



Original Article

Role of NT-proBNP in the Evaluation of Heart Failure with Preserved Ejection Fraction

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ABSTRACT

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Background: Heart failure with preserved ejection fraction (HFpEF) accounts for nearly 50% of heart failure cases and remains diagnostically challenging due to preserved systolic function despite significant diastolic dysfunction. N-terminal pro-B-type natriuretic peptide (NT-proBNP) reflects myocardial stress and may facilitate early diagnosis. **Objective:** To evaluate the role of serum NT-proBNP in the early diagnosis of HFpEF and its association with clinical and echocardiographic parameters. **Materials and Methods:** This cross-sectional analytical study included 112 patients aged 40–80 years presenting with acute dyspnoea and preserved left ventricular ejection fraction (LVEF $\geq 50\%$). Serum NT-proBNP levels were measured and patients were stratified into two groups based on NT-proBNP levels. Clinical, anthropometric, blood pressure, and echocardiographic variables were analyzed. **Results:** Patients with elevated NT-proBNP were significantly older (67.5 ± 10.5 vs 41.9 ± 7.9 years; $p = 0.04$), had higher body mass index (31.4 ± 1.8 vs 24.2 ± 1.5 kg/m²; $p < 0.001$), higher systolic blood pressure (163.3 ± 31.2 vs 139.1 ± 8.9 mmHg; $p < 0.001$), and higher diastolic blood pressure (105.5 ± 4.5 vs 84.6 ± 6.6 mmHg; $p < 0.001$). Mean LVEF was higher in the elevated NT-proBNP group ($72.5 \pm 8.2\%$ vs $62.5 \pm 8.5\%$; $p < 0.001$). Serum NT-proBNP levels were markedly increased (1173.9 ± 21.5 vs 115.3 ± 13.4 pg/mL; $p < 0.001$) and showed a moderate positive correlation with the E/A ratio ($r = 0.483$, $p = 0.001$). **Conclusion:** NT-proBNP is a valuable biomarker for early identification of HFpEF. Elevated levels are associated with advanced age, obesity, hypertension, and impaired diastolic function, supporting its routine use in patients presenting with acute shortness of breath.

Keywords: Heart failure with preserved ejection fraction (HFpEF), N-terminal pro-B-type natriuretic peptide (NT-proBNP), Diastolic dysfunction, Natriuretic peptides

Introduction

Heart failure (HF) is a complex clinical syndrome resulting from the heart's inability to meet the metabolic demands of the body, either due to impaired systolic pumping capacity, termed heart failure with reduced ejection fraction (HFrEF), or due to impaired ventricular relaxation and filling, termed heart failure with preserved ejection fraction (HFpEF), in which elevated preload and end-diastolic pressure occur despite a preserved ejection fraction.^{1,2} HFpEF now accounts for approximately 50% of all heart failure cases and its prevalence is anticipated to rise given an aging global population and increasing comorbidities such as obesity and diabetes.^{1,2} This condition is characterized by a left ventricular ejection fraction (LVEF) of $\geq 50\%$, accompanied by evidence of diastolic dysfunction and elevated natriuretic peptide levels, presenting with typical symptoms of heart failure primarily due to excessive left ventricular filling pressure.^{1,2} Historically, HFpEF was often referred to as diastolic heart failure, emphasizing the crucial role of impaired ventricular relaxation and increased myocardial stiffness rather than reduced systolic contractility.¹

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a 76-amino acid peptide derived from the 108-amino acid precursor proBNP.³ This biologically inert fragment is released by ventricular cardiomyocytes in response to myocardial stretch and biomechanical stress, serving as a vital diagnostic marker in cardiovascular disease.³ NT-proBNP possesses a longer half-life (60-120 minutes) and circulates at higher concentrations in the blood compared to its active counterpart,

B-type natriuretic peptide (BNP), making it more stable and less prone to rapid degradation both *in vivo* and *in vitro*.^{3,4} The robust release of NT-proBNP in response to ventricular wall tension positions it as a key cardiovascular diagnostic marker for detecting early myocardial strain.^{4,5}

While the clinical utility of NT-proBNP is well-established in HFrEF, its role in HFpEF has been an area of active investigation.^{4,6} The varied etiology and complex pathophysiology of HFpEF, often linked to comorbidities such as hypertension, diabetes, and obesity, make its diagnosis and management particularly challenging.¹ Nevertheless, NT-proBNP provides valuable prognostic and diagnostic information in HFpEF, with elevated levels correlating with increased morbidity and mortality.^{7,8} The continuous re-evaluation of NT-proBNP thresholds, especially in diverse patient populations such as those with obesity or renal impairment, is crucial for optimizing its diagnostic accuracy. This study aims to evaluate the role of NT-proBNP in the early diagnosis of heart failure with preserved ejection fraction by correlating its levels with clinical and echocardiographic parameters of diastolic dysfunction.

Materials and methods

This cross-sectional analytical study was conducted in the Department of Biochemistry in collaboration with the Department of Cardiology at a tertiary care hospital, over a period of five months. Informed written consent was obtained from all participants prior to enrolment.

A total of 112 patients aged 40–80 years presenting with acute shortness of breath were included. All patients underwent two-dimensional echocardiography, and only those with preserved left ventricular ejection fraction (LVEF $\geq 50\%$) were enrolled. Based on serum NT-proBNP levels, patients were categorized into two groups: Group 1, comprising patients with LVEF $\geq 50\%$ and elevated NT-proBNP levels, and Group 2, comprising patients with LVEF $\geq 50\%$ and lower NT-proBNP levels.

Patients were recruited consecutively from the casualty and cardiology outpatient departments. Inclusion criteria included preserved ejection fraction with acute dyspnoea and a known history of hypertension, atrial fibrillation, left ventricular hypertrophy, diabetes mellitus, or obesity. Patients with reduced ejection fraction, anaemia, chronic obstructive pulmonary disease, bronchial asthma, renal or liver dysfunction, or other structural heart diseases were excluded.

Venous blood samples were collected under aseptic conditions into plain vacutainer vials and centrifuged for 10 minutes to obtain serum. Serum NT-proBNP was measured using an immunoassay-based analyser (AFIAS-6) according to the manufacturer's instructions. Anthropometric parameters including height, weight, and blood pressure were recorded, and ejection fraction was assessed using 2D echocardiography.

Data were tabulated in Microsoft Excel and analysed using SPSS version 26.0. Results were expressed as mean \pm standard deviation. Intergroup comparisons were performed using the independent Student's t-test, and correlation analysis was conducted using Pearson's correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results

A total of 112 patients with preserved left ventricular ejection fraction (LVEF $\geq 50\%$) were included in the study and stratified into two groups based on serum NT-proBNP levels. Group 1 comprised patients with elevated NT-proBNP levels, while Group 2 included patients with lower NT-proBNP levels.

Patients in Group 1 were significantly older than those in Group 2 ($p = 0.04$). Group 1 also demonstrated significantly higher body mass index, systolic blood pressure, and diastolic blood pressure compared to Group 2 ($p < 0.001$ for all) (Table 1). Although all patients had preserved ejection fraction, mean LVEF was significantly higher in Group 1 than in Group 2 ($p < 0.001$). Serum NT-proBNP levels were markedly elevated in Group 1 compared to Group 2 ($p < 0.001$) (Figure 1).

Analysis of age-stratified data revealed a progressive increase in mean serum NT-proBNP levels with advancing age in Group 1, whereas consistently lower values were observed across all age categories in Group 2 (Figure 2).

Correlation analysis demonstrated a moderate and statistically significant positive association between serum NT-proBNP levels and the E/A ratio ($r = 0.483$, $p = 0.001$), indicating a relationship between elevated NT-proBNP levels and altered left ventricular diastolic function in patients with HFpEF (Figure 3).

Figures and Tables

Table 1: Comparison of clinical and biochemical parameters in patients with heart failure with preserved ejection fraction (HFpEF) stratified by serum NT-proBNP levels. Group 1 included patients with preserved left ventricular ejection fraction (LVEF $\geq 50\%$) and elevated serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, while Group 2 included patients with preserved ejection fraction and lower serum NT-proBNP levels. Data are expressed as mean \pm standard deviation. Intergroup comparisons were performed using Student's t-test, and a p-value < 0.05 was considered statistically significant (*).

Parameters	Group 1	Group 2	p-value
Age (years)	67.5±10.5	41.9±7.9	0.04*
Body Mass Index (kg/m ²)	31.4±1.8	24.2±1.5	<0.001*
Systolic Blood Pressure (mmHg)	163.3±31.2	139.1±8.9	<0.001*
Diastolic Blood Pressure (mmHg)	105.5±4.5	84.6±6.6	<0.001*
Left Ventricular Ejection Fraction (%)	72.5±8.2	62.5±8.5	<0.001*
Serum NT-proBNP (pg/ml)	1173.9±21.5	115.3±13.4	< 0.001*

Figure 1: Comparison of mean serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in both groups in patients with preserved ejection fraction. Group 1 represents patients with elevated NT-proBNP levels, while Group 2 represents patients with lower NT-proBNP levels. Intergroup comparisons were performed using Student's t-test, and a p-value <0.05 was considered statistically significant. The difference in mean NT-proBNP levels was statistically significant.

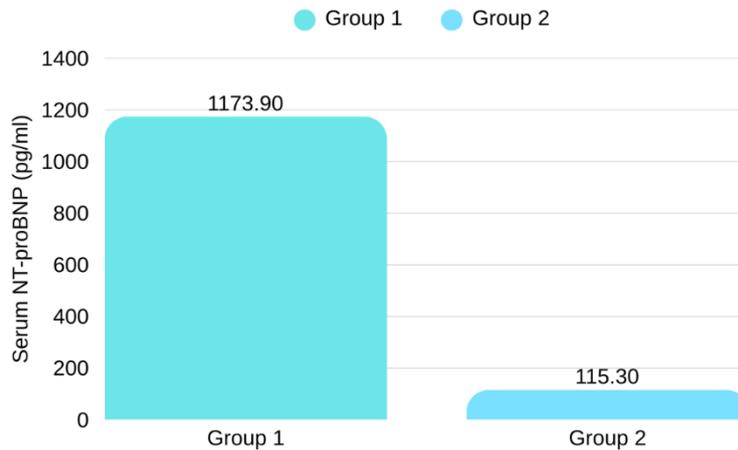


Figure 2: Comparison of mean serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels across different age groups (40–50, 50–60, 60–70, and 70–80 years) in patients with preserved ejection fraction. Group 1 represents patients with elevated NT-proBNP levels, while Group 2 represents patients with lower NT-proBNP levels.

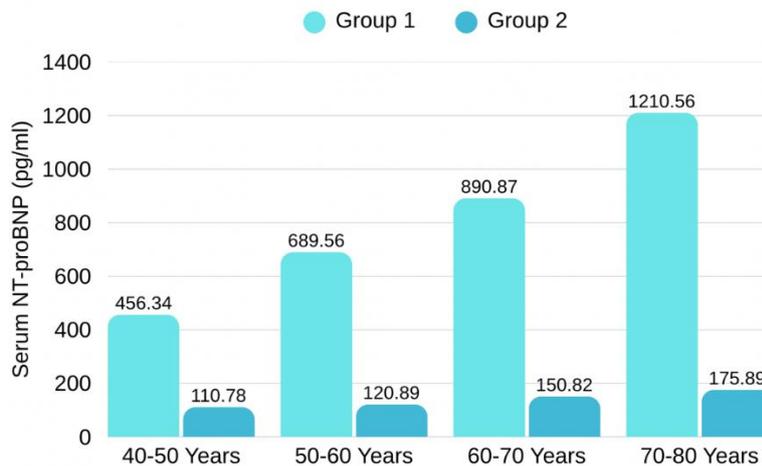
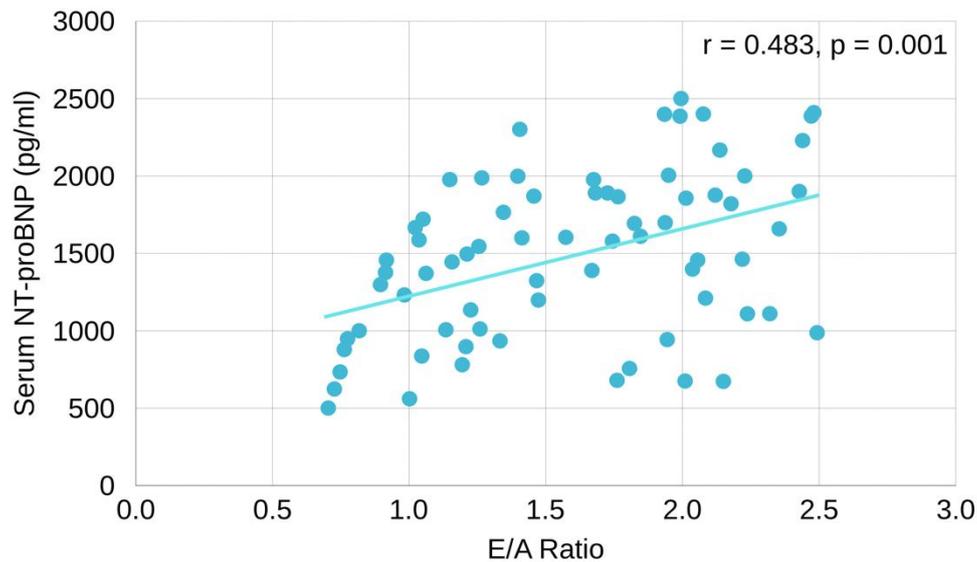


Figure 3: Scatter plot showing the correlation between serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and the E/A ratio in patients with heart failure with preserved ejection fraction (HFpEF). The E/A ratio is an echocardiographic parameter of left ventricular diastolic function, calculated as the ratio of peak early diastolic transmitral flow velocity (E wave) to peak late diastolic flow velocity during atrial contraction (A wave). A moderate positive correlation was observed between serum NT-proBNP levels and E/A ratio (Pearson's $r = 0.483$), which was statistically significant ($p = 0.001$).



Discussion

The role of NT-proBNP in the diagnosis and management of HFpEF is a significant area of contemporary cardiovascular research, given the increasing prevalence and complex pathophysiology of HFpEF.⁹ HFpEF, representing at least half of all heart failure cases, is characterized by symptoms of heart failure despite normal systolic function, as reflected by a near-normal left ventricular ejection fraction (LVEF $\geq 50\%$). This apparent paradox is explained by impaired ventricular relaxation and increased myocardial stiffness rather than reduced pumping capacity.¹ Reduced left ventricular compliance during diastole leads to elevated end-diastolic pressure, resulting in increased left atrial pressure and pulmonary venous congestion, which manifests clinically as acute shortness of breath.¹⁰ HFpEF is frequently associated with comorbidities such as hypertension, diabetes, and obesity, contributing to its heterogeneous clinical presentation and diagnostic complexity.⁹

NT-proBNP is a cardiac biomarker released in response to increased ventricular wall stress and volume overload, making it a valuable indicator of cardiac distress.¹¹ Its clinical utility is well established in HFrEF; however, ongoing research continues to clarify its role in HFpEF, where NT-proBNP levels may be variably elevated despite increased left ventricular filling pressures.⁶ Biochemical estimation of NT-proBNP and its elevation can help distinguish a subset of patients presenting with acute shortness of breath who are suspected of having heart failure.¹²

The current study aimed to evaluate the role of NT-proBNP in the early diagnosis of HFpEF. Serum NT-proBNP levels were significantly higher in patients with HFpEF, particularly among those with advanced age, higher body mass index (BMI), and elevated blood pressure. Group 1, comprising patients with elevated NT-proBNP levels, had a significantly higher mean age (67.5 ± 10.5 years) compared with Group 2 (41.9 ± 7.9 years; $p = 0.04$). This finding is consistent with prior evidence demonstrating that NT-proBNP levels increase with advancing age due to cumulative myocardial and renal changes, as well as age-related decline in left ventricular diastolic function.¹³ The Toon Health Study further identified age as the strongest independent determinant of NT-proBNP levels, even after adjustment for other clinical variables.¹³ Harper et al. also reported that advanced age, female sex, hypertension, and atrial fibrillation are highly prevalent in HFpEF, findings that were consistent with observations in the present study.¹² In line with these findings, age-stratified analysis demonstrated a progressive increase in mean NT-proBNP levels with advancing age in Group 1, while consistently lower values were observed across all age categories in Group 2. This highlights the importance of age-adjusted interpretation of NT-proBNP levels in the diagnosis of HFpEF.¹³

Patients in Group 1 also demonstrated significantly higher BMI (31.4 ± 1.8 kg/m²) compared to Group 2 (24.2 ± 1.5 kg/m²; $p < 0.001$). This finding aligns with existing literature identifying obesity as a major risk factor for HFpEF, contributing to systemic inflammation, increased oxidative stress, and impaired nitric oxide signaling pathways, which promote myocardial stiffening.¹⁴ Although obesity is known to paradoxically lower circulating natriuretic peptide levels due to increased adipose tissue clearance, the significantly elevated NT-proBNP levels observed in obese HFpEF patients in this study suggest that increased myocardial wall stress may outweigh this clearance mechanism in more advanced disease states.^{15,16}

Systolic blood pressure (163.3 ± 31.2 mmHg) and diastolic blood pressure (105.5 ± 4.5 mmHg) were also significantly higher in Group 1 compared to Group 2 (139.1 ± 8.9 mmHg and 84.6 ± 6.6 mmHg, respectively; $p < 0.001$ for both). Chronic hypertension is a major contributor to the development of HFpEF and is associated with myocardial remodeling characterized by increased myocardial stiffness and impaired diastolic relaxation.¹⁴ Beyond pressure overload, hypertension promotes systemic and coronary microvascular inflammation, oxidative stress, and fibrotic remodeling,

ultimately leading to diastolic dysfunction.¹⁴ The observed association reinforces the interplay between hypertension, elevated NT-proBNP levels, and HFpEF pathophysiology.

Although all patients had preserved ejection fraction (LVEF $\geq 50\%$), the mean LVEF was significantly higher in Group 1 ($72.5 \pm 8.2\%$) than in Group 2 ($62.5 \pm 8.5\%$; $p < 0.001$). This finding may reflect altered ventricular–arterial coupling and loading conditions in HFpEF, where LVEF may appear normal or supranormal despite underlying diastolic dysfunction and impaired myocardial relaxation.¹⁴ Mean serum NT-proBNP levels were markedly elevated in Group 1 (1173.9 ± 21.5 pg/ml) compared to Group 2 (115.3 ± 13.4 pg/ml; $p < 0.001$), underscoring the biomarker’s sensitivity to cardiac strain associated with HFpEF.

A crucial finding of the study was the moderate and statistically significant positive correlation between serum NT-proBNP levels and the E/A ratio ($r = 0.483$, $p = 0.001$). The E/A ratio reflects left ventricular diastolic function by assessing the ratio of early diastolic transmitral flow velocity (E wave) to late diastolic flow velocity during atrial contraction (A wave).¹⁷ An altered E/A ratio indicates impaired ventricular relaxation and elevated filling pressures, which are hallmarks of diastolic dysfunction and HFpEF.¹⁸ This correlation supports the utility of NT-proBNP as a non-invasive indicator of underlying diastolic dysfunction in HFpEF.

The overall findings are consistent with previous studies demonstrating the utility of NT-proBNP as a biomarker for diagnosing HFpEF and assessing diastolic dysfunction.⁶ Prior research has shown that NT-proBNP levels are elevated in HFpEF patients compared with controls, and higher levels correlate with echocardiographic markers of diastolic dysfunction within HFpEF populations.^{19,20} Birrell et al. also identified NT-proBNP as a useful biomarker of heart failure.²¹ The diagnostic relevance of NT-proBNP in HFpEF is further reinforced by its inclusion in diagnostic algorithms such as the HFA-PEFF score, which integrates NT-proBNP with functional and morphological parameters for risk stratification.² Current guidelines therefore recommend NT-proBNP measurement as part of a comprehensive diagnostic evaluation for HFpEF, particularly when echocardiographic findings are inconclusive or borderline.⁹

Conclusion

NT-proBNP is a useful and readily available biomarker for the early diagnosis of HFpEF. Elevated NT-proBNP levels were significantly associated with advanced age, higher body mass index, elevated blood pressure, and impaired left ventricular diastolic function as reflected by the E/A ratio. Measurement of NT-proBNP in patients presenting with acute shortness of breath can facilitate early diagnosis, timely initiation of treatment, and potentially reduce adverse cardiovascular events. However, the cross-sectional design and limited sample size restrict causal inference and long-term prognostic assessment, and the exclusion of known confounders such as renal dysfunction may limit generalizability, warranting validation in larger prospective studies.

Conflicts of interest: There are no conflicts of interest.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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