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Original Article

Plasma N-terminal pro-B-type natriuretic peptide: selecting the optimal heart failure marker in children of age up to 18 years

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Abstract: Background: The cutoff values of plasma N-terminal-pro-B-type natriuretic peptide (NT-proBNP) for the heart failure (HF) is vague in children. We determined the NT-proBNP levels that indicated HF in age-stratified groups of children up to age 18. Methods: This is a prospective clinical study and a double blind experiment method. We measured plasma NT-ProBNP concentrations in HF patients less than 1 year old, 1-3 years old, 4-6 years old, and 7-18 years old. HF was defined by a Ross score between 3 and 12, and the optimal cutoff values were determined by analyzing receiver operating characteristic (ROC) curves. Results: In healthy children, NT-proBNP levels dropped gradually as the children got older. There was a negative correlation between NT-proBNP levels and age ($r = -0.741$, $P < 0.001$). The areas under the ROC curves were 0.87 for patients less than 1 year old, 0.83 for 1-3 year olds, 0.91 for 4-6 year olds, and 0.86 in patients 7-18. The 95% confidence intervals were 0.79-0.96, 0.73-0.93, 0.85-0.97, and 0.78-0.95, respectively. J values were 0.81, 0.77, 0.74, and 0.65, respectively. The optimal cutoff values of plasma NT-ProBNP that indicated HF were and 580 ng/l, 529 ng/l, 500 ng/l and 455 ng/l, respectively, for less than 1 year old, 1-3 year olds, 4-6 year olds and 7-18 year olds in patients. Conclusions: Age-stratified NT-ProBNP levels in children from birth to age 18 provide new parameters for the diagnosis of HF, which can help clinicians accurately diagnose HF in pediatric patients.

Keywords: N-terminal-B-type natriuretic peptide, heart failure, cutoff points, age stratification, children under 18 years of age

Introduction

At the current, clinicians diagnose pediatric heart failure (HF) usually adopt Modified Ross score, a gold standard [1]. The Modified Ross score is based on clinical symptoms, so subjective judgments by clinicians can come into play. Objective diagnostic indices, such as NT-ProBNP levels will increase the accuracy and sensitivity of a pediatric heart failure diagnosis.

Elevated levels of plasma NT-proBNP have been widely accepted as a biological marker of heart failure severity [3-8]. Research has also shown that elevated NT-proBNP levels are a sign of systolic dysfunction [9-13], diastolic dysfunction [11], and ventricular diastolic dysfunction [10] in HF.

At present, heart failure is diagnosed in adults under 50 years of age by plasma NT-ProBNP levels greater than 450 ng/l. After age 18, it is reasonable to use the age-adjusted criteria suggested for adults under 50 years of age, which consider HF present if NT-proBNP levels are > 450 ng/l [14]. Unfortunately, there are no similar standards for pediatric heart failure, and the age of the child is rarely considered when NT-ProBNP levels are being evaluated.

Research shows that, during the neonatal period, plasma NT-proBNP significantly increased the first few days after birth, then gradually decreased during infancy and childhood [15]. In this study, the presence of HF was expressed by a Ross score between 3 and 12. The subjects and controls were divided into four age groups:

Table 1. Plasma concentrations of NT-ProBNP(M) in different pathologies and genders in the experimental group

Disease	Total		Male		Female	
	n	NT-proBNP	n	NT-proBNP	n	NT-proBNP
Ventricular septal defects	145	1232.2 ng/l	77	1213.8 ng/l	68	1212.9 ng/l
Atrial septal defects	37	550.0 ng/l	20	526.4 ng/l	17	520.2 ng/l
Tetralogy of Fallot	14	2632.5 ng/l	8	2500.0 ng/l	6	2355.4 ng/l
Patent ductus arteriosus	28	550.0 ng/l	15	680.7 ng/l	13	650.0 ng/l
Aorta stenosis	13	2656.5 ng/l	7	2750.4 ng/l	6	3008.6 ng/l
Single ventricle	8	2962.5 ng/l	4	3000.0 ng/l	4	2908.0 ng/l
Septic shock	41	3650.0 ng/l	21	3500.6 ng/l	20	3488.4 ng/l
Viral myocarditis	22	3753.4 ng/l	12	3655.0 ng/l	10	3500.8 ng/l
Dilated cardiomyopathy	14	4365.6 ng/l	6	4400.0 ng/l	8	4263.2 ng/l
Endocardial fibroelastosis	7	4300.0 ng/l	4	4233.1 ng/l	3	4208.8 ng/l
Cardiac tumor	9	6022.3 ng/l	4	5806.4 ng/l	5	5798.6 ng/l

Total (disease) 338 (n) NT-proBNP (male, 723 ng/l; female, 807 ng/l) Z = -1.23, *P* = 0.269.

less than 1 year old, 1-3 years old, 4-6 years old, and 7-18 years old. The optimal cutoff values of plasma NT-proBNP indicative of HF in each age group was determined by analyzing the specificity, sensitivity, and Youden index of the ROC curves.

Materials and methods

Patients

Design: Prospective, clinical study and a double blind experiment method.

A total of 338 consecutive patients were recruited for the diagnosis HF of age-stratified NT-ProBNP levels in children.

Inclusion criteria: children 18 years of age and younger with Ross scores between 3 and 12 indicating heart failure. There were no gender quotas.

Exclusion criteria: 1) children with Kawasaki disease, nephropathy syndrome, nephritis, meningoencephalitis, febrile convulsions, or pulmonary arterial hypertension disease; 2) children taking beta blockers or diuretics.

All subjects were recruited from the Affiliated Shunde Women and Children's Hospital of Jinan University, the First Affiliated Hospital of Zhongshan University, the Affiliated Gangzhou Hospital of Nanchang University and the Yuexiu District Children's Hospital of Guangzhou between January 2010 and August 2015.

There were 338 pediatric patients with heart failure in the experimental group: 178 males and 160 females with an average age of 5.1 years (age range 0-18). All of them had been diagnosed with heart failure by Ross score. There were 145 ventricular septal defects, 37 atrial septal defects, 28 patients with patent ductus arteriosus, 14 with tetralogy of Fallot, 13 with aortic stenosis, and 8 patients with a single ventricle. Forty-one patients were in septic shock, 22 had viral myocarditis, 14 had dilated cardiomyopathy, 7 had endocardial fibroelastosis, and 9 had cardiac tumors (**Table 1**).

There were 300 selected, healthy children in the control group: 155 males and 145 females with an average age of 5.2 years (age range 0-18). The differences in age and sex between the experimental and control groups did not reach significance.

For some analyses, the children with HF were further stratified into four age groups: < 1 year old (n = 75); 1-3 years old (n = 105), 4-6 years old (n = 46) and 7-18 years old (n = 112). In this study, patients with Kawasaki disease, nephropathy syndrome, nephritis, meningoencephalitis, febrile convulsions, pulmonary arterial hypertension, and who used beta-blockers and diuretics were not allowed to participate because these conditions and drugs affect plasma NT-proBNP concentrations.

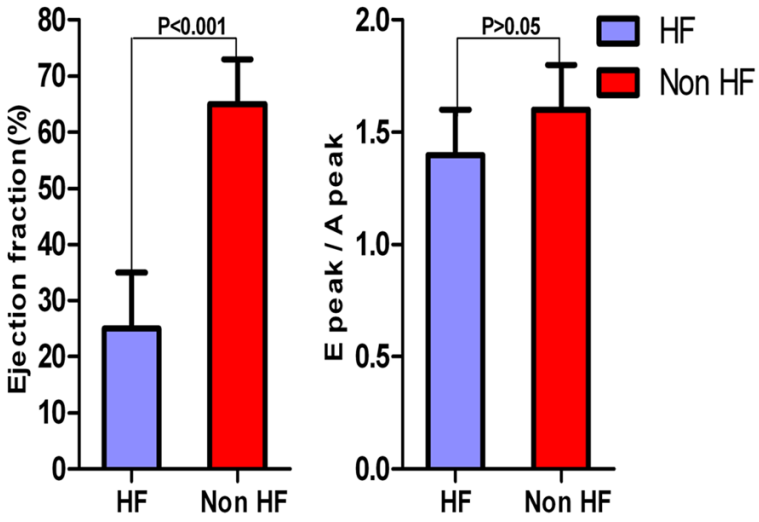

Figure 1. In the heart Doppler examination, the ejection fractions of HF patients in the experimental group and non-HF children in the control group were 24% ± 10.6% and 65% ± 6.9%, respectively, a significant difference ($P < 0.001$); the E peak/A peak of the 2 groups were normal and not significantly different (1.4 ± 0.2 cf. 1.6 ± 0.2). The results suggested a left ventricle systolic dysfunction in all heart failure patients.

Laboratory assays

Measurement of the NT-proBNP levels was fully automated to eliminate human error of any kind. A 2 ml venous blood sample was collected in tubes containing EDTA-K2. Subjects in the experimental group had these samples drawn on admission to the hospital and the control group had their blood drawn during routine check-ups. The plasma NT-ProBNP concentration was measured immediately after the blood draw using a standardized assay and an automated reader (YZB/CAN 1794-2008, Model 91001, Response Biomedical Corporation, Vancouver, Canada).

Data analysis and statistical methods

HF was diagnosed in the experimental group if the patient had a Ross score between 3 and 12. A number of tests were performed to determine the threshold values of plasma NT-proBNP that diagnosed HF in pediatric patients. The analysis included the ROC area under the curve (AUC), the 95% confidence interval (CI), sensitivity, specificity, positive predictive value and the Youden index.

The statistical analyses were performed with SPSS version 17.0 statistical software (SPSS, Chicago, IL, USA). Figures were generated using GraphPad software. (GraphPad Software, La Jolla, USA).

K-S testing was used to investigate the distribution of plasma NT-ProBNP levels in both the experimental and control groups. The results showed that distributions were not normal ($Z = 2.711$, $P < 0.001$; $Z = 1.405$, $P = 0.040$). The Kruskal Wallis test was used to compare the plasma NT-proBNP levels in HF patients and healthy children. Spearman's test was applied for the correlation analysis between plasma NT-proBNP levels and age, ejection fraction, heart rate, breath rate, liver enlargement in all HF patients and healthy children.

ROC curves were employed to determine the optimal cut-off values of plasma NT-ProBNP for heart failure in patients. The area under the ROC curve (AUC), sensitivity, specificity, positive and negative likelihood ratios, and 95% confidence intervals were calculated for the cutoff values. A probability of ≤ 0.05 was taken as significant.

This study was approved by The Affiliated Shunde Women and Children's Hospital of Jinan University ethics committee. Has made the subjects guardian's informed consent.

Results

The plasma NT-proBNP levels distributions were non-normal distribution ($P < 0.001$), therefore we used the median (M) to express.

The ejection fraction and ratios of the E-to-A peaks in the experimental group and the control group

All HF patients had left ventricle systolic dysfunction (systolic HF) with an ejection fraction (*EFs*) < 50% (50-75% is considered normal), and no diastolic HF (ratios of the E-to-A peaks were > 1 and < 3; 1-3 considered normal) in the heart Doppler examination [19, 20] (**Figure 1**).

Table 2. Correlation, comparison and regression analyses in the experimental group for plasma NT-proBNP levels and heart rate, breathe rate, liver enlargement, ejection fraction

Related factors	r	P	F	P	R
Heart rate (time/min)	0.752	0.000	76.32	0.000	0.575
Breath rate (time/min)	0.725	0.000	64.85	0.000	0.548
Liver enlargement (cm)	0.691	0.000	57.56	0.000	0.492
Ejection fraction	-0.695	0.000	79.66	0.000	0.556

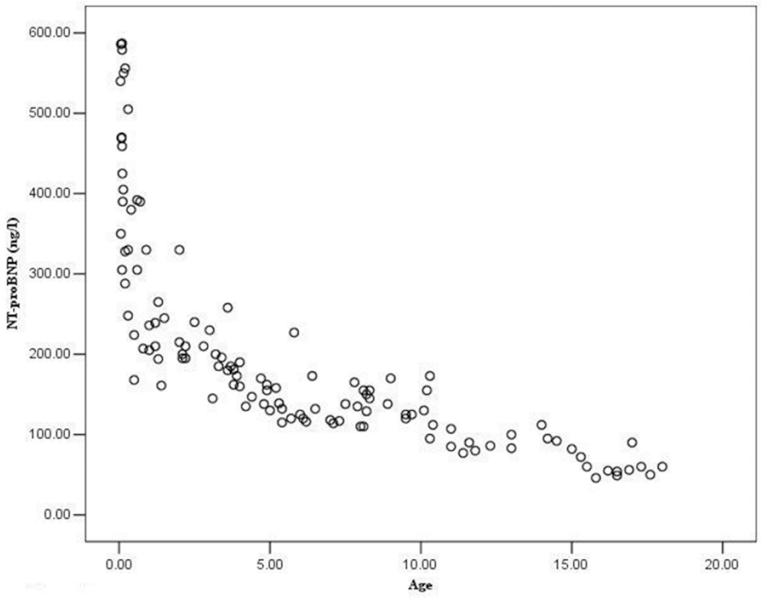

Figure 2. Correlation between NT-proBNP levels and age under 18 years of age in the control group (r = -0.706, *P* = 0.000).

The correlation between plasma NT-proBNP level and heart rate, breathe rate, liver enlargement and ejection fraction in the experimental group

There was a positive correlation between increased plasma NT-proBNP levels and heart rate (r = 0.752, *P* < 0.001), breath rate (r = 0.725, *P* < 0.001), and liver enlargement (r = 0.691, *P* < 0.001); and a negative correlation between increased NT-proBNP levels and ejection fraction in the experimental group (r = -0.695, *P* < 0.001). The f test linear regression analysis reached statistical significance (*P* < 0.001) (**Table 2**).

The plasma NT-proBNP level of comparison in mild, moderate, severe heart failure

HF was diagnosed if the patient had a Ross score between 3 and 12 (1). In the mild HF group, the plasma NT-proBNP levels were 1,050 ng/l (M). They were 3,008 ng/l (M) in the moderate HF group and 9,506 ng/l (M) in the severe HF group. Kruskal-Wallis H testing was used to compare plasma NT-proBNP levels for all three groups (mild, moderate, severe), and the differences between them were significant (X^2 = 46.128, P < 0.001).

The correlation between plasma NT-proBNP levels and age in the control group

The median levels of plasma NT-ProBNP in each age group were compared. In the control group during the 28 days after birth, plasma levels were the following: 0-4 days (M = 1388.5 ng/l; range 750-4615 ng/l), 5-15 days (M = 640.8 ng/l; range 515-850 ng/l); 16-28 days (M = 412.7 ng/L; range 341-462 ng/l). Between 28 days and 1 year old, plasma levels were M = 285.5 ng/L; range 118-426 ng/l). Between 1 and 3 years old, plasma levels were M = 140.8 ng/L; range 80-266 ng/l. Between 4 and 6 years old, plasma levels were M = 123.8 ng/l; range 45-228 ng/l, and between 7 and 18 years old, plasma levels were M = 60.5 ng/l; range 16-188 ng/l.

There was an inverse correlation of NT-proBNP levels with age (r = -0.706, P = 0.000). During the first year of life, NT-proBNP levels decreased rapidly; but they decreased slowly between 1 and 18 years of age (**Figure 2**). Linear regression analysis resulted in the equation Y = 233.25-12.26 X, R^2 = 0.528. The R^2 value of the regression analysis was 0.528, indicating that age accounts for 52.8% of the variability in plasma NT-ProBNP levels in healthy children. The regression analysis was statistically significant using the f test (f = 103.68, P < 0.001).

The correlation between plasma NT-proBNP level and age in the experimental group

In the experimental group, the plasma NT-ProBNP level was gradually reduced with age. In

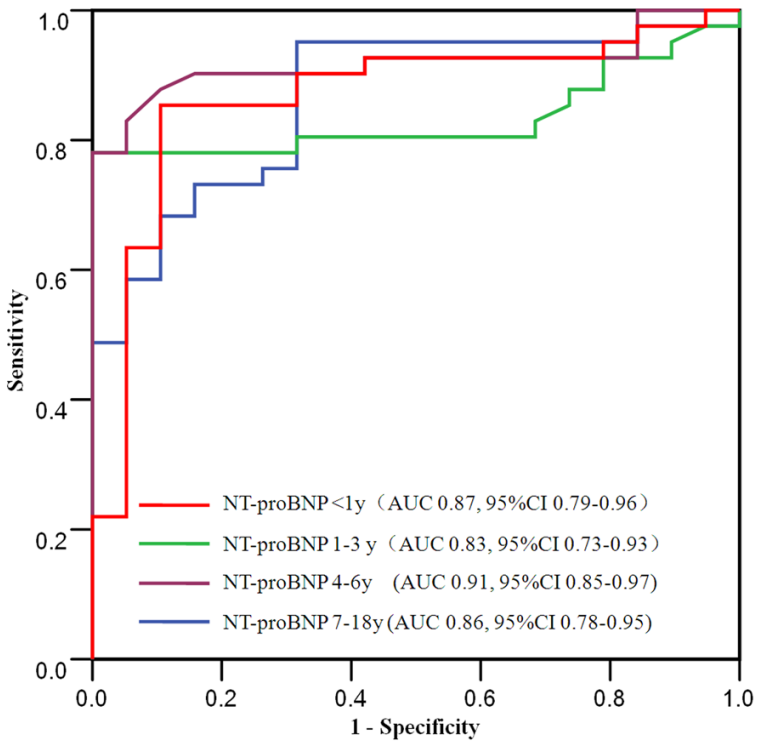

Figure 3. Receiver-operating characteristic curve for the optimal cutoff values of NT-ProBNP that indicated HF in age-stratified groups of children up to age 18 (< 1 year of age, 1-3 years of age, 4-6 years of age and 7-18 years of age).

Table 3. Optimal cutoff values of plasma NT-ProBNP levels in the experimental group stratified by age

Age group	AUC	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	J	Cutoff value (ng/l)
< 1	0.87	85.2	95.8	93.5	0.81	580
1-3	0.83	78.1	98.9	92.9	0.77	529
4-6	0.91	88.2	85.8	92.2	0.74	500
7-18	0.86	74.0	91.0	90.1	0.65	455

the first year of life, M = 3,699 ng/l. In the 1-3 year-old group, M = 3,272 ng/l. In the 4-6 year-old group, M = 2,933 ng/l and in the 7-18 year-old group, M = 2,217 ng/l. The plasma NT-ProBNP levels were similar in males and females, and the Wilcoxon test was not statistically significant between gender groups (Z = -1.23, P = 0.269).

Analysis of the ROC curves of plasma NT-proBNP levels after age stratification in the experimental group

In the experimental group, the ROC curves of plasma NT-ProBNP levels had the following characteristics for patients.

In HF patients under one year of age: AUC = 0.87 with a 95% CI of 0.79-0.96. The ROC analysis showed that the sensitivity and specificity of plasma NT-ProBNP as a diagnostic tool were 0.852 and 0.958, respectively. The J Value was 0.81 and the optimal cutoff values of NT-proBNP for heart failure were 580 ng/l, which yielded 93.5% positive predictive value (**Figure 3**; **Table 3**).

In HF patients between 1-3 years of age, the ROC curve had the following characteristics: AUC = 0.83 with a 95% CI of 0.73-0.93. The ROC analysis showed that the sensitivity and specificity were 0.781 and 0.989, respectively, and J was 0.77. The optimal cutoff values of NT-proBNP for heart failure were 529 ng/l, which yielded 92.9% positive predictive value (**Figure 3**; **Table 3**).

In HF patients 4-6 years of age, the ROC curve had the following characteristics: AUC = 0.91 with a 95% CI of 0.85-0.97. The ROC analysis showed that the sensitivity and specificity were 0.882 and 0.858, respectively, and J was 0.74. The optimal cutoff values of NT-ProBNP for heart failure were 500 ng/l, which yielded 92.2% positive predictive value (**Figure 3**; **Table 3**).

In HF patients aged 7-18 years, the ROC curve had the following characteristics: AUC = 0.86 with a 95% CI of 0.78-0.95. The ROC analysis showed that the sensitivity and specificity were 0.740 and 0.910, respectively, and J was 0.65. The best diagnostic threshold value for NT-proBNP for heart failure was 455 ng/l, which yielded 90.1% positive predictive value (**Figure 3**; **Table 3**).

Determining the optimal cutoff values of plasma NT-ProBNP level that diagnoses heart failure in children under 18 years of age

The optimal cutoff values of plasma NT-ProBNP for the diagnosis of heart failure was 580, 529,

500, and 455 ng/l for ages < 1, 1-3, 4-6, and 7-18.

Discussion

The importance of NT-proBNP levels in the diagnosis and evaluation of heart failure has been widely accepted [3, 6-8]. Research [3, 5, 16-17] has demonstrated that the score has very high diagnostic and prognostic value in adult HF when combined with clinical symptoms, and is also a sign of systolic dysfunction heart failure in adults [9, 11-13]. In adults under 50 years of age, the possibility of heart failure is low when the NT proBNP level is < 300 ng/l (negative predictive value ~90%); but heart failure is likely when the level is > 450 ng/l (positive predictive value also ~90%), more than 50 years of age is > 550 ng/l [14]. In children of age up to 18 years, NT-proBNP cutoff values have not yet been determined. One of the reasons is that the predictive value of plasma NT-proBNP levels varies with age.

Age has a critical influence on plasma NT-proBNP concentrations; levels increase gradually with age, reaching 200-300 ng/l at 50-65 years of age [18, 19]. In the control group, our study revealed that plasma NT-proBNP levels were highest in children between birth and 1 year of age (M = 418.2 ng/l, range 118-4,456 ng/L). M = 140.8 ng/l with a range of 80-269 ng/l in the 1-3 year-old group; M = 123.8 ng/l with a range of 45-228 ng/l in the 4-6 year-old group, and M = 60.5 ng/l with a range of 16-199 ng/l in the 7-18 year-old group. Plasma NT-proBNP levels increased significantly during the first few days after birth, then gradually decreased throughout infancy and childhood. In the experimental group, the plasma NT-ProBNP level: respectively was M = 3,699, 3,272, 2,933, and 2217 ng/l for ages < 1, 1-3, 4-6, and 4-18, which gradually decreased with age. The finding suggests that the predictive value of plasma NT-proBNP levels varies with age.

Consistent with Rauth and Koch's research [11], our study revealed that NT-proBNP levels decrease with age in healthy children and heart failure patients. Currently, there is only limited information on what the significant clinical values should be in children with heart failure [15]. One study [20] suggests that the diagnostic values of NT-proBNP for heart failure in children should be related to the patient's age, but there is a lack of research on this question. Our earlier studies shown that optimal cutoff values of NT-proBNP for heart failure in children 1 to 18 months was ≥ 598 ng/l [21]. In the study, we found that the optimal cutoff values of NT-proBNP for heart failure were 580, 529, 500, and 455 ng/l for ages < 1, 1-3, 4-6, and 4-18, which yielded ~90% positive predictive value.

These data suggest that age-stratified analysis of plasma NT-proBNP levels in children provides new parameters for the diagnosis of HF, can help clinicians to accurately diagnose HF in pediatric patients.

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Disclosure of conflict of interest

None.

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