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ORIGINAL RESEARCH OPEN ACCESS

Correlation of NT-proBNP levels with clinical and echocardiographic features in evaluation of patients admitted with heart failure

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Abstract

Background: Heart failure (HF) is one of the leading causes of hospitalizations in both developed as well as developing nations. The natriuretic peptide N-terminal pro-BNP (NT-proBNP) has long been used for diagnosing and managing HF. The study aimed to determine the correlation of NT-proBNP levels with clinical and echocardiographic features in evaluation of patients admitted with heart failure.

Methods: This is retrospective observational study of 37 patients admitted to the hospital with acute onset dyspnea, over a period of 18 months. In addition to detailed history and physical examination, complete blood counts, random blood sugar, blood biochemistry, and electrocardiography (ECG), bedside echocardiography and x-ray chest were performed on admission to the hospital. Measurement of serum NT-proBNP level was performed as part of evaluation of dyspnea**.**

Results: Average age of the study population was 64 years. The co morbidities among the patients were hypertension (91%), diabetes mellitus (68%), obstructive airway disease (21%), coronary artery disease (16%) and chronic kidney disease (4%). The mean NT-proBNP for each group was LVEF ≥ 50%= 2272, LVEF 40–49% = 8161.5, and LVEF < 40% = 17302.7 (pg/ml).
Conclusion: NT-proBNP levels are proven to be useful in diagnosing and management of heart failure. However, the levels can be affected by many factors such as age, renal function, anaemia and body mass. When interpreting NT-proBNP levels, these factors have to be taken into account while making clinical decision and initiation of appropriate therapy.

Keywords: heart failure; natriuretic peptides; NT- proBNP; hypertension

Introduction

Heart failure (HF) is one of the leading causes of hospitalizations in both developed as well as developing nations. Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (breathlessness, ankle swelling, fatigue etc) that may be accompanied by signs (eg., elevated jugular venous pressure, pulmonary crackles and peripheral edema) [1]. Acute breathlessness or dyspnea is one of the common symptoms of heart failure, inpatients presenting to the emergency department. Dyspnea could be attributed to respiratory, metabolic or infectious causes also. It is important to differentiate heart failure from other causes of dyspnea and initiate appropriate treatment as early as possible. Clinicians are often left with diagnostic uncertainty after evaluating the patient's symptoms, physical examination, ECG and chest x-ray. This can lead to delays the initiation of appropriate therapy.

Multiple studies have suggested that, when used in conjunction with other clinical information, serum

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N terminal pro BNP (NT-proBNP) levels is useful in establishing, or ruling out the diagnosis of HF in patients with acute breathlessness [5]. NT-proBNP appears to be a powerful predictor of LV function and prognosis in various conditions including myocardial infarction and acute coronary Syndrome [4]. Elevated NT-proBNP levels can be also found in many circumstances involving left ventricular (LV) or right ventricular (RV) dysfunction secondary to pulmonary diseases, inflammatory or infectious diseases. Other conditions include high output status without decreased left ventricular ejection fraction (EF), e.g., sepsis, renal failure, cirrhosis of liver or intracranial pathologies [6].

In the recent years, heart failure with preserved ejection fraction (HFpEF) has been increasingly recognized as a pathophysiological entity [2]. It currently represents approximately 50 % of HF cases and associated with high morbidity and mortality [3].

The study aimed to determine the correlation of NT-proBNP levels with clinical and echocardiographic features in evaluation of patients admitted with heart failure.

Materials and methods

We retrospectively analysed 37 patients admitted with acute onset dyspnea (hours to days duration), between January 2021 to July 2022 in AMC Super Speciality Hospitals. Patients who had dyspnea caused by acute coronary syndrome, pneumonia, trauma which were clinically evident on presentation, as well as those with renal failure, ascites caused by cirrhosis were excluded from the study. Patients with age above 18 years were included in the study. In addition to history and physical examination, complete blood counts, random blood sugar, blood biochemistry, blood gas analysis, and electrocardiography (ECG) were taken. Bedside echo-cardiography (ECHO) and x-ray chest were performed on admission to the hospital. Measurement of serum NT-proBNP level was performed as part of evaluation of dyspnea. Diagnosis of heart failure was made by Framingham's criteria. As it was an observational study, there was no intervention on the study patients. Patients received standard heart failure measures. Ethical clearance was obtained from hospital ethics committee, at start of this study.

In our study, the patients of HF were divided into three groups as per the ejection fraction according to the American heart association guidelines *viz* EF < 40% was HFrEF (Heart failure with reduced EF), EF 41–49% was HFmEF (Heart failure with mid-range EF) and EF > 50% was HFpEF (Heart failure with preserved EF).

NT-proBNP levels were measured by enzyme linked fluorescence assay method in the laboratory. Detailed echocardiography with measurement of left ventricular ejection fraction (LV EF), presence of chamber hypertrophy or enlargement and regional wall motion abnormality (RWMA) were assessed. Further workups of the patients were done based on initial results and comorbid conditions. Thyroid stimulating hormone (TSH) and glycosylated haemoglobin (HbA1C) were estimated as needed by the clinical status. Estimated glomerular filtration rate (e-GFR) was calculated by CKD-EPI formula. Relationships between their clinical presentation, NT-proBNP levels and ECHO findings were studied.

Results

In our study, a total of 37 patients diagnosed with heart failure were enrolled. Among 37 patients, 18 were males and 19 were females. The average age among the admitted patients were 64 years. Comorbid conditions in the study group were hypertension (91%), diabetes mellitus (68%), obstructive airway disease (21%), cad (16%), chronic kidney disease (4%), obstructive sleep apnea (0.02%).

Out of 37 patients, 12 patients had history of smoking (32.4%). Six patients were current smokers and 6 were former smokers. Serum NT pro BNP was raised (>300pg/ml) in 29 patients (78.3%) out of 37 patients. Nine patients (21.7%) had normal NT-proBNP levels.

The mean NT-proBNP levels were higher in the 71-80 years (13499 pg/ml) and above 81 years (11282.8 pg/ml) age group compared with less than 70 years age group. In our study, out of 37 patients 26 (70.2%) patients had anemia of various grades. Among 29 patients with elevated NT-proBNP levels, 23 (79.3%) patients had anemia. Out of 8 patients with normal NT-proBNP levels, 5 patients had normal hemoglobin levels (12- 16 gm/dl).

Table 1: Correlation of age with NT-proBNP.

Age group	*No. of patients*	*Max NT-proBNP (pg/mL)*	*Min NT-proBNP (pg/mL)*	*Mean NT-proBNP (pg/mL)*
< 50 years	7	29263	50	6304.3±10482.7
51 - 60 years	6	16466	60	4879.5±6310.5
61 - 70 years	12	12726	50	3598.2±4138.6
71 - 80 years	8	35000	230	13499±14313.0
> 81 years	4	26685	530	11282.8±12200.1

Among 29 patients with elevated NT-proBNP levels, 20 (68.9%) patients had LA enlargement (LA dimension more than 4cm). In 8 patients with normal NT-proBNP levels, 7 patients had non dilated LA. Out of 37 patients, 26 patients (70.2%) had LV hypertrophy by echocardiography. In our study out of 37 patients, all patients had varying degrees of diastolic dysfunction by echocardiography.

Patients were classified into three groups according to LVEF as per the AHA guidelines. The mean NT-proBNP for each group was LVEF ≥ 50%=2272, LVEF 40–49% = 8161.5, and LVEF < 40% = 17302.7 (pg/ml). In our study, 21 patients (56.7%) had normal LV ejection fraction (HFpEF). By literature, HFpEF currently represents approximately 50 % of HF cases (Table 2).

Table 2: Correlation of LVEF with NT-proBNP.

LV EF	*No. of patients*	*Max NT-proBNP (pg/mL)*	*Min NT-proBNP (pg/mL)*	*Mean NT-proBNP (pg/mL)*
< 40%	10	35000	1910	17302.7±12173.6
40% - 50%	6	26685	380	8161.5±9433.5
> 50%	21	12726	50	2272.0±3083.9

In patients in whom NT-proBNP level was within normal limits, the mean e-GFR was more than 60ml/minute (normal e-GFR) (77.75ml/min). The mean e-GFR was less than 60ml/min (58.83ml/min) in patients with elevated NT-proBNP levels. The mean NT-proBNP levels in patients with low e-GFR rate(less than 60ml/min) was 11,606.6 pg/ml. Mean NT-proBNP levels in patients with normal e-GFR rate (more than 60ml/min) was 3199.2 pg/ml (Table 3).

Table 3: Correlation of NT-proBNP with e-GFR.

NT-proBNP (pg/ml)	*No. of patients*	*Max e-GFR (mL/min)*	*Min e-GFR (mL/min)*	*Meane-GFR (mL/min)*
< 300	8	103	44	77.8±20.8
> 300	29	104	6	58.8±25.6

As illustrated in Figure 1, the ROC curve analysis revealed that the Area Under Curve (AUC) was Age=0.315, p=0.078; NT-proBNP=0.371, p=0.0219; LVEF=0.696, p=0.096; e-GFR=0.668, p=0.111. The receiver operating characteristic (ROC) curve analysis indicates that the models used for predicting Age and NT-proBNP do not exhibit statistically significant discriminatory power in distinguishing between different outcomes or levels within the respective parameters. The ROC analysis conducted for predicting left ventricular ejection fraction (LVEF) and estimated Glomerular filtration rate (e-GFR) has yielded significant results. The ROC analysis has demonstrated statistical significance in assessing the predictive performance of the models for both LVEF and e-GFR.

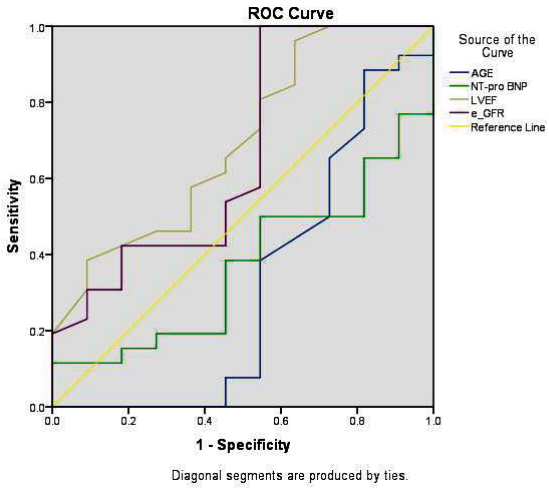

Figure 1: ROC curve analysis based on NT-proBNP, Age, LVEF, e-GFR.

Discussion

This study assessed the correlation of NT-proBNP levels with clinical and echocardiographic features in patients admitted with heart failure. Our study showed that average age at presentation with HF was 64 years. A study by Drozd et al [18] showed the mean age of 69.6 years at admission for HF. The Trivandrum heart failure registry showed that Indian patients with heart failure were 10 years younger (mean age 61 years) when compared with western population [20].

Common comorbidities in the study population were hypertension (91%), diabetes mellitus (68%), obstructive airway disease (21%), coronary artery disease (16%) and chronic kidney disease (4%). The aetiology of heart failure was ischemic heart disease in 59%, diabetes mellitus in 28%, COPD in 16% and CKD 18% of the study population [19]. In this study the cut off levels used for excluding HF was NT-proBNP level of 300 pg/ml. A meta-analysis published in 2015 clearly summarised the value of brain (B-type) natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP) and mid-regional pro-atrial NP (MR-proANP) in the acute setting, uniformly showed a very high negative predictive value when using low cut-off levels (i.e. BNP <100 pg/ml; NT-proBNP <300 pg/ml, MR-proANP <120 pmol/l) [10].

In our study, the mean NT-proBNP levels were higher in the 70 years and above age group compared with less than 70 years age group. A study by Athavale [11] on

the role of NT-proBNP in the diagnosis of heart failure showed a significant positive correlation between levels of NT-proBNP and age. In our study, 26 (70.2%) patients had anemia of various grades. Among 29 patients with elevated NT-proBNP levels, 23 (79.3%) patients had anemia. In a study on a group of 809 patients with coronary heart disease and no history of heart failure, anaemia remained independently associated with NT-proBNP even after adjustment for cardiovascular risk factors [9].

LA area and LA volume are powerful predictors of hospitalization or death among HF patients. Left atrial enlargement is the hallmark of the structural remodelling process. It occurs in response to chronic pressure and volume overload. LA enlargement occurs most commonly in association with diastolic dysfunction, left ventricular hypertrophy, mitral valvular disease, and systemic hypertension [7]. In our study, 20 (68.9%) patients had LA enlargement (LA dimension more than 4cm). 26 patients (70.2%) had LV hypertrophy by Echocardiography.

Lainchbury et al [8] found that among dyspnea patients, plasma NT-proBNP levels among patients with heart failure were significantly higher than those whose dyspnea was caused by other conditions. In our study the mean NT-proBNP levels for patients diagnosed with HFpEF (2272pg/ml) were lower than those with HFrEF (17302.7 pg/ml). In a study by Li et al, the concentration of NT-proBNP in HFrEF group (4756.03±541.53 pg/ml) was significantly higher when compared with HFpEF group (2807.44±249.31 pg/ml) [19].

PRIDE study [12, 14] examined the utility of NT pro-BNP, in addition to clinical judgment in assessment of patients with dyspnea, and concluded that the NT-proBNP measurement is a valuable addition to standard clinical assessment for the identification and exclusion of acute congestive heart failure in the emergency department setting. Multiple studies have shown that patients in acute heart failure had mean NT-proBNP levels >4000 pg/mL compared with 130 pg/ mL in those without heart failure [17]. Therefore, NT-proBNP levels can be utilised early as an adjunct to clinical evaluation when the cause of dyspnea is unclear. NT-proBNP can complement echocardiogram in HF diagnosis, with preserved ejection fraction (HFpEF) [3].

An additional concern with widespread testing of cardiac biomarkers such as BNP and NT-proBNP is the potential for misdiagnosis. Significantly abnormal NT-proBNP results, deemed to be false-positives, have been found in patients with sepsis and pulmonary embolism [13]. Increasing age, anemia and renal dysfunction are associated with increased NT-proBNP levels. Natriuretic peptide levels can be lower than expected in conditions like obesity, flash pulmonary edema, acute mitral regurgitation (due to causes upstream from the LV) and in patients on heart failure medications [16]. NT-proBNP levels are lower in overweight/obesity, even in those with diabetes [15]. In our study, 9 patients who presented with HF had normal NT-proBNP levels at admission.

Limitations: It is an observational study done at a single centre. Follow up of the patients and repeat testing of NT-proBNP levels after treatment was not done. Other factors that could influence NT-proBNP levels like BMI (Body mass index) were not taken into account, as height and weight were not measured on admission.

Conclusion

BNP and NT-proBNP levels have become important diagnostic tools in the diagnosis and management of heart failure. Although NT-proBNP testing has high sensitivity and specificity in the diagnosis of heart failure, the levels can be affected by many confounding factors such as age, renal function, anaemia and body mass. In our study it is observed that the NT-proBNP levels increased with advancing age, as shown by several studies. There was a negative correlation between NT-proBNP levels and LVEF. LA enlargement and LV hypertrophy were present in a majority of the studied population. Low e-GFR and low haemoglobin levels also showed negative correlation with NT-proBNP levels. When interpreting NT-proBNP levels, these factors have to be taken into account while making clinical decision and initiation of appropriate therapy.

Conflicts of interest

Authors declare no conflicts of interest.

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