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# Association of N-terminal Pro-Brain Natriuretic Peptide with Various Clinical and Demographic Variables in Indian Population with Chronic Heart Failure

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## ABSTRACT

### BACKGROUND

Chronic Heart Failure (CHF) is a serious cardiovascular syndrome with increasing incidence and prevalence leading to a huge global health burden. The N-terminal pro-brain natriuretic peptide (NT-proBNP) level is an important diagnostic and prognostic marker of cardiac dysfunction. There is a lack of data regarding the association of various risk factors with the NT-proBNP levels. The present study aimed to evaluate the association of NT-proBNP levels with the clinical variables in known cases of CHF in Indian Population.

### METHODS

In this observational study, data on the association of various clinical variables on date of admission with NT-proBNP levels in known cases of CHF patients who attended the Madhavbaug clinics between January 2019 and December 2019 were analysed. Patients of either gender with symptoms of dyspnoea or exertion or who underwent 2D ECHO and NT-proBNP analysis were included in the study. The variables analyzed were age, CAD status, Dilated cardiomyopathy (DCM), Chronic kidney disease (CKD), MI, LVEF (>40), $VO_{2peak}$ using multivariate regression model.

### RESULTS

Of the data analysed for 723 patients, the majority were males [n = 453 (62.64%)] with a mean age of 60.29 ± 10.91 years. Age, CAD, DCM, CKD and MI showed a significant positive correlation while LVEF (>40) showed a significant negative correlation with logarithm of NT-proBNP levels ($p < 0.05$).

### CONCLUSION

This baseline study provides evidence that several clinical as well as demographic variables: Age, BMI, LVEF, history of CAD, CKD and MI have a significant correlation with NT-proBNP in Indian population with known cases of CHF.

### KEYWORDS

NT-proBNP; Chronic heart failure; Diagnostic marker

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## INTRODUCTION

Chronic heart failure (CHF) is a major public health problem with high rates of mortality and morbidity [1]. The prevalence of CHF in India is about 1% of the total population with an increasing burden on the healthcare system [2]. Multiple risk factors and poor prognosis of the disease lead to a diminished quality of life [3]. Hence, early diagnosis of HF is of utmost importance considering the mortality and overall burden on the healthcare system [3].

Among the numerous cardiac biomarkers used for the diagnosis of cardiac dysfunction, brain natriuretic peptide (BNP) and *N*-terminal proBNP (NT-proBNP) are the most extensively used [4]. Pro BNP is a precursor of BNP which further gets converted to NT-proBNP, a 76 amino acid inactive peptide and BNP, an active 32-amino acid peptide [5]. These NPs are released by the left ventricle in response to cardiac pressure overload, thus leading to increased circulating levels of BNP and NT proBNP levels following cardiac dysfunction [6]. Since the circulating levels of NT proBNP levels are more stable along with a higher half-life, it is considered as a better marker than BNP levels [7].

Along with the diagnosis of CHF, the treatment plays an equally important role. Taking into account the poor quality of life of CHF patients, a multimodal treatment approach is needed. However, there is a lack of information regarding the association of various risk factors with the NT-proBNP levels. If such an association exists, then early diagnosis with the medical intervention will help in the prevention of further development of CAD.

Therefore, in the present study, we evaluated the correlation of NT-proBNP levels and it's associations with various clinical variables at the date of admission in CHF patients. This study could act as a baseline study for further evaluation of the prognostic value of NT-proBNP levels.

## METHOD

### *Study Design and Duration*

This is an observational study conducted from January 2019 to December 2019 at Madhavbaug clinics in Maharashtra, India.

### *Inclusion/Exclusion Criteria*

Patients of either gender with symptoms of dyspnoea on exertion or who underwent 2D ECHO and NT-proBNP analysis.

### *Methodology*

Data was retrospectively collected for variables such as age, CAD status, Dilated cardiomyopathy (DCM), Chronic kidney disease (CKD), MI, LVEF (>40), $VO_{2peak}$ and NT-Pro BNP levels on date of admission. Cardiac stress testing was conducted in those who were eligible for CST. $VO_{2peak}$ was calculated from MET value $VO_{2peak}$ = Met*3.5(standard formula). The correlation between the various variables and NT-proBNP was analyzed.

Written informed consent was obtained from all the participants. The study procedures followed are per the ICMR's Ethical guidelines for biomedical and health research on human participants (2017).

### *Statistical Analysis*

Data analysis was performed using descriptive and inferential statistics. Normality of continuous data was checked using the Kolmogorov - Smirnov test. Continuous data [i.e. Demographics, Abdominal girth (ABG) on DOA (cm), Random blood sugar, fasting blood sugar, haemoglobin, NT-proBNP on DOA, heart rate, Left ventricular ejection fraction (LVEF), blood pressure,

$VO_{2peak}$] were presented as Mean ± Standard Deviation (S.D.). Categorical data [Gender, smoking/tobacco consumption status, history of coronary artery disease (CAD), hypertension, diabetes mellitus, ischemic heart disease, obesity, chole/dyslipidaemia, rheumatic heart disease (RHD), chronic heart failure (CHF), dilated cardiomyopathy (DCM), thyroid function, chronic kidney disease (CKD, PTCA, CABG, MI, Unstable angina (UA)] were presented as numbers and proportions. The LVEF 2D echo parameter was categorized as normal (≥55), mild (45-55), moderate (35-45), and severe (≤35). Paired t-test and Wilcoxon matched-pairs test were used as per the distribution of the data to determine the change in the baseline and post-treatment values for the endpoints. The relation between log-transformed NT-proBNP and some of the above-mentioned variables were analysed using a multivariate regression model for baseline and follow-up data. If the p-value is <0.05, it implies that there is a significant relation between log-transformed NT-proBNP and other variables. If p-value >0.05, then it implies that there is no relation between log-transformed NT-proBNP and other variables. All statistical analyses were performed using SAS® statistical software (Version: 9.4; SAS Institute Inc., USA) at 5% significance.

## RESULTS

### *Demographics*

A total of n = 723 patients were considered eligible for the study. Of these, n = 453 (62.64%) were males while n = 270 (37.3%) were females. The mean age and BMI of the study population were 60.29 ± 10.91 years and 27.4 ± 5.73 kg/$m^2$respectively.The mean NT-proBNP value on the date of admission was 1925.36 ± 4764.61. The study population had various co-morbidities like CAD (38.73%), hypertension (69.43%), diabetes mellitus (53.94%), CHF (14.3%), CKD (4.01%) and DCM (6.78%). 50.21% of the population showed a normal LVEF. The demographic and clinical parameters are presented in Table 1.

| Parameters | N = 723 |
|---|---|
| Age, Years (Mean ± SD) | 60.29 ± 10.91 |
| Gender<br>Male, n (%) | 453 (62.64) |
| BMI kg/$m^2$ (Mean ± SD) | 27.4 ± 5.73 |
| NT-ProBNP, pg/ml (Mean ± SD) | 1925.36 ± 4764.61 |
| CAD [n (%)] | 280 (38.73) |
| Hypertension [n (%)] | 502 (69.43) |
| Diabetes mellitus [n (%)] | 390 (53.94) |
| CHF [n (%)] | 104 (14.3) |
| CKD [n (%)] | 49 (4.01) |
| DCM [n (%)] | 49 (6.78) |
| **LVEF** | |
| Normal (>=55) | 363 (50.21) |
| Mild ( 45-55) | 106 (14.66) |
| Moderate (35-45) | 119 (16.46) |
| Severe (<=35) | 135 (18.67) |

**Table 1:** Demographic and clinical details of the patient population.

### *Correlation Between NT-proBNP Levels with Demographic and Clinical Parameters*

The relationship between the logarithm of NT-pro-BNP levels on DOA and various clinical and demographic parameters was analyzed. A significant positive correlation was observed for age (p = 0.0121) (Figure 1), CAD (p = 0.03), DCM (p = 0.003), CKD (p = 0.0006) and MI (p = 0.01) with NT-proBNP on DOA. On the other hand, a significant negative correlation was seen between weight (p <0.01) (Figure 2), LVEF (p<0.001) (Figure 3).

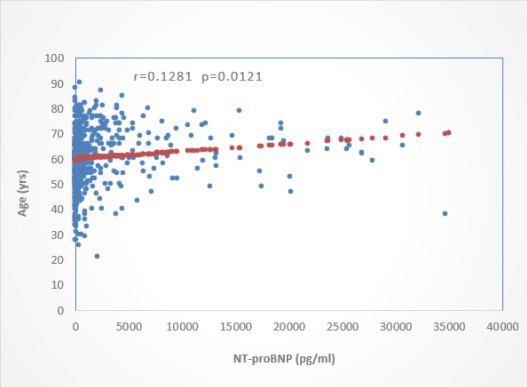


**Figure 1:** Regression analysis between age and NT-proBNP levels.

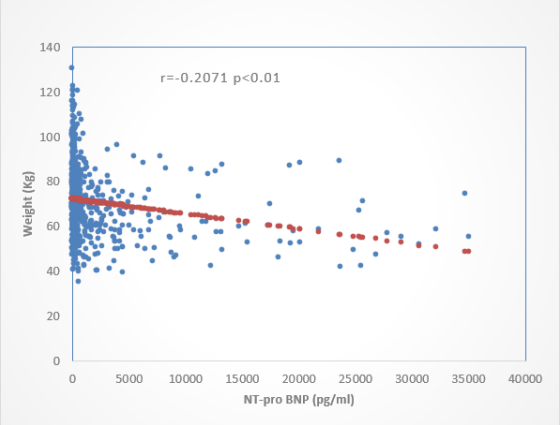


**Figure 2:** Regression analysis between weight and NT-proBNP levels.

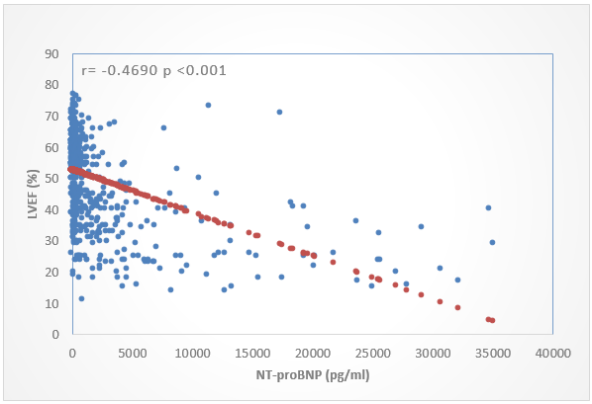


**Figure 3:** Regression analysis between LVEF and NT-proBNP levels.

After elimination of zeros from $VO_{2peak}$, we observed that there is no correlation between $VO_{2peak}$ and NT-proBNP.

## DISCUSSION

NT-proBNP has been used widely as a diagnostic marker in chronic heart failure (CHF) patients [4]. However, it is necessary to take into consideration, other factors such as age, BMI, renal function along with cardiac parameters which play an important role in the elevation of both BNP and NT-proBNP levels [8].

LVEF is the most important cardiac parameter since patients having a poor LV systolic function have elevated natriuretic peptide (NP) levels as compared to those with normal LV function. Thus, the NP levels also help in diagnosing HF and reduced survival at 10 years along with differentiating patients with normal LVEF and impaired LVEF [9].

In the present study, the correlation of parameters such as age, BMI, chronic kidney disease, as well as cardiac variables such as LVEF, DCM, MI, CABG and $VO_{2peak}$ with the NT-proBNP levels on the date of admission was evaluated in the patients admitted for the indication of CHF. Age is a non-modifiable risk factor and it showed a significant positive correlation with NT-pro BNP levels. Our results are in line with previously reported results observed by Zhang et al. [10] in a Chinese population and Tanaka et al. [11] in a Japanese cohort study. NT-proBNP is useful to predict the angiographic severity of CAD as observed by Yesil et al. [12] in a Turkish population. They also observed a positive correlation between the NT-proBNP and the number of coronary vessels involved. In CAD, the heart muscles do not get enough of blood supply leading to a reduced LV function same which is observed in the present study, wherein having a history of CAD is positively correlated with NT-proBNP. NT-pro BNP showed accuracy in identifying heart failure due to left ventricular dysfunction as observed by Emdin et al [13].

Dilated cardiomyopathy (DCM) is a condition where the heart gets enlarged and its muscles get thin, which is idiopathic but it can trigger up NT-proBNP levels as observed in the present study [14]. Similar results were observed by Zoair et al. [15] who found a significant increase in serum NT-proBNP level in patients with DCM as compared to those in the control group. MI usually leaves a scar on LV, leading to regional wall motion abnormalities, which further reduce cardiac output. This might lead to an increased end-diastolic volume which stretches the myocardium to increase NT-proBNP. In the present study, we observed higher NT-proBNP levels in patients having a history of MI. Our results are similar to a study by Radosavljevic

Radovanovic et al. [16] in a Serbian population, wherein they observed higher NT-proBNP values in HF patients with a history of MI.

CKD is a condition where glomerular filtration rate gets slowed which causes a reverse pressure (increase afterload) leading to reduced LV function or vice versa, where LV function drops, cardiac output goes down and so does GFR, leading to CKD [17]. We found a positive correlation of CKD with NT-proBNP levels. Our results corroborated with Takase et al. and Srisawasdi et al. in a study on Japanese and Thai population respectively [18,19].

LVEF is inversely proportional to the end-diastolic volume and directly proportional to stroke volume and cardiac output. Thus, a good LVEF is an indicator of normal LV function [20]. In the present study, elevated NT-proBNP is positively correlated with LVEF <40%. Our results are in line with Belagavi et al. [21] in a study done on the elderly population. $VO_{2peak}$ suggest overall effort tolerance and functional capacity [22]. We observed that NT-proBNP levels were not correlated significantly with $VO_{2peak}$ levels. Passino et al. [23] also demonstrated that measurement of NT-proBNP levels is an effective tool in HF patients undergoing physical training as these levels significantly decrease post-training.

## CONCLUSION

The present study thus shows that various clinical and demographic variables, such as age, BMI, LVEF, $VO_{2peak}$, history of CAD, CKD and MI have a significant correlation with NT-proBNP. However, future large scale studies are necessary to assess the diagnostic and prognostic potential of NT-proBNP for clinical outcomes.

## CONFLICTS OF INTEREST

None.

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