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Association of NT-proBNP in Patients of Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Objective: To determine the association of different levels of N- terminal B-type natriuretic peptide in patients of heart failure with preserved ejection fraction. **Study Design:** Analytical cross-sectional study. **Place and Duration of Study:** Department of Cardiology, Armed Forces Institute of Cardiology Rawalpindi from August 06, 2024 to March 05, 2025. **Methodology**: A total of 368 patients between the age of 20-75 years belonging to both genders with the diagnosis of heart failure with preserved ejection fraction were included in the study. Patients who were obese, had deranged renal profile, atrial fibrillation, and chronic obstructive pulmonary disease were excluded. N- terminal B-type natriuretic peptide levels of all patients were documented and grades of diastolic dysfunction were ascertained. Data analysis was done using SPSS version 25 taking p value of <0.05 as statistically significant. **Results**: The mean age of patients included in the study was 61.4±11.8 years. There were 157 male patients (42.7%) while 211 patients (57.3%) were female. The mean value of NT-proBNP in patients below 50 years of age was 312.9±271.3 ng/L while the mean value for patients above the age of 50 years was 426.3±571.9 ng/L (p=0.075). The median threshold value in patients with diastolic dysfunction Grade I was 389 pg/L. A statistically significant relationship was found between the values of NT-proBNP and the grades of DD (p<0.001). **Conclusion**: N- terminal B-type natriuretic peptide is significantly associated with the degree of diastolic dysfunction in patients presenting with heart failure with preserved ejection fraction.

INTRODUCTION

The earliest description of Heart failure with preserved ejection fraction (HFpEF) was given by Robert Luchi in 1982. Sometimes also labeled as diastolic heart failure, it is a syndrome characterized by presence of clinical features of heart failure (HF) due to increased left ventricular (LV) filling pressures in patients with either normal or nearly normal left ventricular ejection fraction (LVEF) of ≥50%.[1] HF is a major public health concern with an approximate 64 million people affected globally.[2] The lifetime risk for development of HFpEF is on the rise over the turn of the century with the risk estimated at 19.3% in the United States.[3] The exact overall prevalence of HF in the Pakistani population is unknown.

Studies from national literature have reported that the HFpEF has a similar frequency as heart failure with reduced ejection fraction (HFrEF). HFpEF tends to have a female preponderance.[4] The complexity of the pathophysiological mechanisms contributing to development of HFpEF makes it a diagnostic challenge. Various biomarkers including natriuretic peptides, high sensitivity cardiac troponins, and soluble neprilysin have been used as a diagnostic tool for HFpEF.[5] According the European Society of Cardiology (ESC) guidelines published in 2021, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the gold standard markers for both the diagnosis and prognosis of HF.[6]

NT-proBNP is a protein prohormone comprising of 76 amino acids produced in response to cardiac wall stress by the cardiac myocytes in the atria and ventricles. The half life of NT-proBNP is 120 minutes which is six times that of BNP as the formal is not cleaved by the enzyme neurylipsin.[7] The normal levels vary according to age and gender. Increase in the levels of the prohormone have been linked to increased mortality and morbidity over time.[1] NT-proBNP has been used in the diagnosis of HFpEF but there are some limitations reported in literature. Obesity, atrial fibrillation and renal dysfunction tend to influence the levels of NT-proBNP thus confounding the results.[8] A NT-proBNP level of

more than 220 to 300 pg/mL is suggestive of HFpEF.[1,9] Moreover studies have reported that plasma natriuretic peptides may be normal in patients with HFpEF and yet there is significant mortality and morbidity associated with it.[10]

The rationale of this study was that there is scarcity of data in the Pakistani literature on this subject. To the best of our knowledge there is no study in the national literature that describes the association of NT-proBNP in HFpEF. Armed Forces Institute of Cardiology (AFIC) is a center of excellence with a huge influx of patients. In the current era of evidence based cardiology practices, the findings of this research protocol will not only help to ascertain the association of NT-proBNP levels in our subset of the population but will also serve to generate interest for further research protocols on this important topic.

METHODOLOGY

We conducted an analytical cross-sectional study in the Department of Cardiology, AFIC Rawalpindi on a total of 368 patients with the diagnosis of HFpEF after approval from Institutional Ethical Review Board (IERB) of AFIC Rawalpindi vide letter 9/2/R&D/2025/336 dated 20th February 2025. A written and informed consent was signed by all patients before inclusion in the study. The sample size was determined by using the WHO sample size calculator taking the study by Birrell et al as the parent study.[11] The confidence level was taken as 95%, absolute precision as 0.05, anticipated population proportion as 60.3% (patients with diastolic dysfunction and normal LVEF. The total sample size was 368 patients. Non-probability consecutive sampling technique was employed.

Inclusion Criteria: All patients between the age of 20-80 years belonging to both genders and having a body mass index (BMI) of less than 30 Kg/m^2 with the diagnosis of HFpEF were included in the study.

Exclusion Criteria: Patients with deranged renal function tests, BMI of more than 30 Kg/m^2, patients with atrial fibrillation, diabetes mellitus, concomitant valvular heart disease, and chronic obstructive pulmonary disease (COPD) were excluded from the study. Moreover, those patients who did not have two separate readings of NT-proBNP levels three months apart along with echocardiography were also excluded from the study sample.

The demographics details of all patients were documented on a proforma including age, gender, height, weight, BMI, NT-proBNP levels and echocardiography parameters. Two readings six months apart were taken. The degree of diastolic dysfunction, systolic function and LVEF were documented. A detailed history was taken for all patients followed by clinical examination and investigation. Patients were labeled as cases of HFpEF as per the 2023 definition by American College of Cardiology (ACC). Patients having signs and symptoms of HF with LVEF ≥50% were labeled as HFpEF.[12] Follow up of patients was ensured by taking the contact numbers of patients as well as their attendants/guardians.

The echocardiography and diagnosis of all patients were made by a consultant cardiologist with more than 5 years of post-fellowship experience. The grades of diastolic dysfunction (DD) were determined as described by Kossaify et al.[13] The DD Grade I patients were those who had impaired relaxation and decreased suction of the LV, Grade II patients had pseudo-normalization or intermediate DD and an increase in the stiffness of the LV, with raised filling pressure, while Grade III patients were those who had restrictive filling of the LV, a non-compliant LV coupled with an elevation of filling pressure.

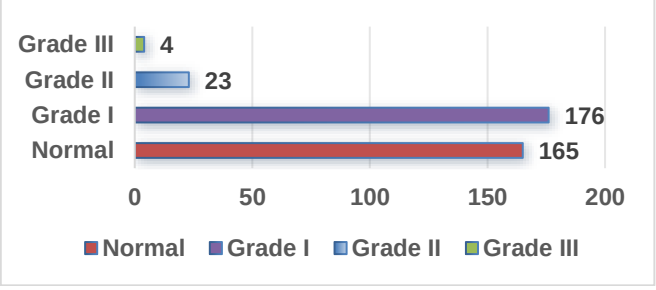
Data of all patients was entered in and analyzed by using Statistical package for social sciences (SPSS) version 25.0. Mean and standard deviation were determined for quantitative variables like age, BMI, and NT-proBNP while qualitative variables like gender, grade of DD, LVEF and mortality were expressed as frequency and percentages. Data was stratified for age and gender. Post-stratification chi square test was applied to analyse the qualitative variables while independent sample T-test was applied to analyse the quantitative variables taking p value of less than 0.05 as statistically significant.

RESULTS

A total of 368 patients completed the study. The overall mean age of patients included in the study was 61.4±11.8 years. There were 157 male patients (42.7%) while 211 patients (57.3%) were female. The mean BMI of patients included in the study was 27.4±1.7 Kg/m^2. The median (IQR) LVEF was 55.0% (51.0-58.0). The overall mean initial NT-proBNP at the start of study was 400.5±518.9 ng/L while the overall mean NT-proBNP level at six months follow up was 433.9±696.9 ng/L. Over the period of six months 171 patients (46.5%) had an increase in the NT-proBNP levels while 197 patients (53.5%) had a decrease in the NT-proBNP level. The overall all cause mortality rate among the patients was 13.6% (50 out of 368 patients). The distribution of the patients according to grades of DD is shown in the graph below.

Graph 1

Grades of Diastolic Dysfunction



The distribution of patients according to grades of DD is shown in the Table 1 below.

Table 1
Distribution of Patients According to Grades of DD.

Variable	Normal diastolic function	Grade I Dysfunction	Grade II Dysfunction	Grade III Dysfunction
Age in years (Mean ± SD)	59.4±12.3	62.6±10.9	63.2±13.3	77.5±1.3
Less than 50 years, n (%)	51 (58.6%)	31 (35.6%)	5 (5.7%)	0 (0.0%)
More than 50 years, n(%)	114 (40.6%)	145 (51.6%)	18 (6.4%)	4 (1.4%)
Gender, n (%)				
Male	65 (41.4%)	84 (53.5%)	7 (4.5%)	1 (0.6%)
Female	100 (47.4%)	92 (43.6%)	16 (7.6%)	3 (1.4%)
NT-proBNP (ng/L)				
Start, Median (IQR)	179 (145-213)	389 (360-447)	1196 (920-1455)	4477 (3596-5498)
Follow up Median (IQR)	162 (110-259)	367 (246-501)	1427 (931-1896)	6101 (5195-6670)

Data analysis revealed that age was an independent predictor of worsening diastolic dysfunction (p=0.02). The mean value of NT-proBNP in patients below 50 years of age was 312.9±271.3 ng/L while the mean value for patients above the age of 50 years was 426.3±571.9 ng/L (p=0.075). Moreover, there is highly significant association between the value of NT-proBNP and degree of diastolic dysfunction (p<0.001). Gender on the other hand was not significantly associated with degree of diastolic dysfunction (p=0.214). Data analysis for determining the relationship of increase or decrease in the levels of NT-proBNP is given in Table 2 below. Lastly the relationship of degree of diastolic dysfunction with mortality is shown in Table 3 below.

Table 2
Relationship of Change in Values of NT-proBNP with Degree of Diastolic Dysfunction.

Degree of Diastolic Dysfunction	NT-proBNP Level		p value
	Increase, n(%)	Decrease, n(%)	
Normal	71	94	0.006
Grade I	79	97	
Grade II	17	6	
Grade III	4	0	

Table 3
Relationship of Degree of Diastolic Dysfunction with Mortality.

Degree of Diastolic Dysfunction	Mortality		p value
	Yes n(%)	No n(%)	
Normal	5	160	<0.001
Grade I	20	156	
Grade II	21	2	
Grade III	4	0	

DISCUSSION

HFpEF still remains a challenging diagnosis. The various mechanisms postulated impacting HFpEF include cardiomyocyte hypertrophy, systolic and diastolic dysfunction, chronic inflammation, interstitial fibrosis, elevated oxidative stress, endothelial dysfunction, and compromised auto-regulation of the micro circulation.[14] As described by Azzo et al, the levels of NT-proBNP carry both a diagnostic and prognostic significance in patients with HFpEF. The study also highlighted that presence of atrial fibrillation, chronic kidney disease and obesity may act as a confounder.[15] In this research protocol of ours, we added the aforementioned confounders in the exclusion criteria. The mean age of patients included in our study was 61.4±11.8 years. A study by Ishaque et al reported the mean age of patients in HFpEF to be 68.1±10.5 years.[4] A comparatively higher mean age of 71.6±10.7 years was reported by Birrell et al.[11] Another important finding of this study is the significant relationship of degree of DD with increasing age (p=0.02). Not Our study comprised of 157 male (42.7%) and 211 female patients (57.3%). Birrell et al reported comparable frequency of male patients (44.1%) and female patients (55.9%).[11] Shiekh et al also reported that HFpEF was more common among the female patients (66.7%).[4] However there was statistically a non-significant difference between the patients in terms of gender on the grades of DD (p=0.214).

The findings of our study revealed that there was a statistically significant relationship between the values of NT-proBNP and the grades of DD (p<0.001). Moreover, our study also highlighted the fact that the increase or decrease in the values of NT-proBNP was also significantly related (p=0.006). Thus NT-proBNP can not only be used as a marker in the diagnosis of HFpEF but it can also serve as an important prognostic follow up marker as well. Moreover, the grade of diastolic dysfunction which was related to the levels of NT-proBNP was also associated with the frequency of all cause mortality in these patients (p<0.001). Sakamoto et al in a study from Japan published in 2024 also reported that NT-proBNP levels were significantly associated with all cause mortality (p<0.001).[16]

The median level for patients with grade I DD in our study was 389 ng/L which was slightly higher than that reported by Birrell et al who reported it to be 325 ng/L. According to the National Institute for Health and Care Excellence (NICE) guidelines the threshold value of NT-proBNP recommended for assessment of patients with HF is 400 ng/L which is almost similar to our finding. The European Society of Cardiology places the limit at a much lower level of 125 ng/L. However this level may be normal for female gender and patients above the age of 50 years.[17]

The cut off thresholds for different age groups were

found to be different for different age groups. Moreover, with advancing age, the level of diastolic dysfunction also increases. A study by Januzzi et al published in 2018 reported that the threshold values of NT-proBNP for labeling patients of HF was 450 ng/L for patients under the age of 50 years, 900 ng/L for patients between 50-75 years of age and 1800 ng/L for those older than 75 years.[18] Lee et al also reported similar findings as Januzzi et al.[19] The findings of our study are in agreement to the criteria suggested by NICE guidelines.

HFpEF is predicted to become the most common variety of HF in the near future. The disease is currently the most prevalent cause of HF in patients above the age of 65 years.[20] The burden of the disease is projected to increase with the latest advancements in healthcare and increase in life expectancy. Measurement of NT-proBNP levels and echocardiography remain the mainstay investigations in the diagnosis of HFpEF. The findings of our study are comparable to those reported in International literature. The limitations of this research protocol was its small sample size and the smaller number of patients with higher grades of DD. Our study also excluded patients with obesity, renal failure and atrial fibrillation which are common comorbidities in patients with HF. Therefore, further studies are recommended with larger sample sizes to gather more evidence which will help to achieve the goal of improving the standard of care for these patients.

CONCLUSION

The findings of our study revealed that NT-proBNP is significantly associated with the degree of diastolic dysfunction in patients presenting with HFpEF. NT-proBNP is both a diagnostic as well as a prognostic marker for HFpEF. The median threshold value in patients with diastolic dysfunction Grade I was 389 pg/L. Higher age was also an independent predictor of worsening diastolic dysfunction.

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