Original Article

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N-Terminal Pro-Brain Natriuretic Peptide Levels in Patients Presenting with Acute Breathlessness in Emergency Department

Internal Medicine Section

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ABSTRACT

Introduction: Breathlessness is one of the most common symptoms in patients presenting to the emergency department. Differentiating Congestive Heart Failure (CHF) from other causes of dyspnea is of extreme importance. N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels may be valuable for the diagnosis of Heart Failure (HF) in patients with acute breathlessness when used in combination with other clinical information.

Aim: To find the utility of NT-proBNP levels in patients presenting with acute breathlessness.

Materials and Methods: This cross-sectional study was conducted on 255 patients presenting with acute breathlessness. Details of clinical history, clinical examination, laboratory tests, Electrocardiogram (ECG), X-ray chest, and 2D echocardiogram were collected from each patient. A 5 mL sample of peripheral venous blood was taken from the patients for the quantitative determination of NT-proBNP levels. Mann-Whitney U test was used to compare medians of continuous variables. Sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy were determined for NT-proBNP levels.

Results: The mean age of the patients was 58.9 years. The median NT-proBNP level was significantly higher in patients who had HF compared to respiratory failure and Hyperventilation Syndrome (HVS). The sensitivity and specificity of NT-proBNP level >450 pg/mL was 76.9% and 90.0%, respectively for patients <50 years of age. The sensitivity and specificity of NT-proBNP level >900 pg/mL was 82.9% and 92.3%, respectively for patients 50-75 years of age. The sensitivity and specificity of NT-proBNP level >1800 pg/mL was 61.5% and 100.0%, respectively for patients >75 years of age.

Conclusion: NT-proBNP measurement is a useful biochemical tool for the emergency room physician in the rapid and reliable diagnosis of HF in patients with acute breathlessness.

Keywords: Heart failure, Hyperventilation syndrome, Respiratory failure, Sensitivity, Specificity

INTRODUCTION

Acute breathlessness is one of the most common symptoms in patients presenting to the emergency department. It could be attributed to respiratory, metabolic, or cardiac diseases. It is extremely important to differentiate Acute Heart Failure (AHF) from other causes of acute breathlessness. HF is a major health problem over the past decade owing primarily to an ageing population and an increase in survival rates in patients with cardiovascular conditions [1,2]. Symptoms and signs of HF considerably overlap those of pulmonary disease [3-6]. The clinicians are often left with considerable diagnostic uncertainty after evaluating the patient's symptoms, physical examination, ECG and chest radiography. That leads to misdiagnosis and delays the initiation of appropriate therapy [5].

Misdiagnosis of HF causes morbidity because, the use of a treatment strategy for other conditions, such as Chronic Obstructive Pulmonary Disease (COPD), may be hazardous to patients with HF and vice-versa. For clinicians, an accurate, sensitive, and specific blood test would be a useful addition to the diagnosis of HF. Observational studies have suggested that, when used in conjunction with other clinical information, NT-proBNP levels may be useful in establishing, or ruling out the diagnosis of HF in patients with acute breathlessness [7-9]. The present study was aimed to find the utility of NT-proBNP levels in patients presenting with acute breathlessness for final diagnosis.

MATERIALS AND METHODS

This cross-sectional study was conducted between April 2016 to November 2017. After approval from the scientific advisory committee (Letter No: RECH/SAC/2015-15/1526) and the Institutional Ethics Committee (IEC) (Letter No: RECH/EC/2015-15/0011), written informed consent was obtained from all the patients. Patients >20 years of age of either sex presenting with acute breathlessness in the emergency room were included. Patients with severe renal insufficiency defined as serum creatinine >2.5 mg/dL were excluded. A sample size of 250 patients was calculated based on a previously published study [10], by using a formula [11] considering 80% power and a 5% probability of type I error to reject the null hypothesis.

A pre-tested study proforma was used to collect the information such as history, clinical examination, laboratory tests, ECG, X-ray chest and 2D echocardiogram. Cardiac failure was defined as clinical evidence of HF; pedal oedema, raised jugular venous pressure, crepitation on auscultation, chest X-ray suggestive of pulmonary oedema (evidence of Kerly A/B line), ECG suggestive of ST-T changes (ischemic sign) and 2D echo finding suggestive of systolic failure or diastolic failure. Systolic HF is defined as Ejection Fraction (EF)- ≤40% with signs and symptoms of HF. Diastolic HF is defined as EF ≥50% with signs and symptoms of HF [3,12].

HF is further divided into three groups [13].

1. HF with reduced ejection fraction (HFrEF)
   - Ejection fraction ≤40% on 2D echo
2. HF with mid-range ejection fraction (HFmrEF)
   - Ejection fraction 40-49% on 2D echo
3. HF with preserved ejection fraction (HFpEF)
   - Ejection fraction >50% on 2D echo

Respiratory failure is defined as history and clinical examination suggestive of bronchial asthma or COPD, chest X-ray suggestive

of signs of consolidation or changes of emphysema, an arterial oxygen tension (P_a, O_2) of <8.0 kPa (kilopascal) (60 mm Hg), an arterial carbon dioxide tension (P_a, CO_2) of >6.0 kPa (45 mm Hg) or both [14]. The HVS included acute psychosis or bipolar disorder and metabolic acidosis. The diagnosis is based on the Nijmegen questionnaire only after the organic disease has been ruled out or optimally controlled. It is often difficult to discriminate from asthma and anxiety disorder [15]. Metabolic acidosis (pH <7.35) is defined as an increased level of H+ ion in body and decrease in HCO_3 level <20 in arterial blood gas. Underlying physical problems were ruled out before the patient was labelled as having HVS [16].

A 5 mL sample of peripheral venous blood was taken from the patients. NT-proBNP was measured with the use of a fluorescence immunoassay kit (VITROS NT-proBNP reagent pack) for the quantitative determination of NT-ProBNP in a blood sample.

STATISTICAL ANALYSIS

Data collected were entered in Excel 2007 and analysis of data was done using Statistical Package for Social Sciences (SPSS) for Windows, Version 20.0 from IBM Corporation, Armonk, NY, USA. The data on categorical variables were shown as n (% of cases) and the data on continuous variables were shown as mean and Standard Deviation (SD). Non-parametric data were presented as median. The statistical significance of the inter-group difference of medians of continuous variables was tested using the Mann-Whitney U test. The diagnostic efficacy indices such as sensitivity, specificity, PPV, NPV and accuracy were determined for detections by NT-proBNP against the composite status of clinical, radiological, ECG and 2D-Echo diagnosis as a gold standard. A p-value <0.05 was considered to be statistically significant.

RESULTS

The mean±SD of the age of the patients was 58.9±13.4 years. The characteristics of the patients are depicted in [Table/Fig-1]. The median NT-proBNP level was significantly higher in patients who had HF compared to patients who had respiratory failure and HVS [Table/Fig-2].

Characteristics	n	%
Age (years)		
<50	69	27.1
50-75	159	62.4
>75	27	10.5
Gender		
Male	185	72.5
Female	70	27.5
Diagnosis		
Heart failure	173	67.8
Respiratory failure	59	23.1
Hyperventilation syndrome	23	9.1

[Table/Fig-1]: Characteristics of the patients.

The sensitivity and specificity of NT-proBNP at level >450 pg/mL was 76.9% and 90.0%, respectively for patients <50 years of age, sensitivity and specificity of NT-proBNP at level >900 pg/mL was 82.9% and 92.3%, respectively for patients 50-75 years of age, and sensitivity and specificity of NT-proBNP level >1800 pg/mL was 61.5% and 100.0% respectively for patients >75 years of age [Table/Fig-3].

DISCUSSION

The present research was conducted to study the utility of NT-proBNP levels in patients presenting with acute breathlessness for the diagnosis of HF. To evaluate the value of NT-proBNP in the diagnosis of HF, the sensitivity and specificity of NT pro-BNP measurements were compared with 2D echo findings. The median NT-proBNP level was significantly higher in patients with HF.

Category	Median NT-proBNP levels (pg/mL)	p-value
Heart failure		
Absent (n=82)	48.5	0.001*
Present (n=173)	3196.0	
Respiratory failure		
Absent (n=196)	2893.0	0.001 *
Present (n=59)	76.0	
Hyperventilation syndrome		
Absent (n=232)	2658.0	0.001*
Present (n=23)	48.0	

[Table/Fig-2]: Distribution of median NT-proBNP levels.
*p<0.05 considered significant; Mann-Whitney U test was used
NT-proBNP: N terminal-pro B type natriuretic peptide

Age group (years)	NT-proBNP levels (pg/mL)	Diagnostic efficacy	Heart failure (%)	Respiratory failure (%)	Hyper ventilation syndrome (%)
<50	>450	Sensitivity	76.9	13.0	15.8
		Specificity	90.0	34.8	40.0
		PPV	90.9	9.1	9.1
		NPV	75.0	44.4	55.6
		Accuracy	82.6	27.5	33.3
50-75	>900	Sensitivity	82.9	34.4	0.0
		Specificity	92.3	12.6	21.3
		PPV	99.2	9.0	0.0
		NPV	32.4	43.2	89.2
		Accuracy	83.6	16.9	20.7
>75	>1800	Sensitivity	61.5	20.0	-
		Specificity	100.0	31.8	40.7
		PPV	100.0	6.2	0.0
		NPV	9.1	63.6	100.0
		Accuracy	62.9	29.6	40.7

[Table/Fig-3]: Diagnostic efficacy of NT-proBNP levels.
NT-proBNP: N terminal-pro B type natriuretic peptide

Lainchbury JG et al., reported that sensitivity and specificity were between 80% and 94% and 70% and 89%, respectively for the diagnosis of HF if NT-proBNP cut-off value was taken as 300 pg/mL [17]. Mueller T et al., reported that cut-off value for the highest diagnostic accuracy was 825 ng/L for NT-proBNP (sensitivity 87%, specificity 81% and diagnostic accuracy 84%) [18]. In present study, sensitivity of NT-proBNP was between 61.5% and 82.9%, whereas specificity was between 90.0% and 100.0%. A study conducted by Wei B et al., reported that the plasma NT-proBNP level in the HF group was significantly higher than in the non-HF group (1,148.2 pg/mL Vs. 484.7 pg/mL) (p-value <0.01). It was further stated that the optimal plasma NT-proBNP cut-off point to diagnose HF was 700 pg/mL with a sensitivity of 75.9%, a specificity of 79.9%, an accuracy of 78.3%, a PPV of 67.9% and an NPV of 85.3% [19].

ProBNP investigation of Dyspnea in the Emergency Department (PRIDE) study conducted by Januzzi Jr JL et al., reported that the median NT-proBNP level in patients who had acute HF was 4,054 pg/mL Vs 131 pg/mL among patients who did not have HF (p-value <0.001). They further reported that NT-proBNP cut-off level of >450 pg/mL for patients <50 years of age and >900 pg/mL for patients ≥50 years of age was highly sensitive and specific for the diagnosis of acute HF (p-value <0.001). The NT-proBNP level <300 pg/mL was optimal for ruling out acute HF, with an NPV of 99%. An increased NT-proBNP was the strongest independent predictor to diagnose acute HF. The NT-proBNP testing was superior to clinical judgment alone for diagnosing acute HF [20].

Bay M et al., concluded that a single measurement of NT-proBNP at the time of hospital admission provided important information about Left Ventricular Ejection Fraction (LVEF). A sensitivity and specificity were 73% and 82%, respectively of raised NT-proBNP (≥357 pmol/L) identified patients with an LVEF of ≤40% (n=157). The NPV of having an NT-proBNP concentration <357 pmol/L was 98% [21]. Costello-Boerrigter LC et al., reported that for detecting an EF 40%, NT-proBNP had sensitivity and specificity in ages from 45 to 65 years was 100% and in age >65 years, it was 91% and 94%, respectively [22]. Goetze JP et al., reported that the mean NT-proBNP plasma concentration was two-fold higher in patients with Left Ventricular Systolic Dysfunction (LVSD) than without LVSD (p-value <0.0001) [23]. Tschöpe C et al., conducted a study on 68 symptomatic patients with isolated diastolic failure and preserved LVEF (≥50%) and 50 patients with regular Left Ventricular (LV) function. The median NT-proBNP plasma levels were elevated {189.54 pg/mL vs. 51.89 pg/mL (p-value <0.001)} and increased with greater severity of the diastolic failure (r=0.67, p-value <0.001). The NPV of NT-proBNP levels was the best of all methods (94%). NT-proBNP levels strongly correlated with indices of LV filling pressure, which was determined by invasive measurements [24]. Ikonomidis I et al., reported that levels of NT-proBNP were significantly higher in the group with LV diastolic dysfunction (p-value <0.05). They further stated that the NT-pro-BNP >941 pg/mL was a reliable predictor of LV diastolic failure [25]. Dong SJ et al., reported that NT-proBNP levels may be a useful adjunct in the characterisation of patients presenting with a history and/or symptoms compatible with LV systolic and/or diastolic failure [26]. Bayés-Genís A et al., reported that the decompensated and masked HF patients had significantly higher NT-proBNP values than patients with non-cardiac dyspnoea (normal ventricular function) (920 pg/mL and 978 pg/mL vs. 50 pg/mL; p-value <0.001 and p-value <0.01, respectively) [27]. Zaninotto M et al., reported that the NT-proBNP measurement is a biochemical tool that can be used for rapid and reliable marker of cardiac involvement in patients presenting in the emergency room with acute-severe dyspnea [28]. Pan Y et al., reported that median (IQR) NT-proBNP, ng/L levels in HFrEF, HFmrEF, HFpEF and Non-CHF patients were 1065 (828, 1923), 607 (431, 1086), 410 (272, 922), and 132 (69, 285) which was statistically significant (p-value <0.05) [29]. Behnes M et al., reported that the median NT-proBNP level was 3497 pg/mL and 320 pg/mL among patients with acute CHF, and without CHF (p-value <0.0001). It was further stated that an NT-proBNP cut-off level <300 pg/mL ruled out acute CHF (NPV 96%; sensitivity 96%). NT-proBNP ≥300 pg/mL was the strong predictor of acute CHF [30].

Limitation(s)

The present study was conducted in a single tertiary care hospital and represents only a small population. A control group without dyspnoea, no known cardiovascular risk factors and no clinical evidence of heart or lung disease were not studied in the present research. There was a preponderance of male patients in the study. A multicentric study with a large population is needed to substantiate the findings of the present research.

CONCLUSION(S)

The median NT-proBNP level was significantly higher in patients who had HF. Sensitivity and specificity of NT-proBNP level >450 pg/mL was 76.9% and 90.0%, respectively for patients <50 years. Sensitivity and specificity of NT-proBNP level >900 pg/mL was 82.9% and 92.3%, respectively for patients 50-75 years. Sensitivity and specificity of NT-proBNP level >1800 pg/mL was 61.5% and 100.0%, respectively for patients >75 years.

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