WEST AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Diagnostic Usefulness of N-terminal Pro-brain Natriuretic Peptide among Children with Heart Failure in a Tertiary Hospital in Lagos, Nigeria

Interet Diagnostic Du N Terminal Pro- Bnp Dans L'insuffisance Cardiaque De L'enfant Dans Un Hopital De Niveau 3 A Lagos, Nigeria

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ABSTRACT

BACKGROUND: **N-terminal pro-brain natriuretic peptide (NT-proBNP) is useful in the diagnosis and management of adult patients with heart failure.**

OBJECTIVE: **The objective of the study was to determine the usefulness of NT-proBNP in diagnosing congestive heart failure (CHF) in children and its correlation with left ventricular ejection fraction (LVEF) and clinical heart failure score.**

METHODS: **Plasma NT-proBNP was measured in 28 children with CHF and age matched controls. Heart failure assessment was done using modified Ross score and all had echocardiography done.**

RESULTS: **Mean plasma NT-proBNP of children with CHF (377.86±1026.49pg/mL) was significantly higher than that of controls (353.61±328.50 pg/mL) (p<0.001). A plasma NT-pro BNP of 951pg/mL was used as the cut off value for heart failure. The sensitivity, specificity, negative and positive predictive values were 57%, 96%, 69% and 94% respectively. NT-pro BNP levels showed a high positive correlation with the modified Ross score (r= 0.502; p<0.001) but low correlation with LVEF (r= –0.137; p>0.3).**

CONCLUSION: **Our findings indicate that measuring NT-pro BNP may be useful as a diagnostic tool in congestive cardiac failure in children. The fact that its levels also correlated positively with modified Ross score thereby objectively determining severity of heart failure suggests that this biomarker may also be useful as an evaluation tool in congestive cardiac failure in children. WAJM 2011; 30(1): 29–34.**

Keywords: **NT-pro BNP, Heart failure, children, modified Ross Score, ejection fraction.**

RÉSUMÉ

CONTEXTE: *Le peptide N-terminal –pro BNP sont a montré son intérêt dans le diagnostic et le suivi de l'insuffisance cardiaque de l'adulte.*

OBJECTIF: *Le but de l'étude est de déterminer l'intérêt du dosage du peptide N-terminal –pro BNP dans le diagnostic de l'insuffisance cardiaque congestive de l'enfant et sa corrélation avec la fonction systolique ventriculaire gauche (Fraction d'éjection ventriculaire gauche) et le score clinique de l'insuffisance cardiaque.*

METHODE: *Le dosage plasmatique du peptide N-terminal –pro BNP était effectué chez 28 enfants présentant une insuffisance cardiaque congestive et chez 28 autres enfants témoins appariés selon l'âge. Tous les patients ont bénéficié d'une évaluation de l'insuffisance cardiaque sur la base du score clinique de Ross modifié et d'une échographie cardiaque.*

RESULTATS: *La moyenne de la N terminal-pro BNP chez les enfants présentant une insuffisance cardiaque (377.86±1026.49pg/mL) était significativement plus élevée que dans le groupe témoin (353.61±328.50 pg/mL) (p<0.001) . Le taux plasmatique de 951pg/ml a été retenu comme seuil de diagnostic de l'insuffisance cardiaque. La sensibilité, la spécificité, la valeur prédictive positive et négative étaient respectivement de 57%, 96%, 69% et 94%. Le taux de N terminal-pro BNP était positivement corrélé au score de Ross modifié (r= 0,502 ; p<0,001) mais la corrélation avec la fraction d'éjection du ventricule gauche était faible (r= - 0,137 ; p>0.3).*

Nos résultats indiquent que le dosage du N-terminal-pro BNP peut être utilisé comme critère diagnostic de l'insuffisance cardiaque congestive de l'enfant. Sa corrélation positive avec le score de Ross modifié suggère qu'il peut être également utilisé comme un bio marqueur de la sévérité de l'insuffisance cardiaque.

WAJM 2011; 30(1): 29–34.

Mots Cles: *N-Terminal-Pro Bnp, Insuffisance Cardiaque, Enfant, Score De Ross Modifie, Fraction D'ejection*

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Abbreviations: CHF, Congestive Heart Failure; **LVEF,** Left Ventricular Ejection Fraction; **NT-proBNP,** N-terminal pro-brain natriuretic peptide.

INTRODUCTION

Heart disease is a significant cause of morbidity and death in children with both congenital structural cardiac anomalies and acquired heart diseases often resulting in heart failure.[1] There is considerable overlap in the clinical manifestations of heart failure and features of other conditions especially respiratory disease that may cause diagnostic dilemma. Echocardiography is essential in assessing cardiac function and identifying cardiovascular causes, particularly anatomic lesions. However, biochemical markers such as troponin and brain natriuretic peptide (BNP) provide additional diagnostic and prognostic value to the usefulness of echocardiography measurements in management of heart diseases.

Brain natriuretic peptide is a 32-amino acid polypeptide hormone produced by the heart ventricle following wall stress from pressure or volume overload, and its levels correlate with the haemodynamics and severity of heart failure in adults.[2–4] This is primarily due to its natriuretic, diuretic and vasodilatory effects. It is co-secreted with a biologically inactive N-terminal fragment (NT-proBNP) which circulates when plasma levels of the biologically active BNP portions are elevated. NT-proBNP appears to be a more sensitive and specific marker of ventricular dysfunction compared to BNP, and has a longer half-life.[5] Furthermore, plasma concentrations of N-BNP are 10 times higher compared with BNP, which potentially makes it easier to devise a stix test for bedside testing.[5] Mueller *et al* [6] demonstrated that although both BNP and NTproBNP had similar sensitivity and specificity for evaluation of symptomatic patients, NT-proBNP had superior sensitivity over BNP for the detection of those patients with asymptomatic left ventricular (LV) dysfunction.

Recent studies[5–7] suggest that BNP and its N-terminal fragment NT-proBNP may be useful diagnostic tools in children with congenital heart disease or cardiomyopathy. However, very few published studies have been conducted in the paediatric population globally and none in sub-Saharan Africa.[8] This study was undertaken to determine the value of NT-proBNP as a diagnostic marker of heart failure in children, and its relationship with ejection fraction and clinical diagnosis of heart failure.

SUBJECTS, MATERIALS, AND METHODS

Study design and case ascertainment

The study was approved by the ethical committee of the Lagos University Teaching Hospital, Lagos South-Western Nigeria. Informed consent was obtained from parents of enrolled children.

Consecutive patients from whom consent was obtained were recruited from the wards, outpatient clinic and those referred to our facility for echocardiography from January 2005 to December 2005. Children with congestive heart failure (CHF) secondary to heart disease were eligible for entry into the study. Exclusion criteria included children with anaemia and/or kidney disease. Blood was collected for complete blood count, electrolytes, urea and creatinine. Clinical diagnosis of heart failure was based on fulfilment of European Society of Cardiology Guidelines[9] in the presence of underlying heart disease. Heart failure severity was measured using the modified Ross clinical score[10] (Table 1). Twenty eight children with CHF secondary to heart disease were enrolled together with twenty-eight controls. At the time of the serum sampling, all the children with CHF were receiving anti-failure drug treatment with frusemide, digoxin, and angiotensin-converting enzyme inhibitors.

Grading of Heart Failure

The modified Ross scoring system was used.[10] Two physicians independently graded the following variables: diaphoresis, tachypnoea, breathing with abdominal retraction, respiratory rate, heart rate, and hepatomegaly. Disagreement was resolved by con-sensus. The symptoms of CHF were graded on a scale of 0, 1, or 2 points according to the severity. The sum of all points was found to form the clinical score (range: 0–12 points). A higher score corresponded to more severe symptoms of heart failure. Patients with a minimum score of 1 point were included in the study (Table 1). The NT-proBNP levels of all 28 children with CHF were not known to the clinical investigators.

Echocardiographic Evaluation

Two-dimensional echocardiography was done for non-invasive measurement of systolic systemic ventricular function using a HP Sonos 2000 echocardiography machine. M-mode measurements of left ventricular function were obtained in a parasternal long axis view. The arithmetic average of 3 measurements was obtained.[11] Using the left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameters (LVESD), the left ventricular ejection fraction (LVEF) was calculated. Echocardiographic measurements were performed on the same day the blood samples were taken. The plasma NT-proBNP levels of all the children were not known to the investigators as at the time of the echocardiography.

NT-proBNP Assay

Whole blood in ethylenediaminetetraacetic acid (EDTA) was used for the NT-proBNP quantification using the Roche Cardiac proBNP Cardiac reader, a point of care analyzer. (Roche Diagnostics GmbH, Mannheim, Germany). Samples were measured to within $\pm$ 0.5% of certified values. This method has a high correlation coefficient of 0.95 and slope of 1.02 in method comparison to the Elecsys proBNP assay.[12]

Statistical Analysis

The data were processed using the SPSS for Windows software (SPSS Inc, Chicago, IL) version 17.0. Numerical averages are presented as mean $\pm$ standard deviation, and comparison between cases and controls were made using Mann-Whitney U test. Categorical variables are presented as frequency and comparisons made using χ^2 test. The cut-off for pro-brain natriuretic peptide was determined by calculating the likelihood ratios for possible cut-off values, and receiver operating characteristic (ROC) curve plotted. To examine the relationship between NT-proBNP level and clinical outcomes, simple logistic regression was performed, and odd ratio with 95% confidence interval was calculated. The level of significant was chosen to be

<0.05. The sensitivity, specificity, positive and negative predictive values and likelihood ratios were used as indicators of test accuracy. Stratified analyses of these indicators were performed for the NT-proBNP levels.

Definitions and Calculations

True positive (TP): Children with congestive cardiac failure correctly classified as positive by the test.

False Negative (FN): Children with congestive cardiac failure incorrectly classified as negative by the test.

True Negative (TN): Children without congestive cardiac failure correctly classified as negative by the test.

False Positive (FP): Children without congestive cardiac failure incorrectly classified as positive by the test.

Sensitivity: The fraction of children with congestive heart failure that the test correctly identified as positive (TP/ TP+FN).

Specificity: The fraction of children without congestive heart failure that the test correctly identified as negative (TN/ FP+TN).

Positive likelihood ratio: ratio between the probability of a positive test result given the presence of congestive heart failure and the probability of a positive test result given the absence of congestive cardiac failure (= True positive rate / False positive rate = Sensitivity / (1-Specificity).

Positive predictive value (PPV): probability that congestive cardiac failure is present when the test is positive = TP/ (TP+FP).

Negative predictive value (NPV): probability that congestive cardiac failure is not present when the test is negative = (TN / (TN+FN).

Left ventricular ejection fraction- LVEDD –LVESD/LVEDD.

RESULTS

There were 28 (14 females and 14males) children with CHF and 28 controls (11 females and 17 males) studied. The children with CHF had ages which ranged from one month to 13 years (mean age in months 48.5±62.24) while that of the controls ranged from one month to 13 years (mean 48.72±62.15 months). Twenty-two (78.6%) of the children with CHF had congenital heart disease, of which 57.1% were left to right shunt lesions of ventricular septal defect. The remaining six children had rheumatic heart disease (RHD) with damages to the mitral and/ or the aortic valves. There was no child with cardiomyopathy (disease of the heart muscle) (Table 2). There were no significant differences in the ages and sex between the two groups as shown in Table 3.

Plasma NT-proBNP

The mean plasma NT-proBNP in control children was 353.61±328.50 pg/ mL (range: 59–1067 pg/mL; median: 199.5 pg/mL). There was no statistical significant difference between NT-proBNP levels of males (n = 17, mean 312.18 pg/mL) and females (n = 11, mean – 417.64 pg/mL; $p > 0.1$) in the control group. The mean plasma NT-proBNP levels in the 28 children with CHF was 377.86±1026.49pg/mL (range: 83-3268; median: 1088) and it was significantly higher than that of controls (p<0.001).

Table 1: Modified Ross Score for Grading of Heart Failure

Feature / Score:	0	1	2
History Diaphoresis	Head Only	Head and Body during Exercise	Head and Body at Rest
Tachypnoea	Rare	Several times	Frequent
Physical Examination			
Breathing	Normal	Retractions	Dyspnoea
Respiratory rate (respirations/min)			
< 1 year	< 50	50 – 60	> 60
1 – 6 years	< 35	35 – 45	> 45
7 – 10 years	< 25	25 – 35	> 35
11 – 14years	< 18	18 – 28	> 28
Heart rate (beats/min)			
< 1year	< 160	160 – 170	> 170
1 – 6years	< 105	105 – 115	> 115
7 – 10years	< 90	90 – 100	> 100
11 – 14years	< 80	80 – 90	> 90
Hepatomegaly	< 2cm	2 – 3cm	> 3cm

Scores for each of the 6 categories are added together. Total scores can range from 0 (no heart failure) to 12 (severe heart failure)

Table 2: Heart Diseases of the 28 Children with Congestive Heart Failure

Heart disease	Male	Female	Total Number of Children (%)
Ventricular septal defect	8	8	16(57.1)
Rheumatic heart disease	3	3	6(21.4)
Endocardial cushion defects	2	1	3(10.7)
Tetralogy of fallot with absent pulmonary valves	1	1	2(7.1)
Aortic aneurysm	0	1	1(3.6)
Total	**14**	**14**	**28(100.0)**

Comparison of weight and biochemical parameters between the two groups of children studied is shown in Table 4. NT-proBNP levels showed a positive correlation with the clinical heart failure score (modified Ross) ($p<0.001$).

Figure 1 shows the receiver operating characteristics (ROC) curve of NT-proBNP values with the left uppermost point of the curve corresponding to 951pg/mL.

In Table 5 is shown a series of cut off values of NT-proBNP measured with the highest likelihood ratio of 16 at NT-proBNP level of 951pg/mL. It also shows corresponding sensitivity, specificity and predictive values.

Among children with congestive heart failure, 16(57.1%) had elevated NT-proBNP level while 12(42.9%) had normal levels of NT-proBNP using 951pg/mL as cut off value. On the other hand, 27(96.4%) of the control children had normal levels of NT-proBNP with only 1(3.6 with elevated NT-proBNP levels, $p < 0.001$ (Figure 2).

The relationship between NT-proBNP and clinical parameters showed that the modified Ross score was the only significant determinant of NT-proBNP level (OR=1.341; $p<0.001$).

When Ross score increases by 1, the likelihood of having elevated NT-proBNP increases by 1.300 and can be as high as 1.592 (Table 6).

NT-proBNP levels showed a positive correlation with the modified Ross score ($r= 0.502$; $p<0.001$) but no correlation with LVEF ($r= -0.137$; $p>0.3$).

Table 3: Distribution of Subjects by Age and Sex

Variable	Congestive Heart Failure	Normal	P value
Age			
< 84 months, n (%)	19 (67.9)	19 (67.9)	1.00
≥ 84 months, n (%)	9 (32.1)	9 (32.1)	
Mean Age (Months)	48.5 ± 62.3	48.7 ± 62.2	0.9
Sex			
Male, n (%)	14 (50)	17 (60.7)	0.42
Female, n (%)	14 (50)	11 (39.3)	

Table 4: Comparison of Weight, Cardiac and Biochemical Parameters between Children with Congestive Heart Failure and Normal Children

Variable	Mean ± SD			
	Heart failure n = 28	Normal n = 28	Mann-Whitney U Statistic	P value
Weight (kg)	13.6 ± 12.0	19.4 ± 17.8	4.94	0.03*
%LVEF	75.64 ± 11.6	75.64 ± 10.2	0.33	0.99
Ross score	7.3 ± 2.6	0 ± 0	47.35	<0.001*
Hb	12.9 ± 1.5	12.1 ± 1.4	4.05	0.04*
NT-proBNP	1377.9 ±1037.8	353.6 ± 328.5	16.17	<0.001*

*Significant diff

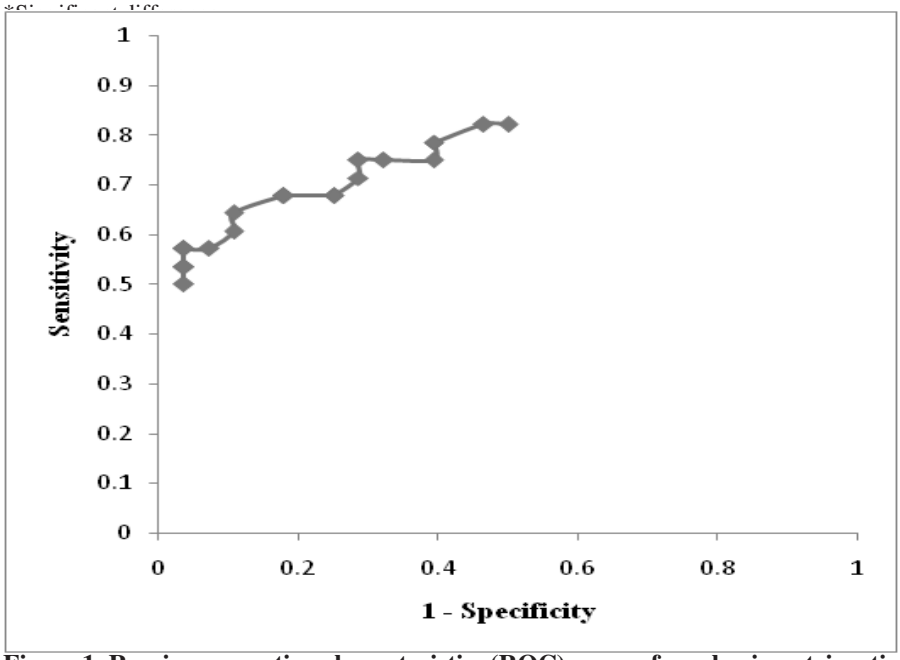

Figure 1: Receiver operating characteristics (ROC) curve of pro-brain natriuretic peptide with a cut off point at 951pg/ml.ml The otimal cut-off value of 951 pg/ml gives a sensitivity of 57.1%, a specificty of 96.4%, and a likelihood ratito of 16.

DISCUSSION

The results from this study show that plasma NT-proBNP levels are significantly higher in children with congestive heart failure when compared with healthy controls. The NT-proBNP assay had a diagnostic specificity of approximately 96%, sensitivity of 57%-, positive predictive value of 94% and negative predictive value of 69% at the NT-proBNP measure with the highest positive likelihood ratio of 16. With the identified high NT-proBNP threshold at 951pg/mL, the test will not mistakenly diagnose congestive heart failure in many children who do not have that thus the high specificity. It will however miss some of the children with congestive cardiac failure thus the reduced sensitivity. The high positive predictive value of the NT-proBNP assay in this study makes measurement of NT-proBNP a potentially useful diagnostic tool for heart failure management in children, especially when there is a need to exclude heart failure.

Previous reports have similarly shown significantly higher levels of NT-proBNP in patients with heart failure irrespective of age.[5, 13, 14] A systematic review to evaluate the diagnostic performance of NT-proBNP in heart failure patients among other things

Table 5: Sensitivity, Specificity, Likehood Ratios (LR), PPV and NPV at different Cut-off values of NT-proBNP Levels

Cut-off Point	Sensitivity	Specificity	Positive Likelihood Ratio	PPV	NPV
200	0.82	0.5	1.64	0.62	0.74
250	0.82	0.54	1.77	0.64	0.75
300	0.79	0.61	2.0	0.67	0.74
350	0.79	0.61	2.0	0.67	0.74
400	0.75	0.61	1.91	0.66	0.71
450	0.75	0.68	2.33	0.7	0.73
500	0.75	0.71	2.63	0.72	0.74
550	0.71	0.71	2.5	0.71	0.71
600	0.68	0.75	2.71	0.73	0.7
650	0.68	0.75	2.71	0.73	0.7
700	0.68	0.82	3.8	0.79	0.72
750	0.68	0.82	3.8	0.79	0.72
800	0.68	0.82	3.8	0.79	0.72
850	0.64	0.89	6.0	0.86	0.71
900	0.61	0.89	5.67	0.85	0.69
950	0.57	0.93	8.0	0.89	0.68
951	***0.57***	***0.96***	***16.0***	***0.94***	***0.69***
960	0.57	0.96	16.0	0.94	0.69
965	0.54	0.96	15.0	0.937	0.68
1000	0.54	0.96	15.0	0.937	0.68
1050	0.50	0.96	14.0	0.93	0.66

Table 6: Simple Logistic Regressions of NT-proBNP (Elevated/Normal) on other Variables

Variable	Odd Ratio	95% CI		β	SE	Z	p
		Lower	Upper				
Age (Month)	1.0033	0.9942	1.0125	0.003	0.005	0.713	0.476
Sex (M : F)	0.4375	0.1370	1.3976	–0.826	0.593	–1.395	0.1630
Weight	0.9983	0.9612	1.0368	–0.002	0.019	–0.090	0.928
Creatinine	17.5195	0.6732	455.9429	2.863	1.663	1.722	0.085
Heamoglobin	1.2226	0.8094	1.8468	0.201	0.210	0.955	0.340
Ross Score	1.3414*	1.1300	1.5923	0.294	0.088	3.357	0.001
LVSF	0.9803	0.9193	1.0453	–0.020	0.0338	–0.607	0.544
LVEF	0.9739	0.9250	1.0254	–0.026	0.026	–1.005	0.315

*Significant

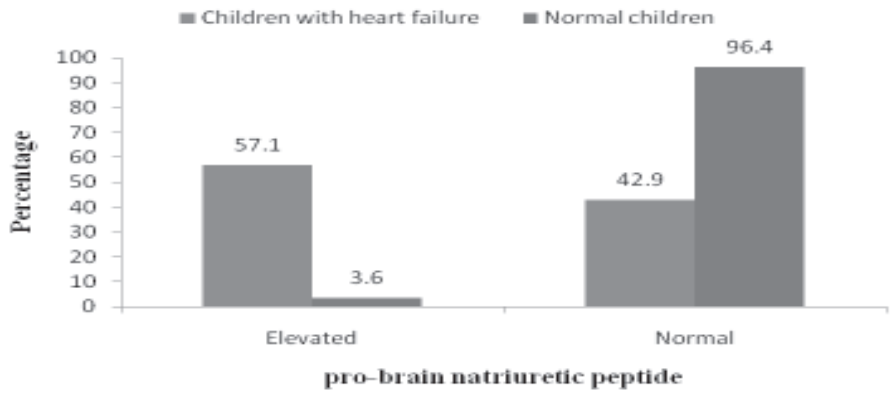

Figure 2: Prevalence of Elevated N-terminal pro-brain Natriuretic Peptide among Children with Heart Disease and Normal Children (χ^2 = 19.01, p = 0.00001)

reported good diagnostic properties as a rule out test for heart failure with pooled sensitivity and specificity values of 92 and 65 percent. These studies were however on adults.[15] Similar studies on children have equally shown that plasma levels of NT-proBNP are good for diagnosing heart failure and may be used as a screening test.[16–18]

Wu *et al* in China reported a sensitivity and specificity of 89.3% and 91.2% respectively when plasma NT-proBNP was used to diagnose congestive cardiac failure in children with ventricular septal defect.[16] We note that the sensitivity in our report is significantly lower at 57%. It is not very clear why. A similar study among the adult population in our centre from the same laboratory yielded a higher sensitivity at 85.7% ruling out operator error.[18]

It is however well established that NT-proBNP levels decrease in most patients who on drug therapy for heart failure, such as ACE inhibitors, beta blockers, and diuretics.[19,20] All the cases in this study had been on treatment for heart failure with digoxin, captopril, and frusemide prior to enrolment. Definitive treatment for majority of these patients who had structural heart lesions is cardiac surgery. This is not easily available or affordable in our setting resulting in children with these con-ditions being on medications for heart failure for a protracted period. This might have contributed to the low levels of plasma NT-proBNP in a number of the children with congestive heart failure unlike their counterparts in developed countries who would get definitive surgical treatment as soon as required rather than prolonged supportive medical treatment.

There was no strong association of plasma NT-proBNP levels with ejection fraction in the present study. Majority of the children with CHF in the study had ventricular septal defect, a congenital heart disease with left to right shunt. In this lesion cardiac contractility is often not affected. This may therefore explain the lack of significant correlationship as similarly reported by Wu et al.[16] In the study among children population that reported a negative correlation between NT-proBNP and ejection fraction, more than two thirds of the patients had dilated cardiomyopathy, a disorder that reduces cardiac contractility and thus ejection fraction.[5]

Similar to other reports, plasma NT-proBNP levels correlated positively with the modified Ross score (r=1.341) in our study. [5, 15, 17] This shows that plasma levels of NT-proBNP can objectively reflect severity of congestive heart failure thus making it a useful tool in evaluation of patients with heart failure.

These findings indicate that measurement of NT-proBNP is a useful tool in the diagnosis and evaluation of children with congestive heart failure with potentially greater usefulness in developing countries where access to advanced technological equipment for both diagnosis and evaluation is lacking; especially in structural heart disease, whether congenital or acquired, where a diagnosis of heart failure is commonly considered and treated, our findings suggest that NT-proBNP, with its high specificity for heart failure would help prevent unnecessary treatment and adverse effects associated with treatment.

We acknowledge that a major limitation of this study is the relatively small sample size and further larger studies with a wider cardiac pathology spectrum are required.

In conclusion, our findings of plasma NT-proBNP concentrations being significantly higher in children with congestive heart failure compared to controls indicate that measuring NT-proBNP may be useful as a diagnostic tool in congestive cardiac failure in children with structural heart disease. The fact that its levels also correlated strongly with the modified Ross score thereby objectively determining severity suggests that this biomarker may also be useful as an evaluation tool in congestive cardiac failure in children.

ACKNOWLEDGEMENTS

This study was supported by a grant from the University of Lagos. We gratefully acknowledge the technical assistance of Bosun Olaleye and Gbenga David in the laboratory. Thanks to Dr Dolapo for assistance in analysis and interpretation of data.

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