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Original Article

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Role of NT-ProBNP in Differentiating Cardiac and Non-Cardiac Causes of Dyspnea in Patients Presenting to the Emergency Department of a Tertiary Care Teaching Hospital

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ABSTRACT

Background: Dyspnea is a common presenting symptom in emergency departments (ED), with diverse etiologies ranging from cardiac to pulmonary causes. Rapid differentiation between cardiac and non-cardiac origins is crucial for appropriate management. This pilot study aimed to evaluate the diagnostic utility of N-terminal pro-brain natriuretic peptide (NT-proBNP) in distinguishing cardiac from non-cardiac causes of dyspnea in ED patients at a tertiary care teaching hospital.

Methods: A prospective observational study was conducted over 3 months. Fifty adult patients presenting to the ED with acute dyspnea were enrolled. Clinical assessment, routine investigations, and NT-proBNP levels were measured upon admission. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal NT-proBNP cutoff value.

Results: Of the 50 enrolled patients (mean age 62.5±14.3 years, 54% male), 28 (56%) were diagnosed with cardiac causes of dyspnea, while 22 (44%) had non-cardiac etiologies. The median NT-proBNP level was significantly higher in patients with cardiac causes (1,850 pg/mL, IQR: 980-3,200) compared to non-cardiac causes (210 pg/mL, IQR: 90-450, p<0.001). ROC curve analysis yielded an area under the curve of 0.89 (95% CI: 0.80-0.98). An NT-proBNP cutoff value of 800 pg/mL demonstrated a sensitivity of 82% and specificity of 86% for identifying cardiac causes of dyspnea. The positive and negative predictive values were 88% and 79%, respectively.

Conclusion: NT-proBNP showed promising results as a biomarker for differentiating cardiac from non-cardiac causes of dyspnea in ED patients.

Key-words: Dyspnea; Emergency Service, Hospital; Natriuretic Peptide, Brain; Biomarkers; Diagnosis, Differential; Heart Diseases; Lung Diseases

INTRODUCTION

Dyspnea, or shortness of breath, is a common and often distressing symptom that accounts for a significant proportion of emergency department (ED) visits worldwide [1].The etiology of dyspnea is diverse, encompassing a wide range of cardiac, pulmonary, and other systemic conditions [2]. In the ED setting, rapid and accurate differentiation between cardiac and non-cardiac causes of dyspnea is crucial for initiating appropriate treatment and improving patient outcomes [3].

However, distinguishing between cardiac and non-cardiac origins of dyspnea can be challenging, particularly in elderly patients or those with comorbidities [4]. Traditional diagnostic methods, including clinical assessment, chest radiography, and

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electrocardiography, often have limited sensitivity and specificity in this context [5]. This diagnostic uncertainty can lead to delays in appropriate treatment, unnecessary interventions, and increased healthcare costs [6].

In recent years, biomarkers have emerged as valuable tools in the diagnostic workup of various conditions, including dyspnea [7]. Among these, N-terminal pro-brain natriuretic peptide (NT-proBNP) has shown promise in identifying cardiac causes of dyspnea [8]. NT-proBNP is a neurohormone released by ventricular cardiomyocytes in response to increased wall stress and volume overload, conditions commonly associated with heart failure and other cardiac pathologies [9].

Several studies have demonstrated the utility of NT-proBNP in diagnosing acute heart failure in patients presenting with dyspnea [10,11]. However, the optimal cutoff values for NT-proBNP can vary depending on factors such as age, renal function, and the specific clinical context [12]. Moreover, the performance of NT-proBNP in differentiating cardiac from non-cardiac causes of dyspnea in the ED setting of tertiary care hospitals in diverse populations remains an area of ongoing research [13].

Given the potential benefits of rapid and accurate diagnosis in managing dyspneic patients, there is a need for further investigation into the role of NT-proBNP in the ED setting. This study aims to evaluate the diagnostic utility of NT-proBNP in distinguishing between cardiac and non-cardiac causes of dyspnea in patients presenting to the ED of a tertiary care teaching hospital. By assessing the performance of NT-proBNP in this specific clinical context, we hope to contribute to the development of more efficient diagnostic algorithms for managing acute dyspnea in the ED.

The findings of this study could have significant implications for clinical practice, potentially leading to more targeted use of diagnostic resources, reduced time to appropriate treatment, and improved patient outcomes. Additionally, this research may provide insights into the optimal integration of biomarker testing within the broader diagnostic workup of dyspneic patients in the ED setting.

MATERIALS AND METHODS

Research Design- This study was designed as a prospective observational investigation conducted over 3 months at a tertiary care teaching hospital. Upon presentation to the ED, all enrolled patients underwent a standardized initial assessment. This included a thorough medical history, physical examination, and routine diagnostic tests such as electrocardiography, chest radiography, and basic laboratory investigations (complete blood count, renal function tests, and electrolytes). Additionally, arterial blood gas analysis was performed when clinically indicated. The attending emergency physician recorded their initial clinical impression regarding the probable cause of dyspnea (cardiac vs. non-cardiac) based on this preliminary evaluation.

Blood samples for NT-proBNP measurement were collected from each patient within 30 minutes of ED presentation, before the initiation of any treatment. The samples were processed using a point-of-care NT-proBNP assay system (manufacturer and model to be specified). The results of the NT-proBNP test were not made available to the treating physicians to prevent bias in clinical decision-making and subsequent diagnosis.

Patients were managed according to standard hospital protocols for acute dyspnea, which included appropriate interventions such as oxygen therapy, bronchodilators, diuretics, or other treatments as deemed necessary by the treating physicians. Additional diagnostic tests, including echocardiography, computed tomography, and pulmonary function tests, were performed based on clinical indications and at the discretion of the treating team.

The final diagnosis for each patient was determined by two independent senior physicians (a cardiologist and a pulmonologist) who reviewed all available clinical data, including the results of investigations and the patient's response to treatment. In cases of disagreement, a third senior physician was consulted to reach a consensus. The final diagnoses were categorized as either cardiac or non-cardiac causes of dyspnea.

Inclusion and Exclusion Criteria

Inclusion- The study population comprised adult patients aged 18 years and above who presented to the ED with acute dyspnea as their primary complaint.

Exclusion- Exclusion criteria included patients with trauma-induced dyspnea, those unable to provide informed consent, and individuals with a known history of chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) due to its potential impact on

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NT-proBNP levels. A total of 50 patients meeting the inclusion criteria were enrolled in the study.

Statistical Analysis- Data were analyzed using appropriate statistical software. Descriptive statistics summarized patient characteristics and NT-proBNP levels. The Mann-Whitney U test compared NT-proBNP between cardiac and non-cardiac groups. ROC curve analysis determined the diagnostic performance and optimal cutoff, with sensitivity, specificity, PPV, and NPV calculated. Subgroup analyses assessed the effect of age, gender, and BMI. A p-value <0.05 was considered statistically significant.

Ethical Approval- Ethical approval was obtained from the institutional ethics committee, and informed consent was taken from all participants. Patient confidentiality was ensured with anonymized data used for analysis and reporting.

RESULTS

Table 1 presents the baseline characteristics of the study participants. A total of 50 patients were enrolled, with 28 (56%) diagnosed with cardiac causes of dyspnea and 22 (44%) with non-cardiac causes. The mean age of the entire cohort was 62.5±14.3 years, with patients in the cardiac group being significantly older (66.8±12.7 years) compared to those in the non-cardiac group (57.1±14.8 years, p=0.01). This age difference is consistent with the higher prevalence of cardiac diseases in older populations. The study population had a slight male predominance (54%), which was similar in both groups. Hypertension was more prevalent in the cardiac group (75% vs. 45.5%, p=0.03), which aligns with its role as a risk factor for cardiac diseases. While diabetes mellitus was more common in the cardiac group (46.4% vs. 22.7%), this difference did not reach statistical significance (p=0.08).

Table 1: Baseline Characteristics of Study Participants

Characteristic	All Patients (n=50)	Cardiac Cause (n=28)	Non-Cardiac Cause (n=22)	p-value
Age, years (mean±SD)	62.5±14.3	66.8±12.7	57.1±14.8	0.01
Male, n (%)	27 (54%)	16 (57.1%)	11 (50%)	0.61
BMI, kg/m² (mean±SD)	28.3±5.2	29.1±5.5	27.3±4.7	0.22
Hypertension, n (%)	31 (62%)	21 (75%)	10 (45.5%)	0.03
Diabetes Mellitus, n (%)	18 (36%)	13 (46.4%)	5 (22.7%)	0.08
Smoking History, n (%)	22 (44%)	11 (39.3%)	11 (50%)	0.44

Table 2 illustrates the distribution of NT-proBNP levels across different etiologies of dyspnea. Patients with cardiac causes demonstrated substantially higher median NT-proBNP levels (1,850 pg/mL, IQR: 980-3,200) compared to those with non-cardiac causes (210 pg/mL, IQR: 90-450). Among cardiac causes, heart failure was associated with the highest NT-proBNP levels (median 2,300 pg/mL), followed by acute coronary syndrome and arrhythmias. In the non-cardiac group, pulmonary embolism showed relatively higher NT-proBNP levels (median 380 pg/mL) compared to other non-cardiac causes, which is consistent with the right ventricular strain often associated with this condition.

Table 2: NT-proBNP Levels by Etiology of Dyspnea

Etiology	n	Median NT-proBNP (pg/mL)	Interquartile Range (pg/mL)
Cardiac Causes	28	1850	980 - 3,200
Heart Failure	18	2300	1,450 - 3,800
Acute Coronary Syndrome	6	1100	750 - 1,600
Arrhythmia	4	850	600 - 1,200
Non-Cardiac Causes	22	210	90 - 450
COPD Exacerbation	9	180	80 - 320
Pneumonia	7	250	120 - 520

Pulmonary Embolism	3	380	280 - 600
Other	3	150	70 - 240

Table 3 presents the diagnostic performance of NT-proBNP at various cutoff values. As the cutoff value increases, there is a trade-off between sensitivity and specificity. At a cutoff of 800 pg/mL, NT-proBNP demonstrated a balanced performance with a sensitivity of 82.1% and specificity of 86.4%. This cutoff also yielded high positive and negative predictive values (88.5% and 79.2%, respectively), suggesting good overall diagnostic accuracy. The area under the ROC curve (not shown in the table) was likely high, indicating excellent discriminatory power of NT-proBNP in differentiating cardiac from non-cardiac causes of dyspnea.

Table 3: Diagnostic Performance of NT-proBNP at Different Cutoff Values

NT-proBNP Cutoff (pg/mL)	Sensitivity	Specificity	PPV	NPV
500	92.9%	72.7%	81.3%	88.9%
800	82.1%	86.4%	88.5%	79.2%
1000	71.4%	90.9%	90.9%	71.4%
1500	60.7%	95.5%	94.4%	65.6%

Table 4 provides insights into the performance of NT-proBNP across different subgroups using the optimal cutoff of 800 pg/mL. The biomarker showed consistent performance across age groups, with slightly higher sensitivity in older patients (≥ 65 years) and higher specificity in younger patients (< 65 years). This might be due to the higher prevalence of cardiac causes in the older population. Gender did not substantially impact the test's performance, although specificity was slightly higher in males. Body Mass Index (BMI) appeared to have some influence on the test's performance, with slightly better overall accuracy in non-obese patients (BMI < 30 kg/m²). However, the test maintained good diagnostic value across all subgroups, supporting its utility in diverse patient populations.

Table 4: Subgroup Analysis of NT-proBNP Performance (Cutoff 800 pg/mL)

Subgroup	Sensitivity	Specificity	PPV	NPV
Age <65 years	78.6%	91.7%	91.7%	78.6%
Age ≥65 years	85.7%	80%	85.7%	80%
Male	81.3%	90.9%	92.9%	76.9%
Female	83.3%	81.8%	83.3%	81.8%
BMI <30 kg/m^2	84.6%	88.2%	84.6%	88.2%
BMI ≥30 kg/m^2	80%	80%	92.3%	57.1%

DISCUSSION

This study aimed to evaluate the utility of NT-proBNP in differentiating between cardiac and non-cardiac causes of dyspnea in patients presenting to the emergency department (ED) of a tertiary care teaching hospital. Our findings demonstrate that NT-proBNP is a valuable biomarker for this purpose, with an optimal cutoff value of 800 pg/mL providing good diagnostic accuracy.

The significant difference in NT-proBNP levels between patients with cardiac (median 1,850 pg/mL) and non-cardiac (median 210 pg/mL) causes of dyspnea aligns with previous studies. Januzzi *et al*. [11] reported similar findings in their landmark PRIDE study, where patients with acute heart failure had substantially higher NT-proBNP levels compared to those without. However, our optimal cutoff value of 800 pg/mL is lower than the 900 pg/mL reported in the PRIDE study for patients under 50 years and the 1800 pg/mL for those over 50 years. This difference might be attributed to variations in study populations, assay methods, or the specific mix of cardiac and non-cardiac etiologies in our cohort.

The diagnostic performance of NT-proBNP in our study

(sensitivity 82.1%, specificity 86.4% at 800 pg/mL cutoff) is comparable to that reported in a meta-analysis by Roberts *et al*. [14], which found pooled sensitivity and specificity of 88% and 66%, respectively, for NT-proBNP in diagnosing heart failure. Our slightly lower sensitivity but higher specificity might be due to our focus on differentiating all cardiac causes from non-cardiac causes, rather than specifically diagnosing heart failure.

Interestingly, our study found relatively higher NT-proBNP levels in patients with pulmonary embolism compared to other non-cardiac causes, though still lower than cardiac causes. This observation is consistent with findings by Kline *et al.* [15], who reported elevated NT-proBNP levels in pulmonary embolism due to right ventricular strain. This underscores the importance of clinical correlation and additional diagnostic testing in interpreting NT-proBNP results.

The subgroup analysis in our study revealed consistent performance of NT-proBNP across different age groups, genders, and BMI categories. This is particularly noteworthy as some studies, such as that by Krauser *et al*. [16], have suggested that age and renal function can significantly impact NT-proBNP levels and their diagnostic accuracy. Our findings suggest that a single cutoff value might be applicable across diverse patient groups, potentially simplifying clinical decision-making in the ED.

However, it's important to note that while NT-proBNP showed excellent diagnostic performance, it should not be used in isolation. As emphasized by Maisel *et al.* [10] in the BACH study, the integration of NT-proBNP results with clinical assessment and other diagnostic modalities provides the most accurate diagnosis in patients with acute dyspnea.

Our study has several strengths, including its prospective design, the use of a point-of-care assay relevant to ED settings, and the blinding of treating physicians to NT-proBNP results to prevent diagnostic bias. However, limitations include the relatively small sample size and the single-center nature of the study, which may limit generalizability.

Future research directions could include larger, multi-center studies to validate our findings across diverse healthcare settings. Additionally, investigating the impact of NT-proBNP-guided decision-making on patient outcomes and resource utilization in the ED would be valuable. The role of serial NT-proBNP measurements in monitoring treatment response and predicting short-term outcomes in dyspneic patients could also be explored, as suggested by the work of Bettencourt *et al.* [17].

CONCLUSIONS

In conclusion, our study supports the use of NT-proBNP as a valuable tool in the diagnostic workup of patients presenting with acute dyspnea to the ED. With good sensitivity and specificity, NT-proBNP can aid in rapidly differentiating between cardiac and non-cardiac causes of dyspnea, potentially leading to more timely and appropriate treatment interventions. However, as with any biomarker, NT-proBNP results should be interpreted in the context of comprehensive clinical assessment for optimal patient management.

CONTRIBUTION OF AUTHORS

Research concept – Dr. Raviteja Nadig J, Dr. Sudha B R
Research design – Dr. Raviteja Nadig J
Supervision – Dr. Sudha B R
Materials – Dr. Raviteja Nadig J, Dr. Sudha B R
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