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Original Article (Pages: 11819-11829)

Clinical and Biochemical Assessments of Circulating B-Type Natriuretic Peptide as a Useful Marker in Pediatric Cardiac Patients

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Abstract

Background

Although the left ventricle is the major site of BNP secretion in response to cardiac pressure or volume overload, the myocytes of both atria and ventricles secrete B- type natriuretic peptide (BNP). This study aimed to assess and compare the plasma levels of BNP in common pediatric cardiac diseases to clarify its pathophysiological role and evaluate its possible diagnostic and prognostic utility in pediatric patients with congenital heart disease (CHD), and heart failure (HF).

Materials and Methods: The study is a prospective, case-control research including 131 pediatric patients selected from Pediatric Department of South Valley University Hospitals in Qena, Egypt, with a variety of cardiac diseases and 70 healthy controls. The patients were categorized into 4 groups: 61 newly diagnosed pediatric patients with CHD, 30 patients with HF, 20 pediatric patients with cardiomyopathy (CM), and 20 children with rheumatic heart disease (RHD). Clinical and echocardiographic assessments for the pediatric patients were performed. Bioassays of plasma BNP using commercially available ELISA assay kits were performed to the study the participants.

Results: The median plasma BNP levels were significantly higher in the CHD, HF and CM groups than the RHD and control groups, with $p<0.001$ for all groups with non-significant differences between both RHD and control groups. BNP levels did not significantly differ in patients with PDA or multiple cardiac anomalies vs. the controls ($p>0.05$).

Conclusion

The validity of plasma BNP in diagnosing HF was significantly superior to its utility in predicting CHD among pediatric patients.

Key Words: Cardiac diseases; CHD; Heart failure, Plasma BNP, Pediatrics.

*Please cite this article as: El-Abd Ahmed A, Hassan MH, Toghan R, Abdellah Ahmed A, Abd-Elmawgood EA. Clinical and Biochemical Assessments of Circulating B-Type Natriuretic Peptide as a Useful Marker in Pediatric Cardiac Patients. Int J Pediatr 2020; 8(8): 11819-829. DOI: **10.22038/ijp.2020.50413.4012**

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Received date: Mar.14, 2020; Accepted date: Jun. 22, 2020

1- INTRODUCTION

Cardiac overload (pressure or volume) results in the secretion of natriuretic peptides (NPs) from the heart (1). NP hormones include many structurally similar peptides, such as B-type natriuretic peptide (BNP), urodilatin peptide, atrial natriuretic peptide (ANP), and C-type natriuretic peptide (CNP). The myocytes of both atria and ventricles secrete BNP, although the left ventricle is the major site of BNP secretion. A precursor protein (proBNP) cleaves into NT-proBNP (inactive) and BNP (active), which has diuretic, natriuretic, smooth muscle relaxant and vasodilator effects (2-5). BNP is considered as one of the best diagnostic markers for cardiovascular diseases (CVDs), not only in adults but also in children; although data on the diagnostic and prognostic accuracy of BNP in children with CVDs are lacking, with no expert recommendation or guidelines for its routine use in various pediatric clinical setting (1, 6-8).

Cantinotti reported the possible clinical situations in which BNP could be helpful, for instance congenital heart disease (CHD) (for evaluation of its severity and monitoring children undergoing corrective cardiac surgery for such anomalies) and acquired pediatric heart diseases (for differentiation of cardiac from pulmonary causes of dyspnea) (9). Considering the lack of studies regarding its possible use as a clinical marker in various cardiac diseases in pediatric patients, the present study aims to assess and compare the BNP plasma levels in pediatric patients with various cardiac diseases (e.g. congenital heart diseases, heart failure, cardiomyopathy and rheumatic heart diseases), and to evaluate its predictive value in cardiac disorders. Furthermore, this study is the first to compare the validity of plasma BNP in predicting CHD vs. HF in pediatric patients.

2- MATERIALS AND METHODS

2-1. Study design and participants

The current prospective case-control study was conducted on 131 pediatric patients (neonates, infants and children) of both sexes with various cardiac diseases selected from the neonatal intensive care unit (NICU), outpatient pediatric clinics, or the inpatient Pediatric Department of South Valley University Hospitals in Qena, Egypt. For validation, 70 unrelated healthy child were selected as a control group, with corresponding age, body mass index and sex to the cases in the study. The control group visited the NICU or the outpatient Pediatric clinics for routine clinical follow-up. The study was approved by the Ethics committee of the Faculty of Medicine of South Valley University Hospitals in Qena, Egypt and was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from the legal guardians of every included child. The duration of study was two years, from August 1, 2017 to July 30, 2019. The body mass index (BMI, i.e. body weight divided by square of height in units of kg/m^2) was calculated for every included subject. All the studied chil had normal BMIs according to their corresponding age and gender in Egyptian growth curves (10). Those with abnormal BMI, abnormal estimated glomerular filtration rate (eGFR), or brain damage and children with diabetes were excluded from the study.

2-2. Investigatory tools

A) Echocardiography

Echocardiographic assessments of all included children were performed using two-dimensional (2D) cardiovascular transthoracic ultrasound (using Vivid 3, 2005, Germany, syncmaster 450 MB). Echocardiography was used to examine systolic and diastolic functions, dimensions of cardiac chambers, cardiac valve lesions, or cardiomyopathies. M-mode tracing was used to evaluate the left

ventricular function in parasternal long axis view. Left ventricular systolic function was assessed by fractional shortening (FS) with the normal reference value (28-44%). Other parameters of left ventricular volume/pressure overload are: left ventricular end-systolic dimension (LVESD in mm), left ventricular end-diastolic dimension (LVEDD in mm), and left ventricular posterior wall thickness at end-diastole (LVPWD in mm). The reference values for these parameters according to the body weight (11) are as follows:

For body weight of 3 Kg: 7-17, 11-29, and 1.5-5.5, respectively; for body weight of 4 Kg: 8-19, 13-30, and 1.5-5.5, respectively; for body weight of 7 Kg: 9-21, 16-33, and 2-6, respectively; for body weight of 10 Kg: 11-23, 18-37, and 2-6.5, respectively; for 13 Kg: 12-25, 21-40, and 2-7, respectively; for body weight of 16 Kg: 14-27, 23-43, and 2.5-7.5, respectively; for body weight of 19 Kg: 15-28, 25-45, and 2.5-7.5, respectively; for body weight 23 Kg:16-30, 27-47, and 3-8, respectively; for body weight 28 Kg: 17-31, 28-50, and 3-8.5, respectively; for body weight of 37 Kg: 18-34, 30-53, and 3-9.5, respectively; for body weight of 46 Kg: 19-36, 31-56, and 3.5-10, respectively; and for body weight of 55 Kg:10-37, 32-58, and 4-11, respectively.

B) Blood samples and BNP assays

3 ml of venous blood samples were obtained from every studied patient and controls, and were transferred into EDTA-containing tubes. The tubes were afterwards centrifuged at 3500 rpm for 15 min at 4 ^{0}C, and the plasma was transferred into 1 ml cryotubes and stored at 80^{0}C for later BNP assays. Plasma BNP levels were measured using ELISA assay kits supplied by Chongqing Biospes Co., Ltd., China Catalog No. BYEK2831, and microplate ELISA readers (EMR 500, USA) according to manufacturer protocol (12, 13). Pediatric patients with heart failure underwent two assays for plasma BNP; once before receiving the anti-failure measures, and again 7 days after receiving the anti-failure therapy (14).

2-3. Data Analysis

IBM SPSS Statistics for Windows version 20 and Medcalc version 15.8.0 were used for data analysis. Qualitative data was expressed as number and percentage, while quantitative data was expressed as median and inter quartile range. For the non-parametric data, Mann-Whinty U test, Kruskal-Wallis H test, and Spearman's correlation were used. Receiver operating characteristic (ROC) curve was constructed to find out the optimum cut off point for plasma BNP (ng/l) in diagnosing CHD and HF with calculation of the AUC (95% CI), sensitivity, specificity, PPV and NPV. Level of significance was considered at $p<0.05$.

3- RESULTS

The current study was conducted on 131 pediatric patients with various cardiac diseases (48 males and 73 females) with their ages ranging from 1 to 171 months. The 70 healthy controls consisted of 33 males (47%), and 37 (53%) females in correspondence with the study patients for age (p=0.06), and sex (p=0.057). The median age in the control group was 54 months, with their age range from 1.67 to 96 months.

3-1. Clinical characteristics and echocardiographic data of the patients groups

The included patients consisted of 61 newly diagnosed pediatric patients with congenital heart disease (CHD); 25 males (41%) and 36 (59%) females with the median age of 4 months and the age range from 0.1 to 120 months. They were categorized according to the type of their congenital heart disease:18 patients (29.5%) with isolated ventricular septal defect (VSD), 10 patients (16.4%) with

isolated atrial septal defect (ASD), 11 children (18%) with isolated patent ductus arteriosus (PDA), 10 patients (16.4%) with pulmonary stenosis, and twelve pediatric patients (19.6%) with multiple congenital heart diseases (those had more than one congenital cardiac defect). 39 children had CHD with left to right shunt (isolated VSD, isolated ASD, and isolated PDA). 30 patients had heart failure (HF) of various etiologies, 14 males (46.6%) and 16 females (53.4%) with the median age of 14 months and age range from 2 to 120 months; 20 pediatric patients with cardiomyopathy (CM); 10 cases (50%) with hypertrophic, non-obstructive (HCM) type; 10 cases (50%) with dilated cardiomyopathy (DCM), 7 males (35%) and 13 females (65%) with median age of 25.8 months and age range from 10.5 to 32.1 months; and 20 children with rheumatic heart disease (RHD), 16 males (80%) and 4 females (20%) with the age range from 111 to 171 months and the median age of 150 months. They were categorized into: 8 cases had mitral valve regurgitation, 2 cases had aortic valve regurgitation, one case had double mitral lesion, and 9 cases had combined valve lesions. CHD and HF groups showed a significantly lower median age than both CM and RHD groups. Also, CM group had a significantly lower median age than RHD group ($p<0.001$ for all). Additionally, there was a significant female predominance among children with CHD and CM, and a significant male predominance among RHD group ($p<0.05$ for all). Left ventricular echocardiographic data of the patients' groups are presented in (**Table.1**), including left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), left ventricular posterior wall thickness at end-diastole (LVPWD), and fraction shortening (FS).

Table-1: Left ventricular echocardiographic parameters of the studied patients' groups.

Variables	Patients' groups			
	CHD (n=61)	Heart failure (n=30)	Cardiomyopathy (n=20)	Rheumatic heart disease (n=10)
LVEDD (mm) Median (IQR)	22 (18 – 28)	20.5 (17.25 – 35.25)	47.5 (23 – 50.25)	41.5 (26 – 55)
LVESD (mm) Median (IQR)	13 (11 – 18)	12 (10 – 23)	39.5 (14.25 – 43)	27 (15 – 34)
LVPWD (mm) Median (IQR)	4 (3 – 4)	4 (3 – 5)	7.5 (5.25 – 9)	6.5 (4.75 – 9)
FS (%) Median (IQR)	39 (35 – 41.5)	35 (35 – 41.25)	17.5 (12.75 – 51.5)	39 (34.75 – 41)

N.B: CHD (congenital heart disease); IQR (inter-quartile range); left ventricular end-systolic dimension (LVESD); left ventricular end-diastolic dimension (LVEDD); left ventricular posterior wall thickness at end-diastole (LVPWD); FS (fraction shortening).

3-2. Plasma levels of B-type natriuretic peptide among the study groups

The median plasma BNP levels were significantly higher among CHD, HF and CM groups (26.4 ng/l, 52.46 and 41.49 ng/l, respectively) than RHD and control groups (2.08 and 2.67 ng/l, respectively), $p<0.001$ for all with non-significant differences between both RHD and control groups regarding to the median plasma BNP levels, $p>0.05$ (**Table. 2**).

Table-2: Plasma BNP levels among the study groups.

Variables	Study Group					P-value
	CHD (n=61)	Heart failure (n=30)	Cardiomyopathy (n=20)	Rheumatic heart disease, (n=10)	Control group (n=70)	
Plasma BNP (ng/l) Median (IQ range)	26.4* (2.68 – 48.88)	52.46* (47.04– 56.49)	41.49* (13.08– 55.63)	2.08# (1.61 – 3.2)	2.67 (2.19 – 3.79)	<0.001

P- value compared the four groups and was calculated by Kruskal Wallis test.
*P-value < 0.05 in comparison with the control using Mann-Whitney test.
P-value > 0.05 in comparison with the control using Mann-Whitney test.
N.B: CHD (congenital heart disease); IQR (inter-quartile range); BNP (B-type natriuretic peptide).

3-3. Plasma levels of B-type natriuretic peptide among pediatric patients with CHD

As regards the type of congenital heart disease among the newly diagnosed pediatric children, the median plasma BNP levels were significantly higher among those with isolated VSD (42.41 ng/l), isolated ASD (6.46 ng/l), and pulmonary stenosis (7.74 ng/l) in comparison to the controls ($p<0.05$ for all), with the highest median value being among pediatric patients with isolated VSD. There were also insignificant differences regarding the median plasma BNP levels between those with isolated PDA or multiple congenital heart diseases compared with the controls (**Table. 3**). Regarding the possible utility of plasma BNP in predicting pediatric patients with CHD, at cut-off point of > 2.685 ng/l, sensitivity, specificity, PPV, NPP and AUC were 64.5 %, 51.4 %, 54.04 %, 62.05 % and 0.659, respectively, with 95% C.I (0.508-0.809) (**Figure. 1**).

Table-3: Comparison between various types of CHD and control groups regarding plasma BNP.

Newly diagnosed pediatric patients with CHD, n=61.	Plasma BNP (ng/l) Median (IQ range)	P-value
Isolated VSD (n=18)	42.41 (1.65– 49.33)	
Control group (n=70)	2.67 (2.19 – 3.79)	0.036
Isolated ASD (n=10)	6.46 (3.69– 39.25)	
Control group (n=70)	2.67 (2.19 – 3.79)	0.021
Isolated PDA (n=11)	4.58 (1.9– 4.58)	
Control group (n=70)	2.67 (2.19 – 3.79)	0.755
Pulmonary stenosis (n=10)	7.74 (2. 69– 34.29)	
Control group (n=70)	2.67 (2.19 – 3.79)	0.038
Multiple congenital heart disease (n=12)	2.88 (1.69– 3.24)	
Control group (n=70)	2.67 (2.19 – 3.79)	0.205

P- value was calculated by Mann-Whitney U test.
N.B: CHD (congenital heart disease); IQR (inter-quartile range).

3-4. Plasma levels of B-type natriuretic peptide among pediatric patients with heart failure

The median plasma BNP levels were significantly higher among pediatric patients with HF before receiving anti-failure therapy (52.46 ng/l) than after (12.27 ng/l) ($p<0.001$) (**Table. 4**). The validity of plasma BNP in predicting pediatric patients with HF at cut-off point > 46.05 ng/l in the form of sensitivity, specificity, PPV, NPP and AUC were 80%, 90.2 %, 79.93%, 90.24%, and 0.904, respectively, with 95% CI (0.827-0.981) (**Figure. 1**). The validity of plasma BNP in diagnosing HF was significantly superior to its utility in predicting CHD among pediatric patients ($p<0.01$).

Table-4: Plasma levels of B-type natriuretic peptide among the included pediatric patients with heart failure.

Variable	Pediatric patients with heart failure, (n=30)		P-value
	Pediatric patients with heart failure before therapy, (n=30)	Pediatric patients with heart failure after anti-failure therapy, (n=30)	
Plasma BNP (ng/l) Median (IQ range)	52.46* (47.04– 56.49)	12.27* (2.24– 15.81)	<0.001

P- value compared the two groups and was calculated by Mann-Whitney test.
* P-value < 0.05 in comparison with the control using Mann-Whitney test.
N.B: CHD (congenital heart disease); IQR (inter-quartile range); BNP (B-type natriuretic peptide).

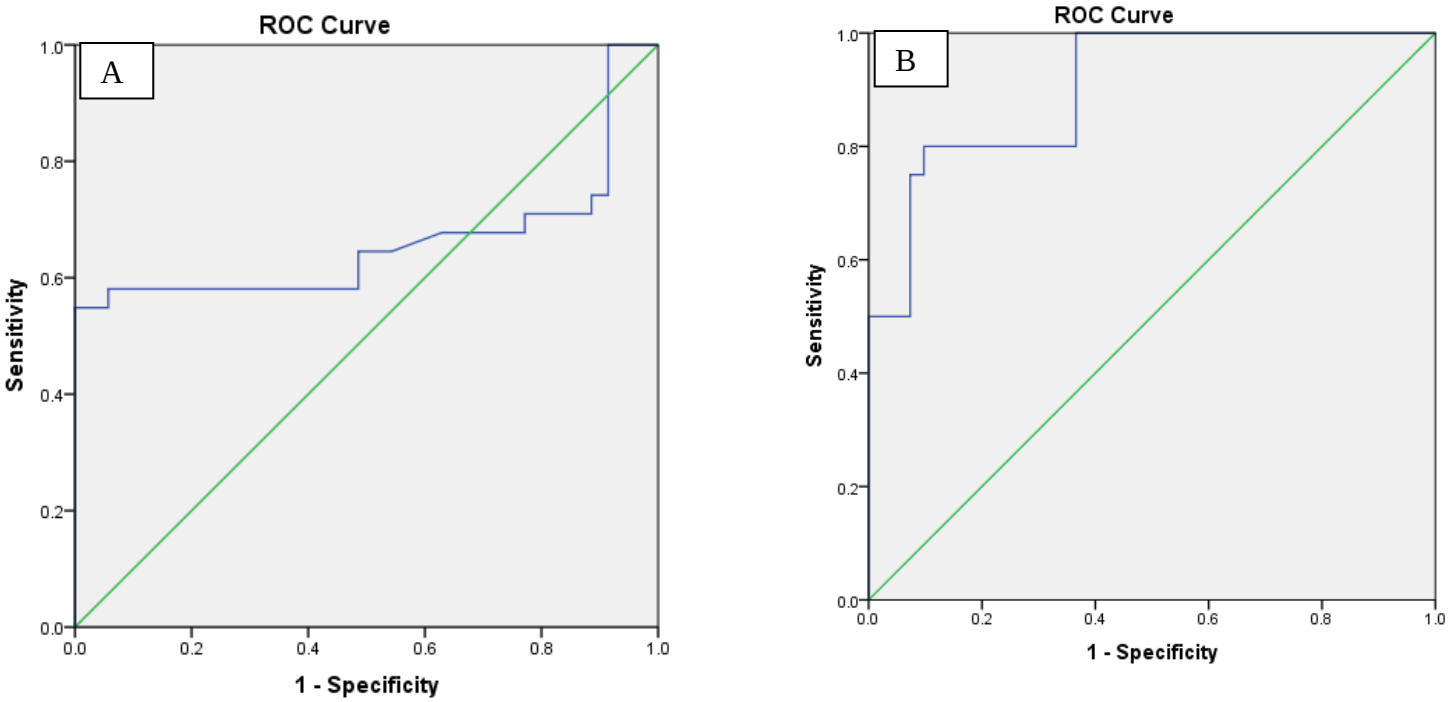

Fig.1: Receiver Operating Characteristic (ROC) curves for plasma BNP in predicting CHD (A), and heart failure (B) among pediatric patients, p<0.01.

3-5. Plasma levels of B-type natriuretic peptide among the pediatric patients with cardiomyopathy

The median plasma BNP levels were significantly higher among pediatric patients with DCM (55.26 ng/l) in comparison with those with HCM (18.04 ng/l) (p<0.001) (**Table. 5**).

Table-5: Plasma levels of B-type natriuretic peptide among the included pediatric patients with cardiomyopathy.

Variable	Pediatric patients with cardiomyopathy, (n=20)		P-value
	Hypertrophic, non-obstructive cardiomyopathy, (n=10)	Dilated cardiomyopathy, (n=10)	
Plasma BNP (ng/l) Median (IQ range)	18.04* (7.17– 28.32)	55.26* (54.47 – 57)	<0.001

P- value compared the two groups and was calculated by Mann-Whitney test.
*P-value < 0.05 in comparison with the control using Mann-Whitney test.
N.B: IQR (inter-quartile range); BNP (B-type natriuretic peptide).

3-6. Correlations of plasma BNP with the left ventricular echocardiographic parameters among groups

There were significant positive correlations between LVEDD and plasma BNP levels among both HF group ($r=0.693$, $p<0.001$), and CM group ($r=0.583$, $p=0.007$); although no significant correlations were observed between the plasma levels of BNP and various left ventricular echocardiographic parameters among both CHD and RHD groups.

4- DISCUSSION

The present study aims to assess the plasma BNP levels among various pediatric cardiac diseases including CHD, HF, CM, and RHD. It also studies the possible correlations between the measured BNP plasma levels and various left ventricular echocardiographic parameters in each cardiac disease that may help to understand the patho-physiological role of BNP in each case. Recently, there is an increasing interest in researches concerned with the burden related to congenital and acquired cardiac disorders and the possibility of recruiting BNP in pediatric patients with CHD, and CM (7, 15-17). However, insufficient data are available as to the utility of BNP in pediatric patients who need to enhance the performance of the already present and/or developing novel cardiac biomarkers (7).

In the present study, a significant female predominance was found among children with CHD and CM, and a significant male predominance among the RHD group. In agreement with our study, two studies have been done by Bassili et al. (18) on CHD among school children in Alexandria, Egypt, which also reported a female predominance among the cases. Similarly, studies by Azhar et al. (19), and Abd El Mohsen et al. (20) on pediatric patients with CM reported a female predominance. On the contrary, a study by Kotit et al. (21) on RHD in school children in Aswan, Egypt, found a male predominance among the study group. The peak age range for development of RHD and acute rheumatic fever (ARF) episodes is from 5 to 14 years old (22). The annual incidence of cardiomyopathy in children below the age of 10 years is about 1.24 per 100,000 children (23). In the current study, CHD group showed a significantly lower median age than both CM and RHD groups, and CM group revealed a significantly lower median age than RHD group. In terms of CHD, isolated VSD was the most frequent CHD in the current study in addition to isolated ASD and pulmonary stenosis, which was in accordance with Bassili et al. (24) on CHD among school children in Alexandria, Egypt. It also was reported that VSD, pulmonary stenosis, and ASD were among the most common cardiac defects. There is a growing interest in utility of BNP in patients with congestive heart failure and also in those with CHD (25).

The findings of the current study showed significantly higher plasma BNP levels among CHD in comparison with controls. Patients with isolated VSD, isolated ASD and pulmonary stenosis exhibiting significantly higher plasma BNP levels in comparison to the controls, with the highest levels found in pediatric patients with isolated VSD. This indicates that BNP levels can reflect the impairment of loaded ventricles as BNP is released by ventricular myocytes in response to pressure and volume load. Many researches were in agreement with our findings (25-28). On the contrary, Koch et al. (25) had reported normal BNP plasma levels in patients with pulmonary stenosis. In the current study, BNP levels among pediatric patients with PDA or multiple congenital heart diseases showed no significant difference from the controls. This indicates that the role of BNP in CHD is evidently more complex, and that a

normal BNP value cannot preclude a cardiac pathology; yet it can reflect a compensated status of the heart. In agreement with our findings, Koch et al. (25) reported similar data. Our results showed significantly higher plasma BNP levels among pediatric patients with HF in comparison to the healthy controls. The plasma level of > 46.05 ng/ml at cut-off point showed that sensitivity, specificity, PPV, NPP and AUC were 80 %, 90.2 %, 79.93 %, 90.24 % and 0.904, respectively, with 95% CI (0.827-0.981) in predicting pediatric patients with HF. The validity of plasma BNP in diagnosing HF was significantly superior to its utility in predicting CHD among pediatric patients. Many researches were in agreement with our findings (29-31).

Serial assays of plasma BNP have increased interest in its role as a guide in treatment of heart failure due to the modulations noticed in plasma levels with therapy, as reduction in its levels was associated with improved clinical outcomes (32-34). Our study found a significant reduction in the serial plasma BNP levels among HF group 7 days after receiving anti-failure therapy with clinical improvement of pediatric patients. This confirms its prognostic value in pediatric heart failure and potential clinical applications of this biomarker, including tracking the progression of the HF and assessing the response to therapy, which are in accordance with Khanam et al. (35).

As to BNP values in children with various cardiomyopathies, data are lacking (36). Our results revealed significantly higher plasma BNP levels among pediatric patients with CM when compared with the control group, with significantly higher levels among DCM compared to HCM. Similarly, Mir et al. (37) reported higher plasma BNP levels among children with dilated CM compared with those with restrictive and hypertrophic types. Additionally, high BNP plasma levels were reported among children whose echocardiography revealed left ventricular enlargement, reduced EF, or diastolic indices abnormalities (38). Also, Zoair et al. (39), Nasser et al. (40), and Niebroj-Dobosz et al. (41) all were in agreement with our findings, indicating that plasma BNP could be a good marker for left ventricular systolic dysfunction among children with DCM. The present study did not detect any significant difference in the plasma BNP levels among the studied RHD children compared with the controls, which is in agreement with a study conducted by Zachariah et al. (42).

On the contrary, in the mentioned study, BNP was shown to be elevated in children with predominantly moderate to severe RHD or acute rheumatic fever (43), which can be explained by the different inclusion criteria. Regarding the correlations between plasma BNP levels and left ventricular function, the current study shows significant positive correlations between LVEDD and BNP levels among both heart failure and cardiomyopathy groups. Many investigators were in agreement with our findings (44-46), indicating that plasma BNP level is associated with cardiac function and damage among such patients.

5- CONCLUSION

The current study confirms the valuable diagnostic and prognostic roles of plasma BNP assay in pediatric patients with HF. Plasma BNP could be helpful in diagnosing pediatric patients with CHD; although it has a superior utility in HF. Also, plasma BNP assay could help in case of children with cardiomyopathy. The current study reports the lack of plasma BNP role in pediatric patients with RHD, so larger scale studies including children with different RHD severities are required to confirm this finding in the future.

6- AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

7- FUNDING

This study was funded by South Valley University, Faculty of Medicine, Qena, Egypt.

8- AUTHORS' CONTRIBUTIONS

Study concept and design: MHH, AEA, EAA and RT; Clinical evaluation of the cases: EAA, AEA and AAA; Literature research: MHH and RT; Sample collections: MHH and AAA; Biochemical and laboratory assays: MHH; Data analysis: MHH, EAA, RT and AAA; drafting the manuscript: MHH; All authors revised and approved the final version of the manuscript.

9- CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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