

# Reliability and Accuracy of Point-of-Care Amino-Terminal ProBrain Natriuretic Peptide in Congestive Heart Failure Patients

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## Abstract

**Background:** Globally, role of amino-terminal pro-brain natriuretic peptide (NT pro-BNP) in diverse aspects of Congestive Heart Failure (CHF) has gained near-consensus status. Such experience is rare in many parts of Africa, and levels may be affected by ethnicity. **Aim/Objectives:** To determine NT pro-BNP levels in Nigerian healthy adults and hospitalised CHF patients; in order to establish its diagnostic accuracy. **Methods:** Controls and CHF patients were examined clinically, with trans-thoracic echocardiography; while plasma NT pro-BNP was measured by a point-of care-immunoassay system (Cardiac Reader<sup>®</sup>). We compared the diagnostic performance of our study-derived NT pro-BNP reference value with others. **Main outcome:** Obtain reference value of NT pro-BNP and compare its diagnostic performance with recommended product value of 125 pg/mL. **Results:** Participants were 42 CHF patients matched for age ( $p=0.26$ ) and gender ( $p=0.78$ ) with 30 controls. NT pro-BNP levels of controls differed significantly by gender (females:  $64.8 \pm 12.3$  versus males:  $98.2 (54.8)$ ,  $p<0.05$ ); and by CHF status ( $86.43 \pm 43.6$  versus  $1915 \pm 1082.1$  pg/mL,  $p<0.001$ ). NT pro-BNP demonstrated negative correlation with left ventricular function ( $r=-0.5$ ,  $p<0.05$ ). Our study NT pro-BNP reference value of 171 pg/mL yielded sensitivity, specificity, NPV, PPV of 88.1%, 93.3%, 90.3%, 95.2%, respectively, performing better than manufacturer's recommended value of 125 pg/mL (sensitivity 85.7%, specificity 86.7%, NPV 87.1%, and PPV 92.5% respectively). **Conclusions:** NT pro-BNP values were significantly higher in CHF patients; and demonstrated significant negative association with left ventricular function. Our point-of care reference value demonstrated better diagnostic performance than manufacturer's cut-off value. This calls for further local studies, using the new cut-off value.

## INTRODUCTION

Congestive heart failure (CHF) is a serious public health problem, with a progressive and lethal course (1,2). Inaccuracy of diagnosis of HF (3,4,5) has attracted attention amongst investigators in different clinical scenarios, such as emergency departments (6), and free living communities (7,8). Inaccurate diagnosis is more likely in early disease, (4,6,7,8) or in conditions of differential diagnosis (1,2,7,9). Indeed, in CHF, absence of physical congestion does not indicate normal filling pressures (10). Further, the CHF characterized by obvious congestion and symptoms represent gross and advanced disease with a prognostic profile, similar to that of certain malignancies (1,7). Thus, earlier recognition and diagnosis of CHF are advocated, in order to commence phase-appropriate therapy, with expected better prognosis (1,2).

Heart failure is a syndrome, thus, no one test captures all

aspects of this disease. There is on-going search for overall tests to aid diagnosis, risk stratification, and prognostication in CHF. Currently, echocardiography is the most useful diagnostic test in CHF (1,2), especially for the classification of systolic and non-systolic failure (1,7,8).

More recently, cardiac neuro-hormones especially the B-type variety, are receiving attention globally for management of CHF (1,2,4,7). The B-type biomarkers, consisting of brain natriuretic peptide (BNP) and amino-terminal pro-BNP, are released from ventricular myocytes, in equimolar concentrations, by different stress triggers, such stretch (6,11,12). The metabolically inert NT-pro BNP persists longer in the circulation, thus has a higher plasma concentration (1,2), so may be considered more appropriate for clinical diagnosis (11,12,13). NT pro BNP is currently enjoying an unprecedented explosion in diverse cardiovascular settings (1,2,6,7,13). Currently, both

American Heart Association (AHA) and European Society of Cardiology (ESC) heart failure guidelines recommend NT pro BNP in the diagnosis of HF (1,2).

In Blacks however, evidence shows that once diagnosis of heart failure is made, there is a more rapid deterioration, and less benefit to certain classes of drugs (14,15). Contribution of ethnicity and race have been suggested for some of these differences (14,15, 16,17). Recently, some investigators have provided data suggesting that race or ethnicity may contribute to different levels of NT pro-BNP in different populations (16,17). We are unaware of similar studies or data for Nigeria and West Africa. Thus, it is pertinent to provide further data in an African setting for use and comparison with other established cut-off or recommended values. Our aim was two-fold:[a] to obtain a study reference value for NT pro-BNP, using a point-of-care equipment; and **to compare the diagnostic performance of the reference value (NT pro BNP) with earlier recommended cut-off values.**

## METHODS

**Study population:** The study was approved by the Ethical Committee of the Lagos University Teaching Hospital, Lagos-Nigeria, and was sponsored by a CRC grant of the University of Lagos, Akoka, Lagos-Nigeria. All participants gave informed consent.

**Study Patients:** The 42 CHF patients were “new” or decompensated heart failure patients referred to the Medical Emergency Department or Cardiology clinic of Lagos University Teaching Hospital, (LUTH) Idiaraba, Lagos, a 600 bed-hospital. LUTH is one of the two Teaching Hospitals providing tertiary medical care to people of Lagos State, Nigeria. The 30 healthy age- and sex-matched subjects were recruited from staff of our Hospital or willing patients’ escorts.

**Inclusion criteria** for the healthy subjects (HS) were as follows: age > 14 years; non-smoker, absence of cardiopulmonary, renal, and liver disease, non-pregnant females, normal results for serum creatinine and a normal echocardiogram. **Exclusion criteria** were age ≤13 years, current and recent smoking history, clinical evidence or past history of significant cardiopulmonary, liver, renal and liver disease, abnormal renal function, defined by creatinine >120 µmol/L, and abnormal echocardiogram.

**Selection criteria** for CHF patients were as follows: clinical

evaluation and echocardiography within 24 hours of admission, satisfying both Framingham criteria for heart failure (7) and the study selection criteria. These are age >14 years, absence of other significant pulmonary and liver disease, evidence of cardiac disease demonstrated as cardiac enlargement (displaced apex beat, cardiomegaly by chest X-ray or echocardiography (2), serum creatinine <160µmol/L. CHF patients were excluded, if there was current or recent history of smoking, significant history of chronic pulmonary, liver, or current renal impairment, defined as serum creatinine level >160 µmol/L.

**Establishing Clinical Congestive Heart Failure:** Clinical evaluation of healthy controls, and for diagnosis of CHF group was performed by the study assistant- a senior registrar or one of the investigators-JNA or ACM. Data were entered into a proforma prepared for the study. Clinical diagnosis of congestive heart failure was based on the Framingham criteria of concurrent presence of two major criteria or one major with two minor criteria (7). The major criteria were paroxysmal nocturnal dyspnoea, jugular venous pressure/distension, pulmonary rales, increased heart size on chest x-ray, third heart sound, hepatojugular reflux. The minor Framingham features were bilateral ankle oedema, nocturnal dyspnoea, dyspnoea on ordinary exertion, hepatomegaly, heart rate >120 beats per minute, pleural effusion, one-third decrease in vital capacity. HF decompensation was based on a heart failure score >2, as described by Troughton et al (18).

**Echocardiography (7,8):** Conventional trans-thoracic echocardiography was performed by JNA or ACM, using a commercially available HP Sonos machine. Two Dimensional echo was obtained, using conventional position and views, with 2-D directed M mode for measurements. Measurements were made on-line, using the ASE convention of leading edge methodology (7,8). Specific M-mode measurements were appropriately made at end diastole and end systole. Fractional shortening (FS) was calculated according to the following formula:  $LVIDd-LVIDs \div LVIDd \times 100\%$ ; where LVIDd: = LV internal dimension in diastole; LVIDs, = LV internal dimension at end-systole. Ejection fraction (EF) was obtained by using the standard cubed formula as follows:  $(LVIDd)^3 - (LVIDs)^3 \div LVIDd^3 \times 100\%$  (7) Depressed LV function was based both on  $FS \leq 29\%$ , and  $EF \leq 50\%$  (2,7,8). Majority of our CHF patients are due to hypertension or cardiomyopathy related causes (5), therefore M-Mode assessment was appropriate. Routine

Doppler studies (colour and pulsed) were performed, including trans-mitral flow, aortic and pulmonary velocities.

Within 24 hours of admission, NT pro BNP measurement was performed, using Cardiac Reader<sup>R</sup> - a commercially available point-of-care equipment (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). The Cardiac Reader<sup>R</sup> is based on the principles of the Roche Elecsys system (12, 13). Blood samples for the NT pro-BNP measurements were collected in 5-ml EDTA bottles. Without any need for centrifugation, freezing, or incubation, 150 µL of plasma was transferred directly to the measuring platform of the equipment; which uses a code chip containing a combination of biotinylated polyclonal and monoclonal anti-NT-pro-BNP antibodies (6,11,12,13). The lower detection limit for the Cardiac Reader equipment is 60 pg per mL, and the turn-around-time for results is 12 minutes. Manufacturer's recommended cut-off value for NT pro BNP level is  $\geq 125$  pg/mL. Tests for controls and CHF patients were performed by study technologists, who were blinded to the study participants' clinical status.

## STATISTICS

Data were entered into the Word Excel spreadsheet with further analyses on Minitab 14 Student version or SPSS version 16. Continuous data were presented as median and mean  $\pm$ SD, while categorical data were in proportions as appropriate. Student T test was employed for comparison of differences for significance. We assessed the sensitivity, specificity, positive and negative predictive values (19) of the study-derived reference value, and the manufacturer's product insert cut-off value of  $\geq 125$  pg/mL. Relationship of NT pro BNP with LV function was by regression. Validity of point-of-care NT pro BNP was established by relation to echocardiographic measures of left ventricular function (fractional shortening and ejection fraction).

## RESULTS

Seventy two participants were included in the study, consisting of 42 CHF patients, matched for age [ $p=0.26$ ] and sex [ $p=0.78$ ]. Causes of CHF were 45% for hypertensive heart disease, 35% for primary dilated cardiomyopathy and 20% for others (consisting of valvular 7.1%, diabetes 7.1% thyrotoxic heart disease 7.1% s, and myocardial infarction 2.4%).

**Figure 1**

Table 1. Clinical, Echocardiographic and NT Pro-BNP Values of Healthy Subjects and CHF Patients

Parameter	Controls	CHF	T value
Pulse rate	76.3 (0.1)	101.1 (21.4)	6.04
Respiratory rate	16.1 (3.2)	30.5 (5.4)	13.06
SBP (mm Hg)	125.0 (8.9)	114.6 (20.6)	2.70
DBP (mm Hg)	79.7 (7.9)	74.2 (15.0)*	1.84
PP (mm Hg)	45.7 (8.1)	40.4 (13.4)*	1.94
NT-Pro-BNP	82.6 (43.9)	1915.6 (1033.3)9.24	
%FS	36.8 $\pm$ 7.8	24.0 $\pm$ 9.8	6.27
%Ejection Fraction	73.8 $\pm$ 16.7	54.1 $\pm$ 16.7	5.40
NT-Pro-BNP (Females)¥	98.2 (54.8)	2024.7 (1067.3)8.80	
NT-Pro-BNP (Males)¥	64.8 (12.3)	1755.0 (1119.1)11.3	

Legend Table 1:\*=p values  $> 0.05$ .; BP=systolic blood pressure; DBP=diastolic blood pressure, PP=pulse pressure; FS=fractional shortening; NT proBNP=pro brain natriuretic peptide, unit for NT pro-BNP=pg/mL; ¥=gender effect: NT pro-BNP values of male and female controls  $p<0.05$ .

In Table 1 is listed the clinical, the echocardiography-derived ventricular function, and NT pro-BNP of healthy subjects (HS) and CHF patients. As expected, the clinical features and ventricular functions were significantly different in controls and CHF [ $p<0.05$ ], with the exception of diastolic blood pressure and pulse pressures [ $p>0.05$ ].

NT pro-BNP levels in healthy subjects and CHF patients were  $86.43 \pm 43.6$  and  $1915 \pm 1082.1$  pg/mL respectively, showing a significant difference ( $t=9.24$ ,  $p<0.001$ ). Thus the reference value mean  $\pm 2$ SD obtained from this study was 171 pg/mL. In healthy group, sex significantly affected NT pro BNP, with females having a higher level:  $98.2 \pm 54.8$  versus  $64.8 \pm 12.3$ pg/mL,  $p<0.05$ . However in CHF, the NT pro-BNP of the female CHF patients, although higher:  $2024.7 \pm 1067.3$  than the male values  $1755.0 \pm 1119.1$  were not significantly so ( $p>0.05$ ).

**Figure 2**

Table 2. Comparison of Median Amino-Terminal Pro-BNP Values by NYHA class of CHF Patients

NYHA class	Proportion of CHF n(%)	NT pro BNP pg/mL
Class 2:	6 (14.3)	1511
Class 3:	15(35.7)	2213
Class 4	21 (50%)	2310

Legend: n=number; NYHA=New York Heart Association; CHF=congestive heart failure

NT pro BNP=amino terminal pro-brain natriuretic peptide, unit=pg/mL

Table 2.,shows median values of NT pro-BNP and clinical severity of CHF, represented by New York Heart Association class (NYHA) of the CHF patients. The NT pro-BNP values increased as clinical severity of CHF increased.

Echocardiographic data: All parameters were within acceptable limits for control subjects (selection criteria). The CHF showed gross pathology, with the following findings: dilated left atrial dimension in 36 (85.7%), and dilated left ventricular dimension in diastole 30(71.4%). Depressed systolic function was noted in more than half of the CHF patients: 64.3% (27of 42) when measured by fractional shortening; and 52.4 % (22 of 42), as measured by ejection fraction respectively.

**Figure 3**

Table 3.

Parameters	Controls	Patients	Statistics	p value
LA (mm)	37.7±2.8	44.4 ±6.6	7.61	0.00
LVIDd(mm)	47±3.4	59±8.2	7.61	0.00
LVIDs (mm)	29.8±2.8	45.5 ±9.8	8.53	0.00
EPSS(mm)	4.9 ±1.7	15.6 ±6.3	9.06	0.00
FS (%)	36.8±7.8	24.0± 9.8	6.27	0.00
EF(%)	73.8 ±16.7	54.1±16.7	5.4	0.00
E wave	83.3+/-11.7	76±14.5	2.17	0.03
A wave	74.9 ±13.1	62.2 ±22.5	2.78	0.01
LV mass	164, 938±28.2	288, 12 ±71.7	8.91	0.00

## SELECTED ECHOCARDIOGRAPHIC PARAMETERS OF HEALTHY SUBJECTS AND HEART FAILURE PATIENTS

Legend: LA=left atrium, EPSS=E point septal separation, FS=fractional shortening%, EF=Ejection fraction, LVIDd=left ventricular internal diameter in diastole, LVIDs =left ventricular internal diameter in systole, E=trans-mitral E wave, A=trans-mitral A wave, LV=left ventricle, LV mass in grams

In Table 3 is the comparison of M-mode echocardiographic dimensions in healthy subjects and the CHF patients, showing significantly different values (p<0.01) in the two groups.

In Figure 1, is shown a series of cut-off values of NT pro-BNP, measured by the point of care assay, with selected diagnostic performance parameters. The recommended manufacturer's performance of >125 pg per mL is noted, showing fair performance and a high positive likelihood ratio. The sensitivity and specificity were both above 85%.

**Figure 4**

Figure 1. Diagnostic Performance of NT Pro-BNP at Different Partition Values, With Emphasis on Manufacturer's Recommended Cut-off Value

Sensitivities, specificities and likelihood ratios (LR) at different cut-off values of prpbnp				
Cut-off value of prpbnp	Sensitivity	Specificity	1-Specificity	LR
95	92.9	76.7	23.3	3.99
100	92.9	80.0	20.0	4.65
105	92.9	83.3	16.7	5.56
110	92.9	83.3	16.7	5.56
113	92.9	83.3	16.7	5.56
115	90.5	83.3	16.7	5.42
120	88.1	83.3	16.7	5.28
122	88.1	83.3	16.7	5.28
123	88.1	83.3	16.7	5.28
124*	88.1	86.7	13.3	6.62
125*	88.1	86.7	13.3	6.62
126	85.7	86.7	13.3	6.44
127	85.7	86.7	13.3	6.44
130	85.7	86.7	13.3	6.44
135	85.7	86.7	13.3	6.44
140	85.7	86.7	13.3	6.44
145	85.7	86.7	13.3	6.44

Legend: prpbnp=amino terminal pro-Brain Natriuretic Peptide; LR= positive likelihood ratio

Table 4. shows the comparison of diagnostic performance parameters of the manufacturer's recommended value (125 pg/mL) versus the study-derived reference value of 171 pg /mL. The sensitivity of both cut-off values was comparable. In addition, the study-derived cutoff value showed higher specificity and predictive values than the manufacturer's cut-off value.

**Figure 5**

Table 4: Comparison of Diagnostic Performance of amino-Terminal Pro-BNP at Different Partition Values; Showing Sensitivities, Specificities, and Predictive Values

NT pro-BNP	sensitivity	specificity	NPV	PPA
125 pg /mL	88.1	86.7	87.1	92.5
171 pg/mL	85.7	93.3	90.3	95.2

Legend: proBNP =pro -brain natriuretic peptide; NPV=negative predictive value; PPA=positive predictive value; 125 pg/mL=manufacture's cut-off value; 171 pg/mL=study reference value.

Figure 2. shows that a significant relationship exists between NT pro-BNP and measures of left ventricular function. NT pro BNP demonstrated a significant, negative relationship to both ejection fraction ( $r=-0.49$ ,  $p<0.001$ ); and fractional shortening ( $r=-0.51$ ;  $p<0.001$ ).

## DISCUSSION

Our study aimed to assess the diagnostic performance of plasma NT pro BNP, as a non-invasive indicator of HF. Our data show comparable performance of the point-of-care NT proBNP measurement with that of similar studies. NT pro BNP was shown as a reliable marker of left ventricular dysfunction.

Our study patients are similar to those evaluated for heart failure in similar settings, with hypertension as the main cause of HF (5,20). The average age of HF patients here was 54 years, similar to Soweto patients (20), but much lower than the seven decades, noted for HF patients elsewhere (6, 8, 9,13). This lower age of our CHF patients might be a reflection of the more severe course of CHF, seen in black cohorts (4, 14, 15).

As previously noted, the lack of reliability and inaccuracy of clinical diagnosis in CHF (4,6,7,9,10) justifies the validation of other simple available modalities in CHF management (1,2,3,8). Our point –of –care assay for measurement of NT pro BNP is a commercial, smaller portable version of the Elecsys assay, and has been previously validated (6,12, 13). The equipment is easy to use, with available results in 12 minutes.

Comparison of NT pro BNP with other studies: Racial and ethnic factors have contributed to different aspects of cardiovascular care (14,15,16,17). In South Africa, Montagnana et al found no difference in the reference values of NT pro BNP levels in apparently healthy Whites or Blacks (16). These discordant suggestions also support the

importance of local studies. In the present study, the mean NT pro BNP in health was  $86.48 \pm 43.9$  pg /mL, with a study reference value of 171 pg/mL, determined from the mean  $\pm 2SD$ . In a pooled analyses of a large European epidemiological data-base, McDonagh's group found a value of 20.0 pg per ml for normal controls. Interestingly, 42.5-112.6 pg/mL was the South African reference value for NT pro BNP (16). Nevertheless, even the guidelines on HF of the European Society of Cardiology (2) suggest a plasma NT pro BNP level of 400 pg, as suitable for suspected heart failure. Hypertension and left ventricular hypertrophy tend to contribute to intermediate levels (7,17). Age and renal dysfunction are other factors which might alter NT pro BNP (13,16, 19, 22), but our study methodology excludes these confounders. Consistent with other studies (6,11,13, 21), our female controls had higher cardio-peptide values. Some investigators have suggested gender specific values (13,21), but not others (2, 16, 22).

NT pro BNP and left ventricular function: Consistent with other studies, less than half of our CHF group had preserved systolic function (1,2,6,13), with NT pro BNP levels higher than those with systolic CHF (9,13). There was also a highly significant linear negative relationship with ejection fraction and fractional shortening ( $r=-0.5$ ,  $p<0.001$ ). This relationship also provides support of NT pro-BNP as a valid surrogate measure for left ventricular function, as supported by others (1,2,9,16, 19). It is interesting that NT pro BNP was significantly elevated in both systolic and diastolic CHF (6,13). This supports that the well-known theory that CHF-syndrome is a final common pathway, practically unrelated to type of failure, or aetiology (1,2,10).

Diagnostic performance: Globally, investigators have proposed different cut-off values for abnormal NT pro BNP as follows: 123pg /mL (21), 125 pg per ml (6), 200 fmol /ml=1685 pg/mL (9) 400 pg /mL (2), 450 pg /mL(13), in addition to the manufacturer's recommended value of 125 pg/mL. This shows great variability and may contribute to reluctance and confusion of practitioners in the use of this promising tool. However, race and ethnicity were not suggested factors of the different cut-off values, by the authors. Our study-derived reference value of 171 pg/mL, showed good overall performance with a sensitivity of 85.7%, specificity of 93.3%, predictive values above 90%. The specificity and predictive values surpassed those using the manufacture's value. This diagnostic performance was significantly higher than that of symptoms, signs and



evidence of congestion compared with haemodynamic parameters of CHF (10), and was comparable to the study findings of others (4,9,22). Nevertheless, our data showed that a lower cut-off value may result in higher sensitivity, unlike the report of Jose et al (9).

**Limitations:** our study group is small, but valid conclusions have been obtained, because of the asymptomatic healthy control group, which is required for studies in diagnostic performance (17). The point-of-care equipment has a lower detection value of 60 pg/mL, thus would be more useful in defining a HF group.

**Conclusion:** NT pro-BNP, measured using the point-of-care equipment showed significant relationship to left ventricular function. The NT pro-BNP values were significantly lower in controls than CHF patients. We are unaware of similar studies in Nigeria and West Africa. Further, our data-derived reference value of 171 pg/mL out-performed the NT pro-BNP cut-off value recommended by the manufacturer.

**Recommendation:** In this African setting, our study -derived reference value demonstrated better diagnostic performance in the accurate diagnosis of CHF. This merits further studies in other localities, and with an increased number of study participants. However, we recommend that, when using the commercial Cardiac Reader<sup>R</sup>, our reference value may provide more accurate evaluation in Nigerians. This also awaits the experience of others.

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