

The Association of Amino Terminal Pro-Brain Natriuretic Peptide Levels with Functional Capacity in Cardiac Failure Patients in a Pakistani Population

AAMENAH MALIK, NADIA MEHMOOD*, SAHAR JAVED, MARIAM MALIK**, MASOOMATALIB***

ABSTRACT

Background: Amino-terminal pro-brain natriuretic peptide (NT-proBNP), a biologically inactive derivative of Brain natriuretic peptide is released from cardiac ventricles as a response to stretch resulting from cardiac failure. It gives a quantitative measure of cardiac failure severity as it rises proportionately. In this regard, NT-proBNP gives a quantitative measure of severity of cardiac dysfunction than clinical judgment alone. Unfortunately, this highly useful biomarker has not yet been routinely incorporated in our national guidelines for heart failure management. No study has been done so far to highlight the role of NT-ProBNP in cardiac failure in our population.

Aim: To study, the association of NT-proBNP levels with cardiac functional capacity.

Methods: 64 patients with CHF (31 men, 33 women) were included in this study. The heart failure symptoms of the patients were classified using the New York Heart Association (NYHA) system and compared with serum levels of NT-ProBNP.

Results: There was a significant positive correlation between levels of NT-proBNP and NYHA class.

Conclusions: The severity of CHF can be objectively assessed by measuring the circulating levels of NT-proBNP. NT-proBNP can provide objective information regarding the severity of the disease and also aid in initial triage and treatment decisions in patients with CHF.

Key words: NT-ProBNP, NYHA, cardiac failure, functional capacity

INTRODUCTION

Cardiac ailments with their high rates of mortality, account for an annual loss of 16.7 million deaths¹. The rise in congestive cardiac failure patients is the fastest in the United States². In India the incidence is 1.57 million per year and prevalence is 18 million patients³. In Pakistan, although the actual figures are not known but it is estimated that approximately 2.8 million people have cardiac failure. Cardiac failure has a 50% five year mortality. Early diagnosis and treatment are therefore of considerable importance⁴.

No single diagnostic criteria have been established as the gold standard for heart failure. Diagnosis of CHF is complicated because its symptoms are vague. Preliminary diagnosis is mostly clinical which is non-specific. Differential diagnosis depends on costly procedures such as echocardiography and nuclear ventriculography. As CHF progresses, therapeutic options become lesser and patient may require mechanical intervention. Early confirmatory diagnosis is vital to reduced morbidity and mortality⁵.

An important advancement in recent years in management of heart failure is measurement of serum B-type Natriuretic Peptide. BNP is a bioactive peptide that is mainly released from the cardiomyocytes in the wall of left ventricles owing to the myocytes stretching. It is synthesized as a precursor prohormone ProBNP which is later cleaved into two fragments: N Terminal -proBNP and BNP, which are released into the blood vessels⁶. BNP is the biologically active fragment and antagonizes the renin angiotensin aldosterone system and prevents volume overload by inducing increased sodium excretion and causes vascular dilatation by inhibition of the sympathetic nerves system.

The more the heart fails, the more it stretches and lesser the left ventricular ejection fraction. The release of NT-ProBNP is directly proportional to myocardial stretch. Hence levels rise significantly with worsening symptoms and worsening Left Ventricular Ejection Fraction which makes it a potential quantitative biomarker for risk stratification. The New York Heart Association functionally classifies cardiac failure into four categories. Serum NT-proBNP levels increased significantly with worsening NYHA class and reflected the rising severity of cardiac insufficiency⁷.

It is thus a reliable biomarker for quantitative assessment of heart failure severity and can aid the

Department of Biochemistry, CMH Lahore Medical College, Lahore

*Department of Pathology, CMH Lahore Medical College, Lahore

**Department of Radiology, Services Institute of Medical Sciences, Lahore

***Department of Biochemistry, Yusra Medical College, Islamabad

Correspondence to Dr. Aamehah Malik, Email: aamenah@gmail.com

clinician in diagnostic and therapeutic decision making specially in scenarios where echocardiography is not readily available. NT-ProBNP taken in emergency department is a rapid test which accurately characterizes disease severity⁸.

MATERIAL AND METHOD

This cross sectional analytical study was conducted at Post graduate medical institute, Lahore in collaboration with Punjab Institute of Cardiology Lahore. NT-ProBNP levels were measured in 64 patients of CHF(30-80 years of age both sexes). Patients with renal disease, acute myocardial infarction or unstable angina were excluded. Serum concentration of NT-ProBNP was estimated by Immunological UV assay and enzyme linked immunosorbant assay (ELISA) . The data was analyzed using SPSS 17.64 patients with CHF (31 men, 33 women; mean age 58.26 +/- 10.59 y) were included in this study. The New York Heart Association (NYHA) classification system grades CHF patients into four classes with class I having no shortness of breath and class IV being the most severe with dyspnea at rest. CHF patients had higher than normal levels of NT-proBNP and a significant positive correlation was observed between serum levels of NT-proBNP and worsening NYHA class.

RESULTS

Based on clinical evaluation the patients were categorised into four categories of worsening heart failure as New York Heart Association Class I, II, III and IV. 46% of the patients belonged to NYHA Class III while 25 % belonged to class II and 28% belonged to class IV. No significant difference was found amongst male and female distribution (Table 1).

Patients were stratified according to the disease severity by NYHA classification with corresponding NT-proBNP concentrations. Table 2 shows the mean NT-proBNP levels in different NYHA classes of heart failure. The overall mean NT-ProBNP level is 7493 pg/ml. The average plasma level varies from 1945 pg/ml in NYHA II to 8011 pg/ml in NYHA III and the rise in NT-ProBNP was significant (p value .002) .The levels increase to 11,689 pg/ml in NYHA IV but the difference in NT-ProBNP levels between NYHA III and IV class were not found to be significant (p value .198) Hence a progressive increase in plasma concentrations was observed when NT-proBNP was plotted against NYHA class of heart failure. Comparing mean NT-ProBNP levels in males and females in different NYHA class, higher values were observed in females but the difference was statistically insignificant with p value 0.392

Table 3 represents the correlation coefficients between NT-ProBNP and NYHA class of heart failure. Plasma levels of the peptide correlate positively(r= 0.286) with worsening NYHA class and this correlation is significant at p value 0.011. Similarly figure 1 illustrates that progressive increase in plasma concentrations were observed when NT-proBNP was plotted according to NYHA class.

The association between NT-proBNP levels and functional capacity in heart failure patients in a Pakistani population

Table 1. NYHA based classification among males and females

NYHA	Total	Male	Female
II	20(25.6%)	15(28%)	5(21.4%)
III	36(46.1%)	23(44%)	13(50%)
IV	22(28.2%)	13(28%)	7(28.6%)

Table 2: Variation of NT-ProBNP levels with NYHA class

NT-Pro BNP levels(pg/ml)	NYHA II (n=20)	NYHA III (n=36)	p-value*	NYHA IV (n=22)	p-value**	TOTAL (n=78)
Male	1802 (n=14)	7880 (n=22)	.009	10053 (n=14)	.506	6787 (n=50)
Female	2272 (n=6)	8217 (n=14)	.108	14550 (n=8)	.254	8754 (n=28)
Total	1945	8011	.002	11689	.198	7493

*Comparison of NT-ProBNP levels between NYHA II, III (t-test)

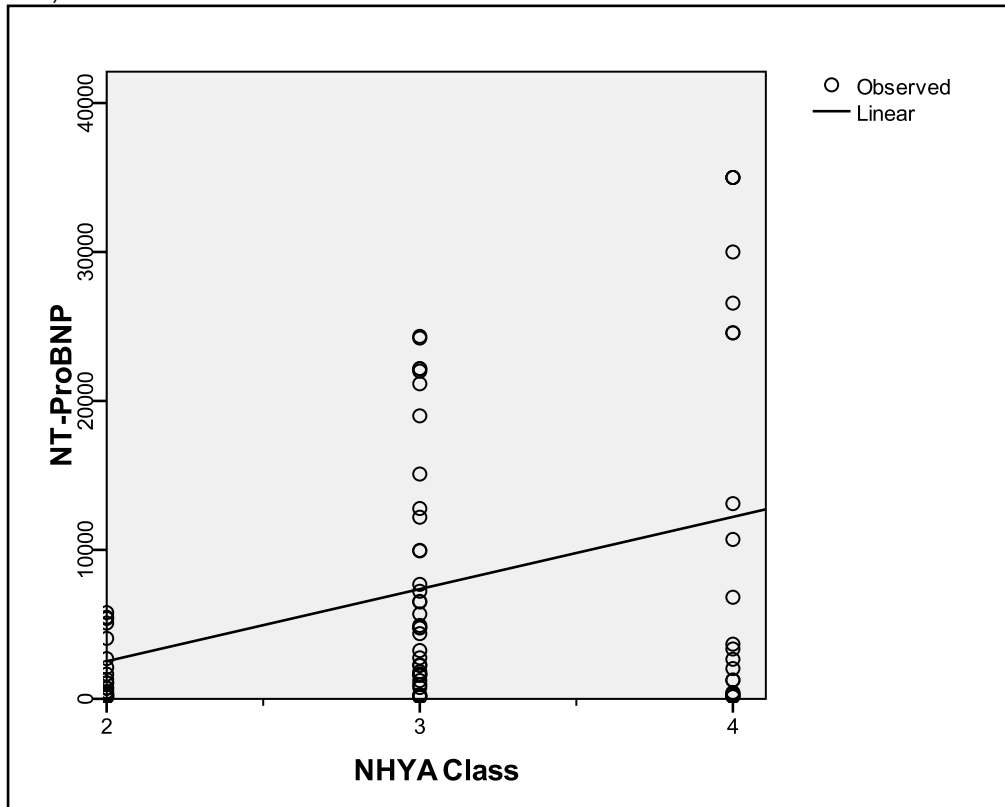
** Comparison of NT-ProBNP levels between NYHA III and IV (t-test)

Table 3. Correlation coefficients between NT-ProBNP and NYHA class

		NTproBNP	NYHA class
NT-proBNP (pg/ml)	Correlation Coefficient	1.000	.286
	Sig. (2-tailed)	.	.011*
	N	78	78
NYHA	Correlation Coefficient	.286	1.000
	Sig. (2-tailed)	.011*	.
	N	78	78

*Correlation is significant at 0.05 level (2-tailed)

Fig. 1: Correlation between NT-ProBNP (pg/ml) and NYHA class showed a positive correlation with r value .286(p value .011)



DISCUSSION

Patients were stratified according to New York Heart Association functional class of heart failure based on severity of shortness of breath and NT-ProBNP serum levels were measured and then compared in the four NYHA categories. Out of the 64 patients enrolled in the study, the distribution of patients based on NYHA classification were 20 cases in class II, 36 cases in class III and 22 cases in class IV. The average plasma level varied from 1986 pg/ml in NYHA II, 8194 pg/ml in NYHA III and 9611 pg/ml in NYHA IV. An increase in serum levels was observed when NT-proBNP was plotted against NYHA class. A positive correlation of NT-ProBNP levels was seen with NYHA class ($P < 0.001$). This was in accordance with a study conducted by Karabulut⁹. A similar study by Seino and Luigi^{10,11} concluded that NT-proBNP levels showed significant progressive rise in relation to the NYHA class. Plasma levels of NT-ProBNP thus increase proportional to the clinical stages of failure.

These findings suggest that NT-ProBNP secretion is an indicator of ventricular dilatation with respect to impending heart failure. NT-proBNP can provide objective information regarding the severity of the disease and also aid in treatment decisions in

patients with CHF. Hence measurement of NT-ProBNP is a reliable laboratory indicator not only for detection of left ventricular failure but also for stratification of its severity. This is in accordance with a study done by Greenwo stated that aided by the NT-proBNP levels, clinicians may optimize the management of patients with CHF¹².

Various factors contribute to the varying severity of cardiac failure and the inter individual differences in presentation. American Heart Association (AHA) guidelines for heart failure evaluation concluded that heart failure progressed more swiftly in the black race possibly owing to social influences or lack of access to advanced medical care¹⁴. Genetic makeup of the individual as regards specific genetic loci can lead to over representation of this complex disease¹⁵. The difference in drug effectiveness based on pharmacogenomics has also been postulated which is explained by inconstant drug clearance and polymorphism of genes encoding enzymes of drug metabolism^{16,17,18}. The aforementioned factors are all non-modifiable as per severity of heart failure but NT-ProBNP is used as an emergency marker which can be monitored and controlled to alleviate the severity of congestive heart failure. NTproBNP results are used to aid in assessment of severity and risk stratification of congestive heart failure¹⁹.

CONCLUSION

A positive association between worsening NYHA class and rising NT-ProBNP levels indicates that this marker increases proportionately with worsening clinical stage of cardiac failure and thus aids in stratification of CHF patients based on severity. This marker hence needs to be routinely implemented for early identification and triage of patients with CHF. NTproBNP is best used in community practices where there is a high prevalence of heart failure and it can be used primarily in primary care settings where echocardiogram or CXR are not readily available and are more expensive.

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