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Original Research Article

ROLE OF N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE (NT-PROBNP) IN DIFFERENTIATING CARDIAC FROM NON-CARDIAC CAUSES OF ACUTE DYSPNEA: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Acute dyspnea is a common emergency presentation with diverse cardiac and non-cardiac causes. NT-proBNP, a stable marker of ventricular wall stress, has been proposed as a rapid tool to differentiate cardiac from non-cardiac dyspnea and to predict outcome. The objective is to evaluate the role of NT-proBNP in differentiating cardiac from non-cardiac causes of acute dyspnea and to assess its association with mortality in cardiac causes.

Materials and Methods: This prospective observational study enrolled 99 adults aged 20-80 years presenting with acute dyspnea to the Emergency Medicine department over 18 months. NT-proBNP was measured by the ELFA method at presentation. Patients were categorized as cardiac or non-cardiac dyspnea, and followed for CCU admission and in-hospital outcome. Student's t-test and chi-square test were used for analysis, with $p<0.05$ considered significant.

Results: Of 99 patients, 52 (52.5%) had cardiac and 47 (47.5%) had non-cardiac dyspnea. Mean NT-proBNP was markedly higher in cardiac dyspnea (3088.77 pg/mL) than non-cardiac dyspnea (258.66 pg/mL, $p<0.001$). A cutoff of >600 pg/mL identified cardiac dyspnea with 92.3% sensitivity and 93.6% specificity ($p<0.001$). CCU admission was required in 33 patients, predominantly with cardiac dyspnea ($p<0.001$). Mortality was higher in cardiac dyspnea (7/52 vs 1/47, $p=0.03$), and mean NT-proBNP was significantly higher among non-survivors than survivors (5066 vs 1632 pg/mL, $p<0.001$). NT-proBNP also correlated significantly with echocardiographic abnormalities ($p<0.001$), though not with specific cardiac pathology subtype ($p=0.324$).

Conclusion: NT-proBNP is a reliable, rapid, and non-invasive biomarker for differentiating cardiac from non-cardiac causes of acute dyspnea, and independently correlates with CCU requirement, echocardiographic dysfunction, and mortality, supporting its routine use in emergency risk stratification.

Keywords: NT-proBNP; acute dyspnea; heart failure; biomarker; emergency medicine; mortality.

INTRODUCTION

Acute dyspnea is one of the most frequent and diagnostically challenging presentations encountered in emergency departments worldwide. It is defined as the subjective sensation of breathing discomfort, variably described by patients as breathlessness, chest tightness, air hunger, or

difficulty in breathing.[1] Because dyspnea may arise from a wide spectrum of etiologies ranging from benign to life-threatening, rapid identification of the underlying cause is essential for timely management and improved outcomes.

The differential diagnosis of acute dyspnea broadly spans cardiac causes—such as acute heart failure, cardiomyopathy, ischemic heart disease, and valvular dysfunction—and non-cardiac causes, including COPD, asthma, pneumonia, pulmonary embolism, metabolic acidosis, anemia, and anxiety-related conditions.[2] Overlapping comorbidities, particularly in elderly patients, further complicate diagnosis, and dyspnea itself is recognized as an independent predictor of morbidity and mortality, underscoring the need for accurate and early etiological differentiation.

The perception of dyspnea is governed by complex central and peripheral physiological pathways, including medullary and pontine respiratory centres, carotid and aortic body chemoreceptors, and pulmonary stretch and skeletal muscle afferents; an imbalance between respiratory demand and ventilatory capacity underlies the subjective sensation of breathlessness.[3] Traditional diagnostic tools—clinical examination, chest radiography, electrocardiography, arterial blood gas analysis, and echocardiography—can be time-consuming, operator-dependent, or inconclusive in the emergency setting, prompting growing interest in biochemical markers that enable rapid differentiation of cardiac from non-cardiac breathlessness.[4]

Brain natriuretic peptide (BNP) is a 32-amino acid hormone released predominantly from ventricular myocardium in response to wall stretch, pressure overload, and volume expansion.[5] Pro-BNP is cleaved into biologically active BNP and the inactive N-terminal fragment, NT-proBNP; although released in equimolar amounts, NT-proBNP has a longer half-life and greater plasma stability, making it more suitable for clinical measurement. In pathological states such as heart failure, ventricular production of BNP and NT-proBNP is markedly upregulated, so elevated circulating levels reflect myocardial stress and ventricular dysfunction, providing a biochemical window into cardiac hemodynamic status.[6]

NT-proBNP has gained clinical significance as a sensitive and specific biomarker for heart failure in patients with acute dyspnea, with reported correlation to severity of ventricular dysfunction, functional class, and prognosis, and marked elevations associated with increased hospitalization, adverse cardiovascular events, and mortality. Given the diagnostic uncertainty often encountered in emergency settings, this study was designed to evaluate the role of NT-proBNP in distinguishing cardiac from non-cardiac causes of acute dyspnea and to assess its association with mortality among patients with cardiac causes.

Aims and Objectives

1. To differentiate acute dyspnea into cardiac or non-cardiac origin with the help of NT-proBNP.
2. To determine the level of NT-proBNP associated with increased mortality among patients with cardiac causes of dyspnea.

MATERIALS AND METHODS

Study design and setting: This prospective observational study was conducted in the Department of Emergency Medicine at P.E.S. Institute of Medical Sciences and Research (PESIMSR), Kuppam, Andhra Pradesh, a tertiary care teaching hospital serving both urban and rural populations, over a period of 18 months.

Study population and eligibility: All patients aged 20-80 years presenting with acute dyspnea to the Emergency Medicine department during the study period were considered eligible. Patients below 20 years of age, those with previously diagnosed chronic heart failure, a history of blunt chest trauma, or documented accidental foreign body aspiration were excluded.

Sample size and sampling: A purposive sampling method was used to recruit consecutive eligible patients presenting during the study period, yielding a total of 99 patients.

Study procedure: Patients presenting with acute dyspnea were evaluated clinically as per standard emergency protocols, with initial assessment and stabilization followed by relevant investigations. Blood samples were sent to the Department of Biochemistry for estimation of NT-proBNP using the ELFA (Enzyme-Linked Fluorescent Assay) method. Clinical findings, investigation results, echocardiographic assessment, and final diagnosis (cardiac or non-cardiac) were documented in a structured proforma, and patients were followed through their hospital course for CCU admission and in-hospital outcome (survived or died).

Variables: Independent variables included age, sex, smoking status, NT-proBNP level, cardiac pathology subtype, and echocardiographic findings. Outcome variables were etiological classification (cardiac vs non-cardiac), CCU admission, and in-hospital mortality.

Statistical analysis: Data were entered in Microsoft Excel and analysed using SPSS version 23.0. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test; continuous variables were expressed as mean ± standard deviation and compared using the independent-samples Student's t-test between two groups, or one-way ANOVA across more than two groups. A two-sided p value <0.05 was considered statistically significant.

RESULTS

A total of 99 patients presenting with acute dyspnea were enrolled, of whom 52 (52.5%) were classified as cardiac and 47 (47.5%) as non-cardiac in etiology. The baseline demographic and clinical profile of the cohort, stratified by etiology, is summarized in Table 1. The 20-30 year and 61-70 year age groups were each the largest, contributing 21.2% of the cohort; among cardiac patients the 51-60 year group predominated (n=11), whereas among non-cardiac patients the 61-70 year group was most common (n=12), though this age distribution did not differ significantly by etiology (p=0.25). Overall, 52.5% of patients were female and 47.5% male, with an even split by sex within the cardiac group and a modest female preponderance in the non-cardiac group (p=0.74). Just over half the cohort (53.5%) had a smoking history, distributed similarly between cardiac and non-cardiac groups (p=1.00), indicating that none of age, sex, or smoking status reliably discriminated cardiac from non-cardiac dyspnea in this cohort.

Table 1: Baseline demographic and clinical profile according to etiology of dyspnea (N=99)

Parameter	Cardiac (n=52)	Non-cardiac (n=47)	Total (n=99)	p value
Age group (years)				
20–30	10	11	21 (21.2%)	
31–40	10	9	19 (19.2%)	
41–50	6	7	13 (13.1%)	
51–60	11	2	13 (13.1%)	
61–70	9	12	21 (21.2%)	
71–80	6	6	12 (12.1%)	0.25
Gender				
Male	26	21	47 (47.5%)	
Female	26	26	52 (52.5%)	0.74
Smoking status				
Smoker	28	25	53 (53.5%)	
Non-smoker	24	22	46 (46.5%)	1.00
Overall etiology of dyspnea				
n (%)	52 (52.5%)	47 (47.5%)	99 (100%)	—

NT-proBNP levels according to etiology, and the diagnostic performance of a >600 pg/mL cutoff, are presented in Table 2. Mean NT-proBNP was markedly and significantly higher in cardiac dyspnea (3088.77 pg/mL) than in non-cardiac dyspnea (258.66 pg/mL, p<0.001). Applying the >600 pg/mL cutoff, 92.3% of cardiac patients (48/52) tested positive compared with only 6.4% of non-cardiac patients (3/47, p<0.001), yielding a sensitivity of 92.3%, specificity of 93.6%, positive predictive value of 94.1%, and negative predictive value of 91.7% for cardiac etiology.

Table 2: NT-proBNP levels according to etiology and diagnostic performance of the >600 pg/mL cutoff

Parameter	Cardiac	Non-cardiac
Mean NT-proBNP (pg/mL) by etiology		
Mean NT-proBNP (pg/mL)	3088.77	258.66
Independent t-test	p < 0.001	
NT-proBNP diagnostic cutoff (>600 pg/mL)		
NT-proBNP > 600 pg/mL — n (%)	48 (92.3%)	3 (6.4%)
NT-proBNP ≤ 600 pg/mL — n (%)	4 (7.7%)	44 (93.6%)
Chi-square test	p < 0.001	
Diagnostic accuracy of the 600 pg/mL cutoff		
Sensitivity	92.3%	
Specificity	93.6%	
Positive predictive value	94.1%	
Negative predictive value	91.7%	

Clinical outcomes and their relationship with NT-proBNP are shown in [Table 3]. Overall in-hospital mortality was 8.1% (8/99), and was significantly higher among patients with cardiac dyspnea (7/52) than non-cardiac dyspnea (1/47, p=0.03). CCU admission was required in 33 patients overall, again predominating heavily in the cardiac group (30/52) compared with the non-cardiac group (3/47, p<0.001). Mean NT-proBNP was significantly higher among patients who died (5066 pg/mL) than among survivors (1632 pg/mL, p<0.001), reinforcing its prognostic as well as diagnostic value.

Table 3: Clinical outcomes, CCU admission, and NT-proBNP levels by outcome

Parameter	Cardiac	Non-cardiac	Total	p value
Outcome				
Survived — n	45	46	91 (91.9%)	
Died — n	7	1	8 (8.1%)	0.03
CCU admission				

Required — n	30	3	33	
Not required — n	19	47	66	<0.001
Mean NT-proBNP (pg/mL) by outcome				
Survived	1632	—	—	
Died	5066	—	—	<0.001

NT-proBNP levels according to specific cardiac pathology and echocardiographic findings are detailed in [Table 4]. Among the 52 cardiac patients, mean NT-proBNP was numerically highest in congestive heart failure (3931.2 pg/mL) and lowest among the cardiac subtypes in ischemic cardiomyopathy (2903.9 pg/mL), with dilated cardiomyopathy and hypertensive heart disease intermediate; however, these differences between cardiac pathology subtypes were not statistically significant (p=0.324). In contrast, when the full cohort was stratified by echocardiographic finding, NT-proBNP was lowest in patients with normal LV function (209.6 pg/mL) and markedly and significantly elevated in those with global hypokinesia, LV dysfunction, dilated LV, or reduced LVEF (range 3099-3449 pg/mL, p<0.001), demonstrating a strong correlation between NT-proBNP and objective evidence of ventricular dysfunction.

Table 4: NT-proBNP levels according to cardiac pathology subtype and echocardiographic findings

Category	n	Mean NT-proBNP (pg/mL) ± SD	p value
Cardiac pathology (n=52) — one-way ANOVA			
Congestive heart failure	13	3931.2 ± 1463.3	
Dilated cardiomyopathy	17	3319.8 ± 1580.3	
Hypertensive heart disease	13	2974.7 ± 1505.7	
Ischemic cardiomyopathy	9	2903.9 ± 1338.5	0.324
Echocardiographic finding (N=99) — one-way ANOVA			
Normal LV function	47	209.6 ± 94.5	
Dilated LV	8	3205.1 ± 1390.0	
Global hypokinesia	12	3436.6 ± 1683.1	
LV dysfunction	18	3448.7 ± 1506.4	
Reduced LVEF	14	3099.4 ± 1535.2	<0.001

DISCUSSION

This prospective study of 99 patients presenting with acute dyspnea demonstrates that NT-proBNP is a robust biomarker for distinguishing cardiac from non-cardiac etiology, and that it additionally tracks with echocardiographic severity, need for intensive care, and mortality.

The age distribution observed here—with cardiac dyspnea predominating in the 51-60 year group and non-cardiac dyspnea in the 61-70 year group, though without overall statistical significance (p=0.25)—is broadly consistent with Shaikh et al., who found that patients with cardiac dyspnea were significantly older than those with non-cardiac causes,[7] and with Mueller et al., who observed a progressive rise in heart failure prevalence with advancing age.[8] The predominance of cardiac dyspnea in the 51-60 year group likely reflects the cumulative burden of hypertension, diabetes, and atherosclerosis manifesting clinically at this stage, with reduced ventricular compliance and increased myocardial stiffness raising intracardiac pressures; the shift toward non-cardiac dyspnea in older patients may instead reflect the rising prevalence of COPD and age-related decline in respiratory muscle strength. That age alone did not reach significance as a discriminator reinforces the need for objective biomarkers rather than demographic profiling.

Gender and smoking status likewise failed to distinguish cardiac from non-cardiac dyspnea in this cohort (p=0.74 and p=1.00 respectively), consistent with Mueller et al,[8] who found gender did not significantly influence the cardiac/non-cardiac split, and with Maisel et al., who reported no significant sex-based difference in BNP diagnostic accuracy.[9] The near-equal sex distribution among cardiac patients may reflect the evolving epidemiology of heart failure, including a rising incidence of heart failure with preserved ejection fraction among post-menopausal women, while the comparable smoking prevalence across groups likely reflects smoking's shared role as a risk factor for both ischemic heart disease and COPD.

The near-equal overall split between cardiac (52.5%) and non-cardiac (47.5%) causes mirrors the substantial proportion of heart failure among dyspneic patients reported in the landmark Breathing Not Properly study by Maisel et al,[9] and in the cohort described by Mueller et al,[8] and highlights the genuine diagnostic overlap clinicians face, since conditions such as pulmonary edema, pneumonia, COPD, and anxiety disorders can present with similar clinical features.

The markedly higher mean NT-proBNP in cardiac dyspnea (3088.77 vs 258.66 pg/mL, p<0.001) observed here is consistent with Shaikh et al,[7] who reported an even larger absolute separation (10,918 vs 461 pg/mL), and with Januzzi et al., who similarly found significantly elevated NT-proBNP in heart failure compared with non-cardiac dyspnea.[10] Mueller et al. also demonstrated that incorporating NT-proBNP significantly improved diagnostic accuracy in patients presenting with dyspnea.8 This separation is explained by the pathophysiology of NT-proBNP release from

ventricular myocytes in response to wall stress and volume overload, features largely absent in non-cardiac dyspnea.

The >600 pg/mL cutoff performed with high sensitivity (92.3%) and specificity (93.6%) in this cohort, in close agreement with the excellent diagnostic accuracy reported for BNP and NT-proBNP thresholds by Maisel et al,[9] and Januzzi et al,[10] the latter specifically validating NT-proBNP thresholds with high sensitivity and specificity across cutoff ranges in the PRIDE study. The very low false-positive rate among non-cardiac patients supports the use of this threshold as an effective rule-in and rule-out test in the emergency setting.

Mortality was significantly higher in cardiac dyspnea (7/52 vs 1/47, p=0.03), and mean NT-proBNP was significantly elevated among non-survivors compared with survivors (5066 vs 1632 pg/mL, p<0.001), findings that parallel Januzzi et al.'s observation that elevated NT-proBNP independently predicts adverse outcomes and mortality,10 and Mueller et al.'s report that elevated NT-proBNP correlates with higher rates of hospitalization, intensive care need, and death.8 Progressive myocardial dysfunction, arrhythmia, and hemodynamic instability in cardiac dyspnea plausibly underlie this excess mortality, while many non-cardiac causes carry a more favourable prognosis when appropriately treated.

Similarly, CCU admission was required overwhelmingly in the cardiac group, consistent with Mueller et al.'s finding that elevated NT-proBNP predicts need for intensive cardiac care,[8] and Maisel et al.'s observation that BNP correlates with heart failure severity and hospitalization need.[9] This reflects the intensive monitoring, intravenous diuretic and inotropic therapy, and arrhythmia management that cardiac dyspnea frequently demands, in contrast to the general-ward management often sufficient for non-cardiac causes.

NT-proBNP did not differ significantly across cardiac pathology subtypes (p=0.324), echoing Januzzi et al.'s observation that considerable overlap exists in NT-proBNP levels across different cardiac pathologies despite its diagnostic value for cardiac involvement overall,[10] and Maisel et al.'s finding that BNP correlates with heart failure severity but not reliably with specific underlying etiology.9 This likely reflects the fact that NT-proBNP responds to shared hemodynamic stressors—elevated ventricular pressure and volume overload—rather than to a specific disease process, a limitation compounded by relatively small subgroup sizes in the present cohort.

By contrast, NT-proBNP correlated strongly and significantly with echocardiographic findings (p<0.001), lowest in normal LV function and markedly elevated in global hypokinesia, LV dysfunction, dilated LV, and reduced LVEF, in keeping with Januzzi et al.'s and Mueller et al.'s reports that NT-proBNP closely tracks ejection fraction and ventricular dilation.[8,10] This is explained by the direct stimulus of increased end-diastolic pressure, wall stress, and neurohormonal activation on myocardial NT-proBNP secretion, reinforcing the complementary relationship between this biomarker and echocardiographic imaging in the evaluation of dyspnea.

Strengths and Limitations

- The sample size of 99 patients was relatively modest, limiting statistical power for subgroup analyses, particularly in differentiating between individual cardiac pathologies.
- The study was conducted at a single tertiary care centre, which may introduce referral bias and limit generalizability to primary care or community settings.
- NT-proBNP levels can be influenced by confounding factors such as renal dysfunction, age, and obesity, which were not fully adjusted for in this analysis.
- Only a single NT-proBNP value at presentation was used; serial measurements were not performed, limiting assessment of dynamic change and its prognostic significance over time.

CONCLUSION

This study demonstrates that NT-proBNP is a highly effective biomarker in the evaluation of acute dyspnea, with significantly elevated levels in cardiac compared to non-cardiac causes and excellent diagnostic performance at a cutoff of >600 pg/mL. NT-proBNP levels also correlated strongly with clinical severity, echocardiographic dysfunction, need for CCU admission, and in-hospital mortality, while demographic factors such as age, sex, and smoking status did not reliably distinguish etiology. Although NT-proBNP did not differentiate between specific cardiac pathology subtypes, its overall diagnostic and prognostic value supports its integration into routine emergency evaluation of dyspnea as a rapid, reliable, and non-invasive tool to guide early diagnosis, risk stratification, and management.

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