Evaluation of N-Terminal Pro Brain Natriuretic Peptide as a biomarker for clinical severity of heart failure in pediatric population

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Background and study aim: Brain Natriuretic Peptide (BNP) and N-Terminal pro-Brain Natriuretic Peptide (NT-pro BNP) are frequently used in the diagnosis of congestive heart failure (CHF), especially for distinguishing between patients with dyspnea of cardiac and pulmonary origin. The present work aimed at evaluating N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) as a biomarker for diagnosis of congestive heart failure (CHF) in pediatrics and as well as its severity and hence, helping early diagnosis of CHF in absence of rapid echocardiographic examination.

Subjects and Methods: The patients group (group I) consisted of 45 children (24 males and 21 females) aging between 45 days and 12 years. All having the inclusion criterion of CHF. They were subclassified into: group I-1 including 15 patients having dilated cardiomyopathy (DCM), group I-2 including 15 patients having congenital heart disease (CHD) and group I-3 including 15 patients that have developed CHF due to non-cardiac causes. The control group was formed of 15 healthy children (group II) matched in age and gender with the patients groups. All children were subjected to full history taking, physical examination, classification of clinical severity of CHF cases according to Modified Ross Score, imaging and laboratory investigations including serum level of NT-proBNP.

Results: The study revealed that serum NT-proBNP showed a highly statistically significant increase in CHF cases three groups (I-1, I-2 and I-3) in comparison to the control group (group II) ($P<0.001$). NT-proBNP level showed highly statistically significant positive correlation with CHF class of clinical severity ($P<0.001$). Regarding echocardiographic parameters NT-proBNP showed a highly significant positive correlation with left ventricular end diastolic dimensions (LVEDD) and left ventricular end systolic dimensions (LVESD), and a highly significant negative correlation with left ventricular (LV) ejection fraction (EF), fractional shortening (FS) and mitral valve E/A ratio. At cutoff level of 1500 pg/ml, the sensitivity of NT-proBNP as a diagnostic biomarker in children with CHF was 98% and the specificity was 100%.

Conclusion: NT-proBNP is significantly statistically correlated with clinical severity of CHF and echocardiographic parameters of CHF cases of different causes .We highly recommend a long-term study on the value of the level of NT-proBNP as a prognostic risk parameter.

INTRODUCTION

CHF is a clinical syndrome where the heart is unable to provide the output required to meet the metabolic demands of the body; however, the causes and mechanisms of CHF are significantly different between adults and children **[1]**. There is no single diagnostic test for CHF because it is largely a clinical diagnosis based on a

careful history and physical examination **[2].** In early stages of CHF, various compensatory mechanisms are evoked to maintain normal metabolic function **[1]**. The clinical syndrome of CHF is a final common pathway of most forms of cardiovascular disease **[3]**. Several studies have reported the prevalence of CHF to vary between 3% and 9% **[4-6]**. Thus, it is a pediatric emergency that must be anticipated and excluded in every acutely ill child **[6]**. CHF has multiple causes: predominant among these in developed countries are the primary cardiomyopathies, which account for 60% of children requiring a cardiac transplant, and the congenital heart diseases **[7]**. In addition, certain systemic processes such as inflammatory diseases, metabolic disorders, endocrine derangements, and kidney disease result in an unknown number of cases **[8]**.

B-type natriuretic peptide (BNP) is a member of a four natriuretic peptide family that shares a common 17-peptide ring structure. The N-terminal fragment (NT-pro-BNP) is biologically inert, but both are secreted in the plasma in equimolar quantities and both have been evaluated for use in the management of CHF **[9]**. BNP stimulates natriuresis and vasodilation with consequent afterload reduction, inhibits renin- angiotensin-aldosterone release and sympathetic nervous activity, and reduces fibrosis. BNP and NT-pro-BNP are frequently used in the diagnosis of CHF and distinguishing between patients with dyspnea of cardiac or pulmonary origin. 'Normal' values of these peptides vary depending on the type of test used. The performance characteristics of these tests vary depending on the patients on whom they are used and the manufacturer. For this reason, the determination of reference values for this peptide represents such a challenge **[9]**.

SUBJECTS AND METHODS

This case control study was carried out at Pediatric Cardiology Unit, Pediatric Intensive Care Unit and Medical Biochemistry Department in Zagazig University Hospitals during the period from March 2012 to September 2014.

Subjects :
The study covered 60 subjects that will be divided into the following groups:

Group I : (CHF patients):
Forty five patients in pediatric age groups ranging between 1.5 months and 12 years, 21 (46.7%) males and 24 (53.3%) females. All the patients in group I have the inclusion criterion of having clinical CHF signs and symptoms, and they will be subdivided into 3 groups:
Group I-1: Fifteen patients having DCM.

Group I-2: Fifteen patients having CHD : 7 cases of common atrio-ventricular canal (CAVC) (47%), 3 cases of combined atrial septal defect (ASD) and ventricular septal defect (VSD) (20%), 2 cases of combined ASD, VSD and pulmonary stenosis (PS) (13%), one case VSD (6.7 %), one case of double inlet left ventricle (DILV) (6.7%) and one case of tricuspid atresia (6.7%).

Group I-3: Fifteen patients that developed CHF secondary to non cardiac causes involving: 6 cases of severe pneumonia (40%), 4 cases of acute severe asthma (27%), one case of severe bronchiolitis (6.7%), one case of severe bronchopneumonia (6.7%), one case of Acute Respiratory distress Syndrome(ARDS) (6.7%), one case of right lung collapse (6.7%) and one case of anemic heart failure on top of acute severe hemolysis(6.7%).

Exclusion criteria including:
1- Recent cardiopulmonary surgery.
2- Current hemodialysis.

Group II (control group):
Fifteen healthy individual as a control group, the subjects of this group are matched in age and gender to the patients groups.

All children in this study were subjected to complete history taking, general examination including vital signs and anthropometric measures, cardiac examination, chest examination, abdominal examination and clinical assessment of CHF with grading of severity according to Modified Ross Score.

X-ray chest and heart and standard 12 lead Electrocardiography (ECG) were performed. Echocardiographic study was performed in all patients using Ultrasound Machine, Vivid7 (GE medical system, Horten, Norway). Echo-cardiographic examination included LVEDD, LVESD, and LV systolic function in the form of left ventricular EF and FS using two-dimensional echocardiography and M-mode echocardiography. Also mitral valve E/A ratio was performed by continuous wave (CW) Doppler. By echo-cardiography, EF % <50% was systolic heart failure and mitral valve E/A ratio <1 was diastolic heart failure [(10)].

Blood for NT-proBNP assay was taken from peripheral venous puncture (3 ml) and collected in serum separator tubes (SST) within 3 hours of

the echocardiography and allowed samples to clot for 30 minutes before centrifugation for 15 minutes. Serum was removed and stored at -20°C until the time of analysis. All reagents were brought to room temperature before use. NT-proBNP was analyzed using a research NT-proBNP ELISA Kit (EIAAB and USCN Life Company, China).

Statistical analysis:

All data were collected, tabulated and statistically analyzed using Statistical Package for the Social Sciences (SPSS version 18). Quantitative data were expressed as the mean ± SD & median (range). Continuous data were checked for normality by using Shapiro Walk test. Independent Student t-test was used to compare two groups of normally distributed data. Mann-Whitney test was used to compare two groups of non normally distributed data. ANOVA (Analysis of variance) was used to test the difference about mean values of parameters of normally distributed data among the groups of study. Kruskal-Wallis test was used to compare more than two groups of non normally distributed data. Spearman's coefficient was calculated to assess relationship between study parameters, (+) sign indicate direct correlation and (-) sign indicate inverse correlation, also values near to 1 indicate strong correlation & values near 0 indicate weak correlation. All tests were two sided, $P<0.05$ was considered statistically significant (S), $P<0.001$ was considered highly statistically significant (HS), and $P\geq0.05$ was considered non statistically significant (NS).

RESULTS

Group I involved our CHF cases who showed different stages of CHF either acute or chronic or resolving CHF. Group II consisted of 15 healthy control subjects matched in age and sex with the groups of CHF cases. There are statistically non significant differences in our study between the groups of cases and the group of control regarding age, gender, body weight and length. There are statistically non-significant difference between the three groups of cases regarding symptoms and signs (Hepatomegaly, dyspnea, edema, orthopnea and cyanosis) . According to clinical severity, CHF cases (45cases of group I) were classified according to Modified Ross Score into : Five cases (11.1%) as Ross IA (mild CHF), 11 cases (24.4%) as Ross IB (moderate CHF) and 29 cases (64.4%) as Ross IC (severe CHF) . There is statistically non-significant difference between the three groups of CHF cases (Group I-1, I-2 and I-3) regarding distribution of cases clinical severity of CHF according to Modified Ross Score (Table 1).

Table (1): Comparison of Modified Ross Score among the cases groups

Variable	GroupI-1 (DCM) (n=15)		Group I-2 (CHD) (n=15)		Group I-3 (NCCHF) (n=15)		χ^2	P
	N	%	N	%	N	%		
Modified Ross:								
Ross IA	0	0	1	7	4	27	8.61	0.072 NS
Ross IB	4	27	2	13	5	33		
Ross IC	11	73	12	80	6	40		

DCM= Dilated cardiomyopathy
CHD= Congenital heart diseases
NCCHF= non cardiac causes of CHF
χ^2= Chi-square test
NS= Non Significant

Some echocardiographic diameters left ventricular EF, FS and mitral valve E/A ratio) showed statistically highly significant decrease in the three groups of cases (groups I-1, I-2 and I-3) compared to the control group (group II) with p value < 0.001, while LVEDD and LVESD showed statistically highly significant increase in the three groups of cases (groups I-1, I-2 and I-3) compared to the control group (group II) with p value <0.001 (Table 2, Fig. 1), but there is statistically non significant difference between groups of cases (groups I-1, I-2 and I-3) regarding the echocardiographic parameters (EF, FS, LVEDD, LVESD and mitral valve E/A).

Table (2): Comparison of ECHO findings of the studied groups cases and control

Variable	Group I-1 (DCM) (n=15)	Group I -2 (CHD) (n=15)	Group I-3 (NCCHF) (n=15)	Group II (Control) (n=15)	F	p
EF (%): Mean ± SD	40.27 ± 5.43	45.2 ± 10.05	44.8 ± 9.6	71.33 ± 4.59	49.16	<0.001 HS
FS (%): Mean ± SD	20.2 ± 4.14	23.27 ± 5.08	23 ± 6.07	39.47 ± 4.24	47.15	<0.001 HS
LVEDD(mm) Mean ± SD	46.33± 4.25	41.80± 8.86	40.93± 9.37	32.33± 6.38	9.11	<0.001 HS
LVESD(mm) Mean ± SD	35.27 ± 5.09	31.73± 7.9	30.6± 8.19	20.0± 4.7	14.57	<0.001 HS
E/A: Mean ± SD	1.04 ± 0.25	0.97 ± 0.11	1.08 ± 0.18	1.54 ± 0.20	26.8	<0.001 HS

EF = Ejection fraction
FS = Fractional shortening
HS=High Significance
LVEDD= Left ventricular end diastolic dimensions
LVESD = Left ventricular end systolic dimensions
E/A ratio= Mitral valve E/A ratio

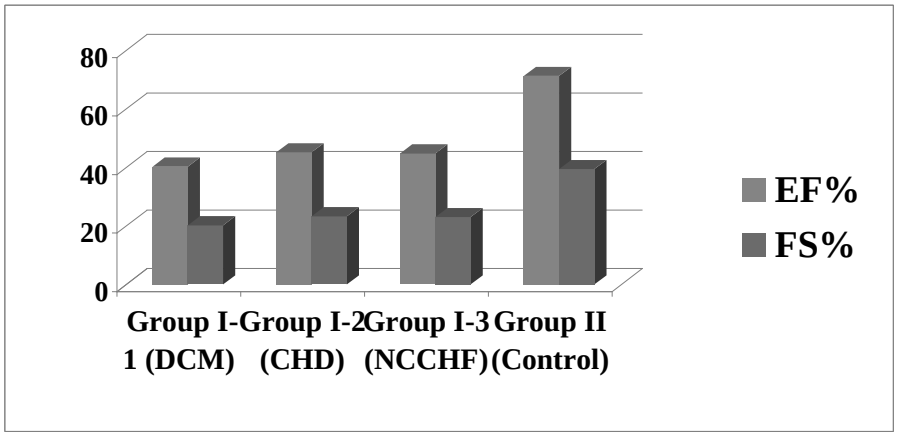

Figure (1): Comparison between groups of CHF cases and control group as regard EF and FS.

The serum level of NT-proBNP showed statistically highly significant statistical increase in groups of cases (I-1, I-2 and I-3) compared to the control group (group II) with p value < 0.001.(Table 3, Fig. 2), but there is statistically non significant difference between the three groups of cases regarding the serum level of NT-proBNP with p value > 0.05 (Table 4).

Table (3): Comparison of NT-proBNP level of the studied groups (cases and control)

Variable	Group I-1 (DCM) (n=15)	Group I-2 (CHD) (n=15)	Group I-3 (NCCHF) (n=15)	Group II (Control) (n=15)	Kw	p
NT- ProBNP (pg/ml)						
Median	6200	6300	4800	179		<0.001
Range	4800 - 10800	530 - 6800	1900 - 6800	89 - 1100	36.18	HS

KW= Kruskal Wallis test
HS= Highly Significant

Table (4): Comparison of NT- ProBNP level of cases groups

Variable	Group I-1 (DCM) (n=15	Group I-2 (CHD) (n=15)	Group I-3 (NCCHF) (n=15)	KW	p
NT- ProBNP (pg/ml)					
Median	6200	6300	4800	5.59	0.06
Range	4800 - 10800	530 - 6800	1900 - 6800		NS

KW= Kruskal Wallis test
NS= Non Significant

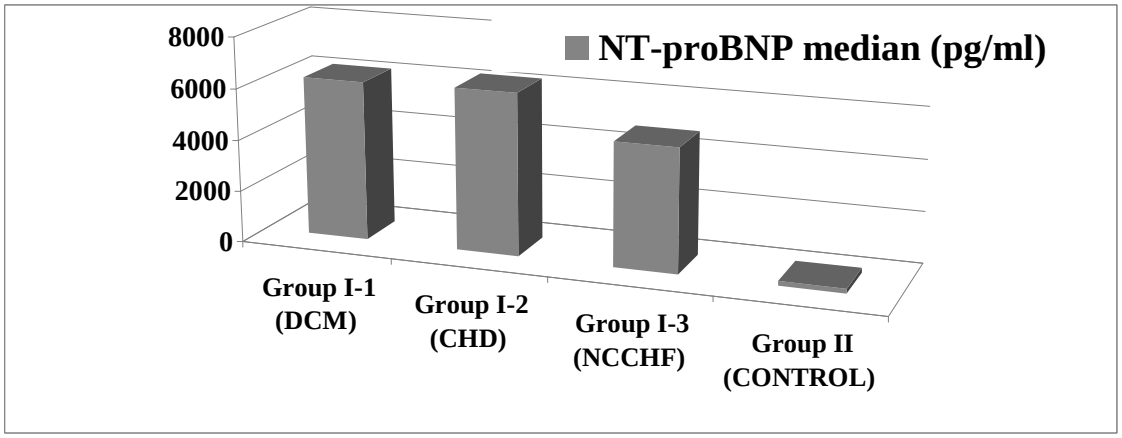

Figure (2): Comparison between groups of CHF cases and control group as regard the serum level of NT-proBNP

There is statistically highly significant difference between the three classes of Modified Ross Score in CHF cases regarding the serum level of NT-proBNP (Table5).

Table (5): Relation between NT-ProBNP level of Group I (45 cases of CHF) and Modified Ross scoring

Variable	Ross IA (n=5)	Ross IB (n=11)	Ross IC (n=29)	KW	p
NT- ProBNP (pg/ml)					
-Median	1900	4800	6300	31.47	<0.001
-Range	530- 3800	4200 – 5500	5800 – 10800		HS

KW= Kruskal Wallis test
HS= Highly Significant

The serum level of NT-proBNP showed statistically significant increase in cases of HFrEF compared to cases of HFpEF with p value < 0.05 (Table 6, Fig. 3). Also, The serum level of NT-proBNP showed statistically highly significant increase in cases of HFpEF compared to control group with p value <0.001 (Table 7, Fig. 3).

Table (6): Comparison between HFpEF and HFrEF regarding the serum level of NT-proBNP

Variable	HFpEF (EF>50%) (n=6)	HFrEF (EF<50%) (n=39)	MW	p
NT- ProBNP (pg/ml)				
Median Range	4900 530 - 6300	6200 1900– 10800	59	0.049 S

HFpEF = heart failure with preserved ejection fraction
S= Significant
HFrEF= heart failure with reduced ejection fraction
MW = Mann-Whitney test.

Table (7): Comparison between HFpEF and controls regarding the serum level of NT-proBNP

Variable	CHFpEF (EF>50%)(n= 6)	Control (n= 15)	MW	p
NT- ProBNP (pg/ml)				
Median Range	4900 530 - 6300	179 89 - 1100	1.000	<0.001 HS

HFpEF = heart failure with preserved ejection fraction
HS= highly significant
HFrEF= heart failure with reduced ejection fraction
MW = Mann-Whitney test.

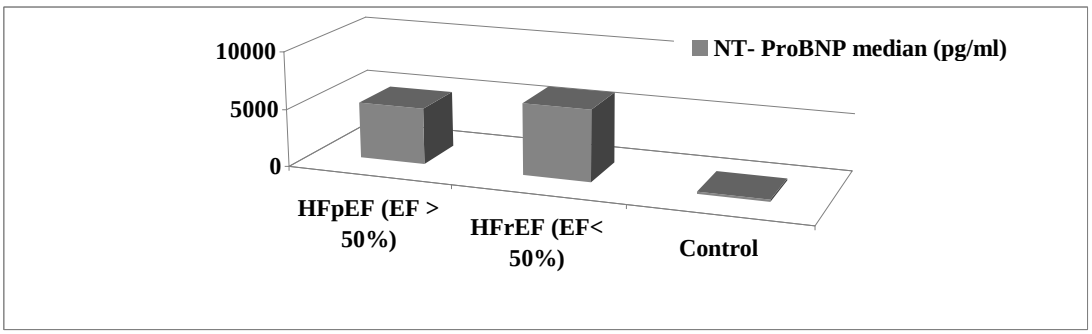

Figure (3): Comparison between cases of HFpEF and cases of HFrEF regarding the erusm level of NT-p roBNP

There is highly significant statistical positive correlation between serum NT-proBNP and Modified Ross Score in the 45 cases of CHF with p value <0.001. NT-proBNP showed statistically highly significant positive correlations with LVEDD and LVESD with p value < 0.001 for each, and highly significant negative correlations with left ventricular EF and FS with p value <0.001 for each item, and statistically significant negative correlation with mitral valve E/A ratio with p value = 0.001. Serum NT-proBNP showed non statistically significant correlations with age, body weight, length, heart rate, respiratory rate and CBC parameters in the 45 cases of CHF(Table 8, Fig. 4-8).

Table (8): Correlation between NT- ProBNP level in patients of CHF and age, body weight, length, vital signs, Modified Ross Score, CBC and ECHO findings

Variable	r (n = 45)	P (n = 45)
Age	-0.017	0.913NS
Body weight	-0.056	0.714NS
Length	-0.099	0.529 NS
Heart rate	0.039	0.804 NS
Respiratotry rate	-0.05	0.746 NS
Modified Ross score	**0.848**	**< 0.001 HS**
Hb (gm /dL)	-0.02	0.898 NS
RBCs (x 1000)	0.097	0.524 NS
WBCs (x 1000)	-0.052	0.733 NS
Platelets (x 1000)	-0.040	0.792 NS
LVEDD (mm)	**0.634**	**< 0.001 HS**
LVESD (mm)	**0.742**	**< 0.001 HS**
EF%	**-0.634**	**< 0.001 HS**
FS%	**-0.568**	**< 0.001 HS**
E/A ratio	**- 0.585**	**0.001 HS**

NS = non-significant, HS = highly significant, HB= Hemoglobin, RBCs= Red Blood Cells, WBCs = White Blood Cells, EF = Ejection fraction, FS = Fractional shortening, LVEDD= Left ventricular end diastolic dimensions, LVESD = Left ventricular end systolic dimensions, E/A ratio= Mitral valve E/A ratio.

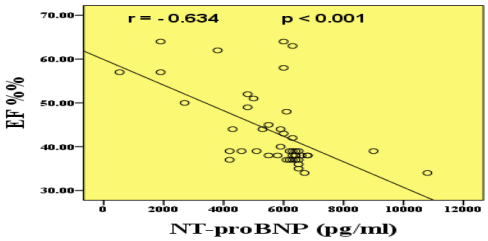

Figure (4): Correlation between NT- ProBNP level and left ventricular EF%

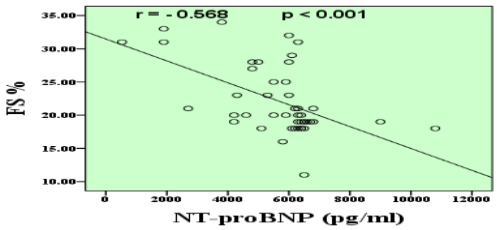

Figure (5): Correlation between NT- ProBNP and left ventricular FS%

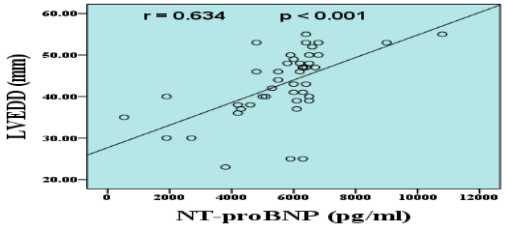

Figure (6): Correlation between NT- ProBNP level and LVEDD

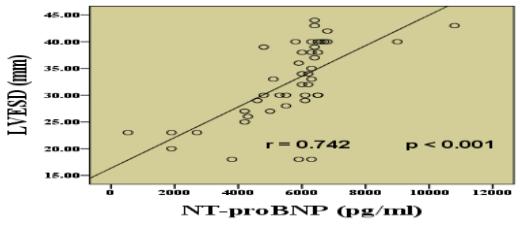

Figure (7): Correlation between NT- ProBNP level and LVESD

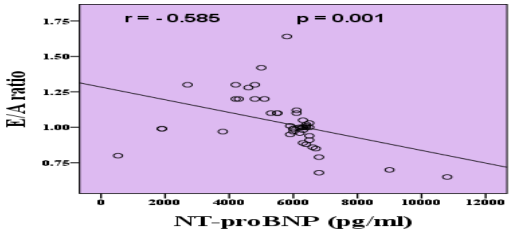

Figure (8): Correlation between NT- ProBNP level and mitral valve E/A ratio

The best cutoff value of NT-proBNP in diagnosis of CHF was 1500 pg/ml with 98% sensitivity and 100% specificity and the p value <0.001 (Table 9).

Table (9): Validity of NT- ProBNP in diagnosis of CHF

Cutoff	AUC	Sensitivity	Specificity	p-value
1500	0.99	98%	%100	<0.001 HS

AUC= Area under the curve
HS= Highly Significant

DISCUSSION

Brain natriuretic peptide (BNP) is one of the cardiac markers for CHF. It correlates with symptoms of CHF and may indicate LV volume and pressure overload in the presence of shunt **[11]**. The N-terminal fragment of proB-type natriuretic peptide (NT-proBNP) is secreted from cardiac myocytes together with BNP. Both BNP and NT- proBNP have been used to identify the presence and to determine the severity of CHF in children **[12,13]**. Most of the pediatric studies demonstrate an increase in natriuretic peptide levels in proportion to the symptomatic severity and the degree of remodeling in diverse pediatric cardiac diseases **[14]**. In this study, we hypothesize that changes in NT-proBNP serum levels are associated with changes in echocardiographic indices of LV systolic and diastolic function in children in CHF in cases of DCM, CHD and CHF of non cardiac origin, so we studied whether the rapid bedside determination of NT-proBNP level could be used for diagnosis of CHF and to predict the severity.

There was no statistically significant difference between the groups of cases (DCM, CHD and cases of non cardiac origin of CHF in our study regarding the proportion of CHF classes of clinical severity according to modified Ross score. Among whole cases, Ross IA (Mild CHF) represented 11.1% (5 cases), Ross IB (Moderate CHF) represented 24.4% (11 cases), and Ross IC (Severe CHF) represented 64.4% (29 cases).

With respect to the echocardiographic parameters in our study, there was statistically highly significant decrease in EF% and FS % (representing systolic dysfunction) in CHF cases of group I (1, 2 and 3) as compared with the control group (group II) with p value <0.001. In addition, there was statistically highly significant increase in LVEDD and LVESD in the patient groups as compared with the control group with p value <0.001. There is statistically significant decrease in E/A ratio (representing diastolic dysfunction) in the CHF cases groups as compared to the control group with p value <0.001. This has agreement with Zoair et al., who studied 20 cases of DCM and 20 healthy controls, they found that there is statistically significant difference between the group DCM cases and the control group regarding EF%, FS%, LVEED and LVESD, with p value of 0.001 for each parameter. The study did not include E/A ratio **[15]**. Also, Elwan et al. who studied 42 patients (24 ASD and 18 VSD, 11 of them in CHF) and 15 healthy controls found statistically significant difference between cases of CHD (ASD, VSD with and without CHF) and control group regarding LVEED and LVESD **[16]**.

In our patients of CHF, there was a highly statistically significant increase in the level of NT-proBNP in CHF cases in group I (1, 2 and 3) compared to the control group (group II) with p value <0.001. While there is no significant statistical difference among the three groups of cases (I-1, I-2 and I-3) regarding NT-proBNP level. There is statistically significant difference between the grades of clinical severity in CHF cases classified according to Modified Ross Score (RossIA, Ross IB and Ross IC) regarding the level of NT-proBNP with p value <0.001. Koura et al. (17) supported our study as they had a cross sectional (comparative) study where 30 children divided into 11 cases of DCM and 19 cases of LRS (left to right shunt). They conclude that the NT-ProBNP level is elevated in both LRS and DCM in pediatric age. This elevation is more remarkable with heart failure and increased pulmonary artery pressure (PAP) in both diseased groups. Also, Narin et al. agreed with our study, as they found a statistically significant difference between NT-ProBNP levels in each Ross clinical group not only before treatment but also on assessment on the 7th day of treatment in the patient group (p < 0.001) **[18]**.

In our study, there was statistically highly significant increase in the level of serum NT-proBNP in cases of CHFpEF in comparison to control group with p value <0.001. Also, there was statistically significant decrease in the level of serum NT-proBNP in cases of HFpEF in comparison to cases of HFrEF with p value <0.05. This has agreement with Masutani et al. who studied 18 pediatric patients with HFpEF and 22 patients with HFrEF; as they found plasma BNP levels were elevated in both CHF groups, but to a significantly smaller degree in HFpEF than in systolic heart failure (SHF) patients **[19]**.

Our results showed there is no correlation between serum NT-proBNP and patients' age, body weight, length, heart rate, respiratory rate and CBC parameters (HB, RBCs, WBCs and platelets) in group I (45 CHF patients) . But we found statistically highly significant positive correlation between serum NT-proBNP and the class of clinical severity according to Modified Ross Score with p value <0.001. Regarding echocardiographic parameters NT-proBNP showed highly significant positive correlation with LVEDD and LVESD, and highly significant negative correlation with ejection fraction and fractional shortening with p value <0.001. Also, NT-proBNP showed significant negative correlation with mitral valve E/A ratio with p value = 0.001. Elwan et al. supported our study as they found significant positive correlations between NT-proBNP concentration with LVEDD, LVESD, systolic pulmonary artery pressure (SPAP), and shunt size, and there was significant negative correlation with EF and FS, in cases of CHD (ASD, VSD with and without CHF), but in our study we did not examine SPAP and their study did not include mitral valve E/A ratio **[16]**.

The results of our study showed that, using a cutoff point of NT-proBNP as 1500 pg/ml, the sensitivity of NT-proBNP as a diagnostic biomarker in children with CHF was 98% and the specificity was 100%. This has agreement with Zoair et al. who used a cutoff point of NT-proBNP as 1500 pg/ml as a diagnostic biomarker in children with DCM, the sensitivity was 85% and the specificity was 100% **[15]**. However, Rusconi et al. who studied CHF in 36 pediatric patients with DCM-found that NT-proBNP level above 1000 pg/ml clearly identified the sickest patients. NT-proBNP levels between 450 and 1000 pg/ml did not distinguish between symptomatic and asymptomatic patients **[20]**. With a marked difference from our study, Narin et al. used the NT-proBNP cut off value of 174.3 pg/ml to distinguish healthy children from the patients with left ventricular systolic dysfunction caused by cardiomyopathy **[18]**, this may be due to the difference in properties of the kit used.

NT-ProBNP level is significantly elevated in CHF with different causes (DCM, CHD and non cardiac causes of CHF) and in cases of HFpEF in pediatric age. So, we recommend the use of NT-ProBNP as a routine marker for diagnosing suspected patients with symptoms and signs suggesting CHF for rapid evaluation of cardiac functions, especially in absence of reachable echocardiographic examination.

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Conflicts of interest: None.
Ethical approval: Approved.

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