD)cm/s	6.5 ± 2.4	4.3 ± 1.7	0.004
s´ lateral, mean (SD) cm/s	7.3 ± 2.4	4.7 ± 2.9	0.004
Left ventricular ejection fraction, mean (SD) %	27.4 ± 7.3	15.7 ± 4.3	<0.001

Lateral MPI, Myocardial performance index assessed by tissue Doppler imaging from the lateral corners of the mitral annulus; Septal MPI, Myocardial performance index assessed by tissue Doppler imaging from the medial corners of the mitral annulus; e´, Early diastolic velocity; a´, Late phase of diastolic velocity; s´ septal, Systolic velocity; E, Transmitral early filling velocity; E/e´, Transmitral early filling velocity/early diastolic velocity

DISCUSSION

In this study, we showed that systolic and diastolic dysfunction as evaluated by echocardiography was associated with elevated NT-proBNP levels in children with idiopathic DCM. In addition, the

correlations between the NT-proBNP level and the septal MPI, an indicator of global systolic and diastolic dysfunction, and the LVEF were the strongest values among other echocardiographic parameters. The importance of our findings is that TDI is widely used in the evaluation of heart failure in our daily practice with high sensitivity and high reproducibility, which is not influenced by heart rate variability and preload. Moreover, given the unavailability of the NT-proBNP test in centers and the need for blood sampling in different visits, as well as the good association between NT-proBNP and TDI parameters, noninvasive echocardiographic examinations can be used as an appropriate tool for evaluating DCM among children.

Koura et al [25] evaluated the relationship between NT-proBNP and DCM or left-to-right shunting in children and showed that NT-proBNP was significantly higher in patients with increased pulmonary arterial pressure and heart failure than in children without them. In addition, NT-proBNP was elevated in 90.9% of the patients with DCM. Kocharian et al [26] studied the level of NT-proBNP to detect the severity of diastolic abnormalities in children with cardiac failure. Based on their findings, higher levels of NT-proBNP correlated with heart failure severity and the MPI, which may be used as a biomarker to rule out diastolic dysfunction. These findings are in line with our findings insofar as patients with DCM had elevated NT-proBNP levels and also there was a significant positive correlation between the MPI and peptides.

Systolic and diastolic functions are correlated since the diastolic function is influenced by end-systolic volumes, a consequence of systolic contraction, and the LVEF is dependent on filling, which is changed by LV filling pressure, a consequence of LV relaxation. [27] Mohammed et al [20] showed that both s′ and e′ were decreased in children with cardiomyopathies. Goto et al [28] found that the BNP level and its combination with mitral annular velocity during the early diastole (e´) could identify isolated LV diastolic dysfunction without heart failure in patients with coronary artery disease. Another study used TDI parameters and showed that the S-wave velocity and the e′/a′ ratio were significantly decreased, and the isovolumetric contraction and relaxation times of the mitral annulus and the mean difference between the time-to-peak systolic strain of the basal septal and basal lateral segments were significantly prolonged in children with DCM compared with the control group. [19] Mak et al [29] found that BNP weakly correlated with the E/e′ ratio measured by TDI, which is an estimation of the LV filling pressure. The BNP level combined with the E/e' ratio may provide a better predictor of elevated LV filling pressures in patients with suspected diastolic dysfunction. In our study, we also showed that elevated NT-proBNP significantly correlated with systolic and diastolic velocities measured by TDI. We found that e´ measured from the lateral corners of the mitral annulus had the strongest correlation with NT-proBNP ($\rho = -0.591$; $P=0.001$). In addition, systolic and diastolic velocities measured by TDI from the mitral valve annulus were significantly lower in the high NT-proBNP group than in the low NT-proBNP group.

The MPI parameter is a measurement of systolic and diastolic dysfunction, while other TDI parameters are isolated systolic or diastolic functions of the myocardium. Kocharian et al [26] showed that the MPI was directly associated with increased NT-proBNP in children with heart failure. In contrast, Maisel et al [30] found that in adult patients with LV dysfunction defined by TDI measurements, BNP was significantly higher in patients with abnormal E/e′, and there was a

significant correlation as well. On the other hand, there was a stronger correlation between BNP and combined systolic and diastolic dysfunction. They observed that BNP could not differentiate between systolic and diastolic dysfunction. We also found that elevated NT-proBNP was associated with systolic, diastolic, and combined LV dysfunction in patients with idiopathic DCM. However, we observed a better correlation between systolic dysfunction and elevated NT-proBNP. Given the findings of previous studies and those of the current investigation, it seems that BNP levels are influenced by systolic and diastolic dysfunction, and we cannot differentiate between the 2 functions by using NT-proBNP alone. Moreover, this biomarker might not be implicated as a tool for differentiating systolic and diastolic dysfunction. The septal MPI may overestimate the severity of LV diastolic dysfunction compared with the lateral MPI; however, a lack of invasive measurements precluded us from evaluating such differences. [31] Further large-scale studies are warranted to show the importance of NT-proBNP in children with DCM in demonstrating its diagnostic and prognostic implications.

The NT-proBNP level is influenced by sex and age. Nir et al [24] showed that among healthy children, the level of NT-proBNP was very high at birth and it decreased with advancing age with a significant drop occurring after 1 month. In addition, the levels varied between the sexes only among children aged between 10 and 14 years (medians: boys, 38 pg/mL; girls, 56.5 pg/mL). In our study population, only 1 child was less than 1 year old and 1 child was older than 14 years. Among patients between 10 and 14 years of age, the level of NT-proBNP was comparable, and the correlations between echocardiographic parameters were similar to those in all the children together.

Not only can NT-proBNP predict the risk of events in acute heart failure better than the NYHA/Ross symptom severity scale, [32] but also it reflects the severity of heart failure in children. [33] Given the results of our current investigation and previous studies, it appears that echocardiographic parameters might be a good surrogate for NT-proBNP levels. We think that when the NT-proBNP test is unavailable and we seek to avoid repeated blood sampling from patients, echocardiographic TDI parameters might be a valuable tool for evaluating children with DCM.

Study Limitations

The main limitation of our study is the small sample of patients, which may have influenced our findings. Secondly, we did not compare our findings with those in a healthy control group. However, subgroup analysis based on NT-proBNP levels may be of great importance to further explore the significance of this biomarker in children with DCM. Finally, all the echocardiographic examinations were performed by an echocardiographer, but we did not evaluate the intraobserver variability for the echocardiographic measurements.

CONCLUSIONS

Our findings demonstrated that the NT-proBNP serum level was elevated in children diagnosed with DCM, and there were significant correlations between the levels of NT-proBNP and the systolic and diastolic functions and the MPI measured by TDI. This study supports the use of noninvasive echocardiographic evaluations, particularly TDI parameters, as diagnostic tools among children with DCM.

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