Section: Miscellaneous

Original Research Article

ECHOCARDIOGRAPHIC FINDINGS AND TISSUE DOPPLER STUDIES IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) AND THEIR RELATION WITH NT-PROBNP LEVELS

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ABSTRACT

Background: Aim: Heart failure with preserved ejection fraction (HFpEF) is a complex condition with limited treatment options. This study aimed to examine the correlation between echocardiographic findings, tissue Doppler indices, and NT-proBNP levels in HFpEF patients to improve prognostic accuracy and risk stratification. **Introduction:** HFpEF is defined by impaired diastolic function despite preserved left ventricular ejection fraction (LVEF ≥ 50%). It involves diastolic dysfunction, left atrial enlargement, and pulmonary hypertension. However, the relationship between echocardiographic parameters and NT-proBNP remains unclear.

Material and Methods: This cross-sectional study was conducted at Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh Muslim University, between August 2022 and August 2024. A total of 130 HFpEF patients (LVEF ≥ 50%) were recruited. Exclusion criteria included systolic heart failure and chronic obstructive pulmonary disease. Echocardiography and tissue Doppler imaging were performed, and NT-proBNP levels were measured. Correlations were analyzed between NT-proBNP, diastolic dysfunction, left atrial volume index (LAVI), pulmonary artery systolic pressure (PASP), and global longitudinal strain (GLS).

Results: The mean age was 55.88 ± 10.50 years, with 60% females. Common symptoms included dyspnea (97.7%), fatigue (57.7%), and cough (43.8%). Hypertension (74.6%) and diabetes (78.5%) were prevalent. Diastolic dysfunction (92.2%), left atrial enlargement (mean LAVI: 37.34 ± 5.25 mL/m²), and LV hypertrophy (32.3%) were noted. NT-proBNP (1471.38 ± 3065.46 pg/mL) correlated with diastolic dysfunction, PASP (p=0.0361), orthopnea (p=0.0353), ECG abnormalities (p=0.0202), and serum creatinine (p=0.0341), but not with age, BMI, or LVEF.

Conclusion: NT-proBNP correlates with diastolic dysfunction and left atrial enlargement, reinforcing its role as a key HFpEF biomarker. Echocardiographic markers, including E/e′ ratio, GLS, and PASP, aid risk stratification. Given the high comorbidity burden, multicenter studies with advanced imaging and biomarkers are needed to refine HFpEF management.

Keywords: Heart Failure with Preserved Ejection Fraction (HFpEF), NT-proBNP, Echocardiography, Diastolic Dysfunction, Left Atrial Volume Index, Pulmonary Artery Systolic Pressure, Global Longitudinal Strain, Risk Stratification.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a distinct and increasingly recognized form of heart failure, characterized by impaired diastolic function. Unlike heart failure with reduced ejection fraction (HFrEF), in which the heart's ability to contract is compromised, HFpEF is defined by the heart's inability to relax properly during diastole. As a result, there is inadequate filling of the heart chambers despite normal systolic function. This condition is also referred to as diastolic heart failure due to the crucial role diastolic dysfunction plays in its pathophysiology. While the heart's ability to contract and pump blood remains relatively unaffected, the underlying dysfunction in relaxation can lead to the development of HFpEF over time. The increasing prevalence and complexity of HFpEF have sparked growing interest in understanding its pathophysiology and identifying potential therapeutic approaches tailored to this unique subset of heart failure.

HFpEF has gained prominence in clinical research over the past few decades, particularly as studies have uncovered the critical role of diastolic left ventricular (LV) dysfunction in the development and progression of heart failure. Research in hypertrophic hearts with thickened LV walls has provided important insights into the physiological mechanisms underlying diastolic dysfunction. This dysfunction is particularly evident in hypertrophic cardiomyopathy and other conditions where diastolic filling is impaired despite relatively normal systolic function.[1] Furthermore, the concept of LV remodelling following even minor myocardial infarctions has added another layer of complexity to the understanding of HFpEF. These remodelling processes, initially adaptive in nature, can predispose the heart to long-term dysfunction, further exacerbating the risk of HFpEF development.[2] This dual line of inquiry—diastolic dysfunction and post-infarction LV remodelling—has become integral in explaining the mechanisms that drive HFpEF pathogenesis.

The growing recognition of HFpEF as a multifactorial condition has led to increased research into its diverse etiologies, including inflammation, oxidative stress, and microvascular dysfunction. These factors highlight that HFpEF is not merely a disease of myocardial stiffness, as previously thought, but rather involves a complex interplay of various physiological and pathological processes. The elevated global burden of HFpEF underscores the importance of a comprehensive understanding of its pathophysiology, which is crucial for the development of targeted therapeutic strategies.[3]

One of the most striking epidemiological aspects of HFpEF is its rising prevalence, which is now considered to account for approximately half of all cases of heart failure worldwide.[4] This increase in prevalence emphasizes the need for an in-depth understanding of the factors that contribute to the development and clinical manifestation of HFpEF. Additionally, significant differences in the prevalence of HFpEF by sex have emerged, with women, particularly those over the age of 64, being more susceptible to this condition compared to men. Research indicates that age-related factors, particularly in post-menopausal women, significantly contribute to the higher incidence of HFpEF in older populations. In fact, the prevalence of HFpEF may even exceed that of HFrEF in the elderly, underscoring the need for age- and sex-specific strategies for diagnosis, prevention, and treatment.[5]

Despite advances in understanding HFpEF, its clinical management remains challenging due to its heterogeneous nature. Unlike HFrEF, which has established treatments, therapeutic options for HFpEF are limited. One major challenge is the lack of a unified understanding of its mechanisms. Chronic inflammation and oxidative stress play a key role in HFpEF development, leading to endothelial dysfunction and impaired myocardial oxygenation. Additionally, oxidative stress causes the accumulation of reactive oxygen species (ROS), contributing to cellular damage, fibrosis, and diastolic dysfunction in HFpEF.[6]

Recent research has identified key molecular mechanisms in HFpEF pathophysiology, including chronic inflammation, cardiac fibrosis, and oxidative stress. Elevated levels of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), contribute to ongoing myocardial damage. Profibrotic pathways, activated by transforming growth factor-beta (TGF-β), interleukin-11 (IL-11), and angiotensin II (AngII), promote extracellular matrix deposition, leading to cardiac fibrosis. This fibrosis impairs myocardial relaxation, a hallmark of HFpEF. Additionally, dysregulation of the nitric oxide (NO) pathway and reduced cGMP levels further disrupt cardiac relaxation in HFpEF patients.[7]

To further investigate the complex pathophysiology of HFpEF, advancements in diagnostic imaging and biomarkers have been instrumental. Techniques such as echocardiography and tissue Doppler imaging are now essential tools for assessing diastolic dysfunction, left atrial enlargement, and left ventricular hypertrophy, all key characteristics of HFpEF. Tissue Doppler imaging, in particular, enhances the diagnostic capability by providing real-time assessment of myocardial velocities, particularly during diastole, offering valuable insights into left ventricular relaxation and compliance.[8] NT-proBNP, a biomarker associated with myocardial stress and neurohormonal activation, has proven useful in diagnosing and predicting the prognosis of HFpEF patients. Elevated NT-proBNP levels are indicative of increased myocardial stress, providing clinicians with important information regarding the severity of

the condition and the likelihood of adverse outcomes.[9]

Despite the growing availability of diagnostic modalities, significant gaps remain in our understanding of the relationships between echocardiographic parameters, tissue Doppler indices, and NT-proBNP levels in HFpEF patients. The interplay between these diagnostic tools is not yet fully understood, hindering the ability to effectively risk-stratify and manage HFpEF patients. A more comprehensive understanding of how these diagnostic parameters interact is essential for improving patient care and optimizing treatment strategies.[10]

The primary goal of this study is to examine the relationship between echocardiographic findings, tissue Doppler indices, and NT-proBNP levels in patients diagnosed with HFpEF. By exploring the correlations among these parameters, the study aims to improve prognostic accuracy, assist with risk stratification, and guide therapeutic decision-making in managing HFpEF. Ultimately, the findings could help refine clinical management by enabling a more personalized approach to patient care.[11] This research is particularly important given the ongoing challenges in HFpEF management and the need for better diagnostic and therapeutic strategies. Through this study, we aim to bridge the current knowledge gap, enhancing our understanding of HFpEF and contributing to improved patient outcomes.

MATERIALS AND METHODS

This study, conducted at Jawaharlal Nehru Medical College and Hospital (JNMCH), Aligarh Muslim University, from August 2022 to August 2024, included patients with heart failure symptoms and preserved ejection fraction (≥50%). Approved by the Institutional Ethics Committee (IECJNMC/750, dated 19/10/2022) and registered with the Clinical Trial Registry of India, this open-labeled, cross-sectional study assessed 130 patients selected from outpatient and inpatient cardiology units. Inclusion criteria required LVEF ≥50%, while exclusion criteria ruled out conditions like systolic heart failure, congenital heart disease, and chronic obstructive pulmonary disease. Echocardiography and tissue Doppler imaging were performed, and NT-proBNP levels measured to correlate imaging findings with myocardial stress, enhancing diagnosis and risk stratification in HFpEF.

RESULTS

The study included 130 participants diagnosed with heart failure with preserved ejection fraction (HFpEF) using the HFA-PEFF score. The demographic, clinical, comorbidity, echocardiographic findings are presented below.

The mean age of the participants was 55.88 ± 10.50 years (range: 34-79). The majority (57.7%) were aged between 40-69 years. Females constituted 60% of the study population. The mean BMI was 24.46 ± 3.19 kg/m², ranging from 18.6 to 31.4 kg/m².

Among the study population, 97.7% reported dyspnea on exertion, 57.7% had fatigue, 7.7% had orthopnea, 18.5% experienced angina, 43.8% had cough, and 6.9% had edema. Hypertension was present in 74.6% of participants, with 97.9% receiving antihypertensive medication. Diabetes mellitus was found in 78.5% of participants. Coronary artery disease was diagnosed in 38.5%, chronic kidney disease in 12.3%, and 40% had a history of smoking. [Table 1]

Table 1: Clinical and demographic characteristics of the study and control groups

Symptom	Frequency (n)	Percentage (%)	95% CI
Dyspnea on Exertion	127	97.7	92.9% - 99.4%
Fatigue	75	57.7	48.7% - 66.2%
Orthopnea	10	7.7	4.0% - 14.1%
Angina	24	18.5	12.4% - 26.4%
Cough	57	43.8	35.2% - 52.8%
Edema	9	6.9	3.4% - 13.1%

Smoking was reported in 40% of participants, while 74.6% had hypertension, with 97.9% on antihypertensive medications (ACEi/ARBs: 97.9%, CCBs: 64.9%, Diuretics: 34.0%). Among those with hypertension, 61.9% had controlled blood pressure. Diabetes mellitus was present in 78.5% of participants. Coronary artery disease (CAD) was observed in 38.5% (DVD: 7.7%, SVD: 28.5%, TVD: 2.3%). Chronic kidney disease (CKD) was present in 12.3% of participants. [Table 2]

Table 2: Distribution of Comorbidities Among Study Participants

Comorbidity	Present (n, %)	Absent (n, %)	95% CI
Smoking	52 (40.0%)	78 (60.0%)	31.6% - 49.0%
Hypertension	97 (74.6%)	33 (25.4%)	66.1% - 81.7%
Diabetes Mellitus	102 (78.5%)	28 (21.5%)	70.2% - 85.0%
Coronary Artery Disease (CAD)	50 (38.5%)	80 (61.5%)	30.2% - 47.4%
Chronic Kidney Disease (CKD)	16 (12.3%)	114 (87.7%)	7.4% - 19.5%

The mean HbA1c level among participants was 7.58 ± 1.48%, with a median (IQR) of 7.45 (6.4-8.6) and a range of 4.9 - 12.4%. NT-proBNP levels showed a wide distribution, with a mean of 1471.38 ± 3065.46

pg/mL, a median (IQR) of 826 (651.75-1021.75) pg/mL, and a range extending from 212 to 25,000 pg/mL. Regarding lipid profile parameters, the mean triglyceride level was 128.84 ± 32.65 mg/dL (median: 121 mg/dL, range: 66 - 254 mg/dL), while HDL had a mean of 42.09 ± 10.52 mg/dL (median: 41 mg/dL, range: 12 - 72 mg/dL). LDL levels averaged 96.98 ± 26.97 mg/dL, with a median of 96.5 mg/dL and a range of 46.5 - 200 mg/dL. The mean total cholesterol level was 182.20 ± 56.34 mg/dL, with a median of 184 mg/dL and a range spanning 62 - 328 mg/dL.[Table 3]

Table 3: Distribution of Clinical Investigation Parameters

Parameter	Mean Â± SD	Median (IQR)	Range
HbA1c (%)	7.58 Â± 1.48	7.45 (6.4-8.6)	4.9 - 12.4
NT-proBNP (pg/mL)	1471.38 Â± 3065.46	826 (651.75-1021.75)	212 - 25000
Triglycerides (mg/dL)	128.84 Â± 32.65	121 (104.25-148)	66 - 254
HDL (mg/dL)	42.09 Â± 10.52	41 (36-48)	12-72
LDL (mg/dL)	96.98 Â± 26.97	96.5 (78-110)	46.5 - 200
Total Cholesterol (mg/dL)	182.20 Â± 56.34	184 (149.25-214)	62 - 328

Fundus examination revealed that 49.2% of participants had a normal fundus, while 39.2% exhibited non-proliferative diabetic retinopathy (NPDR). Hypertensive retinopathy was observed in 11.5% of cases, categorized as Grade I (3.8%), Grade II (4.6%), and Grade III (3.1%). [Table 4]

Table 4: Distribution of participants in terms of Fundus findings

Fundus	Frequency	Percentage	95% CI
Normal	64	49.2%	40.4% - 58.1%
Grade I HTN RP	5	3.8%	1.4% - 9.2%
Grade II HTN RP	6	4.6%	1.9% - 10.2%
Grade III HTN RP	4	3.1%	1.0% - 8.2%
NPDR	51	39.2%	30.9% - 48.2%

ECG findings demonstrated that 83.1% of participants had a normal sinus rhythm, whereas 16.2% presented with atrial fibrillation with controlled ventricular rate (AF with CVR). A rare occurrence of atrial fibrillation with fast ventricular rate (AF with FVR) was noted in 0.8% of cases. These findings suggest a high prevalence of cardiovascular risk factors among the participants, with notable involvement of both metabolic and cardiac parameters. [Table 5]

Table 5: Distribution of participants in terms of ECG findings

ECG	Frequency	Percentage	95% CI
AF With CVR	21	16.2%	10.5% - 23.9%
Sinus Rhythm	108	83.1%	75.3% - 88.9%
AF With FVR	1	0.8%	0.0% - 4.8%

Echocardiographic evaluation revealed that 94.6% of participants had no regional wall motion abnormality (RWMA), while 5.4% exhibited mild abnormalities, including mild septal hypokinesia (2.3%), mild inferior wall hypokinesia (0.8%), mild posterior wall hypokinesia (0.8%), mild inferoseptal hypokinesia (0.8%), and anterior wall hypokinesia (0.8%). Left ventricular hypertrophy (LVH) was identified in 32.3% of participants. [Figure 1]

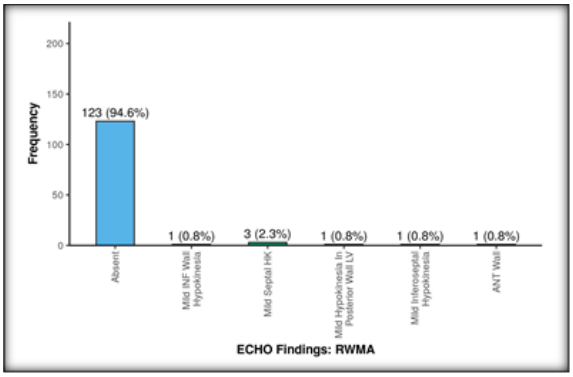

Figure 1: Bar graph showing distribution of RWMA in 2D-echo among participants

The mean left ventricular ejection fraction (LVEF) measured using the Biplane Simpson's method was 60.44 ± 4.64% (range: 52 - 74%), while the M-mode method recorded a mean LVEF of 60.22 ± 4.37% (range: 52 - 72%). [Figure 2&3]

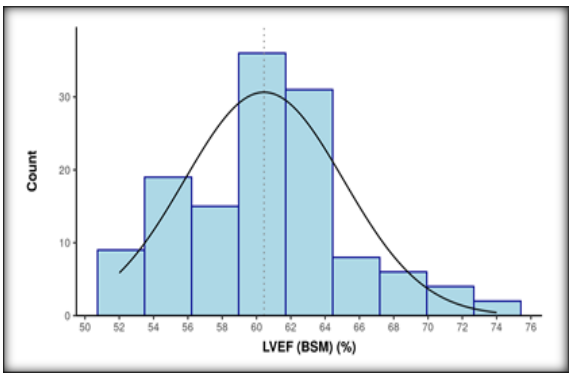

Figure 2: Distribution of LVEF (BSM) (%)

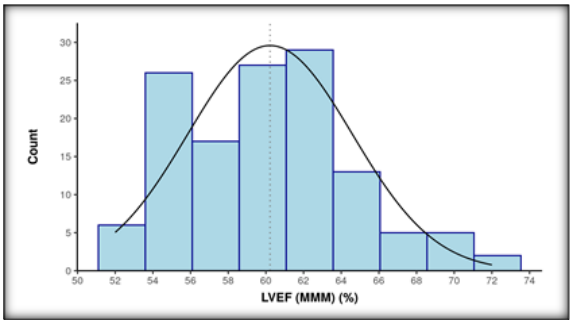

Figure 3: Distribution of LVEF (MMM) (%)

Diastolic dysfunction was prevalent, with 43.1% of participants classified as Grade I, 49.1% as Grade II, and 7.8% as Grade III. The mean E/e' ratio, an indicator of left ventricular filling pressure, was 12.68 ± 2.44, with a median of 12.50 (IQR: 10.83 - 15). [Figure 4]

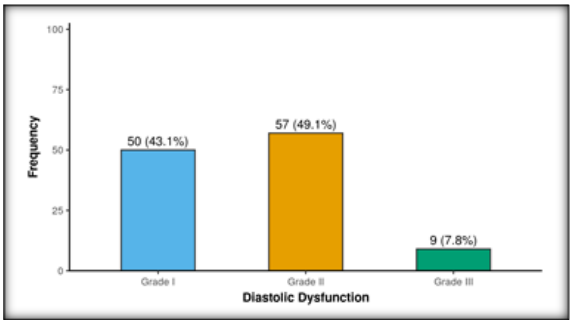

Figure 4: Distribution of Diastolic Dysfunction

Tricuspid regurgitation (TR) was absent in 61.5% of participants, while 32.3% exhibited trivial TR and 6.2% had mild TR. The mean pulmonary artery systolic pressure (PASP) was 24.26 ± 6.88 mmHg (range: 15 - 40 mmHg). The average left ventricular global longitudinal strain (LV GLS) was -22.48 ± 3.19, with a median of -22.8 (-24.7 to -20.42), reflecting preserved myocardial deformation. [Figure 5]

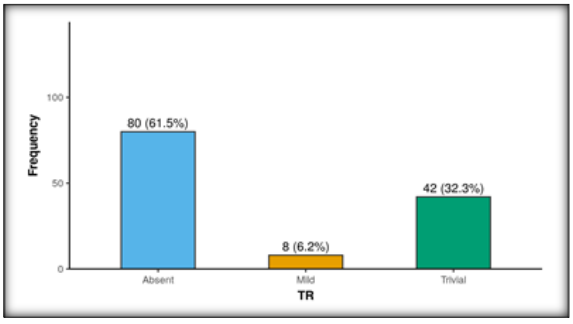

Figure 5: Bar graph showing distribution of Tricuspid Regurgitation(TR) among participants

Assessment of left atrial volumes showed a maximum LA volume of 59.10 ± 12.36 mL, a pre-atrial contraction volume of 47.02 ± 12.49 mL, and a minimum LA volume of 35.92 ± 15.37 mL. The body surface area (BSA) was 1.68 ± 0.16 m². The left atrial volume index (LAVI Max LA/BSA) was 37.34 ± 5.25 mL/m², while the left atrial ejection fraction (LAEF) was 40.92 ± 16.12%. The left atrial emptying fraction index (LAEFI) had a mean value of 26.92 ± 9.16(Figure 6,7&8).

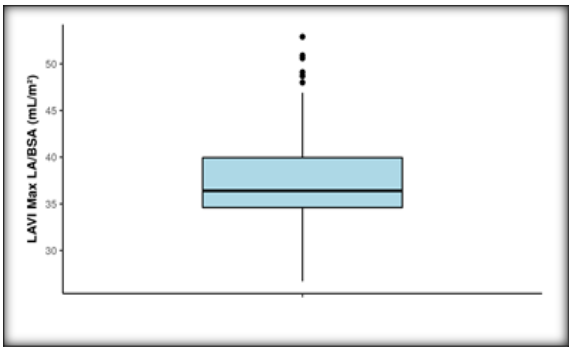

Figure 6: Box Plot of Left Atrial Volume Index (LAVI Max LA/BSA) among Study Participants

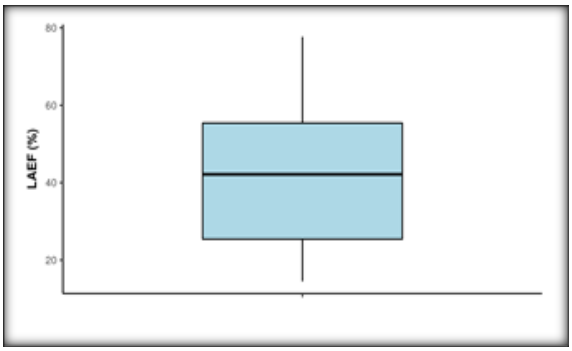

Figure 7: Box Plot of Left Atrial Ejection Fraction (LAEF) among Study Participants

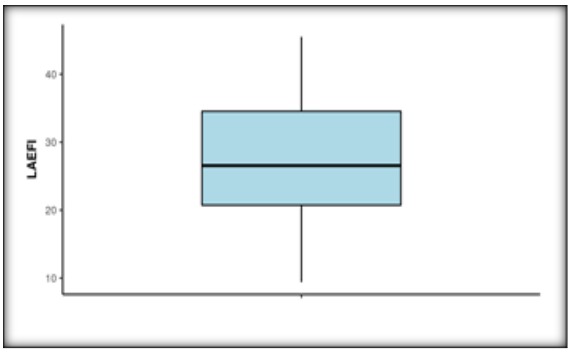

Figure 8: Box Plot of Left Atrial Emptying Fraction Index (LAEFI) among Study Participants

These echocardiographic findings demonstrate a high prevalence of diastolic dysfunction and left atrial structural changes, emphasizing their importance in the assessment and characterization of HFpEF.

A statistically significant positive correlation was observed between NT-proBNP and diastolic blood pressure (p=0.0361), orthopnea (p=0.0353), ECG findings (p=0.0202), troponin-I levels (p=0.0201), and serum creatinine (p=0.0341). No significant correlation was found between NT-proBNP and age, gender, BMI, diabetes, hypertension, or LVEF (p>0.05)

DISCUSSIONS

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome characterized by heart failure symptoms despite a left ventricular ejection fraction (LVEF) of 50% or greater. Unlike heart failure with reduced ejection fraction (HFrEF), which is defined by diminished LVEF and increased left ventricular (LV) volumes, HFpEF is marked by abnormal LV filling and elevated filling pressures, leading to symptomatic heart failure. While HFpEF was historically termed "diastolic heart failure" and HFrEF "systolic heart failure," it is now understood that HFpEF involves a more intricate interplay of diastolic, systemic, and vascular factors, which distinguishes it from HFrEF. Importantly, HFpEF is closely associated with the metabolic syndrome, obesity, insulin resistance, and systemic inflammation, all of which contribute to its pathoph1ysiology and distinguish it from other forms of heart failure.[1]

This study sought to investigate echocardiographic and tissue Doppler imaging findings, alongside NT-proBNP levels, to better understand their interplay in HFpEF pathophysiology and diagnostic utility. Key findings from this study align with and expand upon existing literature, providing insights into demographic, clinical, and imaging characteristics of HFpEF patients.[2]

The study population had a mean age of 55.88 years and comprised 60% female participants, with a mean BMI of 24.46 kg/m². These findings are consistent with studies by Verbrugge et al. (2022) and Johansson et al. (2022), which identified similar age distributions, gender ratios, and BMI values, although variations in BMI were noted in other cohorts.[12,13] Symptoms such as dyspnea on exertion (DOE) and fatigue were prevalent, reported by 97.7% and 57.7% of participants, respectively. These symptoms are hallmark features of HFpEF, as highlighted in previous studies, including those by Johansson et al. and Verbrugge et al,[12,13] The presence of other symptoms like orthopnea, angina, cough, and edema was less common but consistent with findings from Chrysohoou et al. (2024) and Bshiebish et al. (2019).[14,15]

A significant portion of the study population had hypertension (74.6%), diabetes mellitus (78.5%), or a history of smoking (40%). These comorbidities are well-documented contributors to HFpEF pathophysiology, as corroborated by Shah et al. (2019) and Wang et al. (2022).[16,17] Diabetes and systemic inflammation are key drivers of cardiac remodeling and diastolic dysfunction, underscoring the importance of integrated management strategies for these patients.

Echocardiographic parameters revealed significant diastolic dysfunction, with a mean E/e′ ratio of 12.68 and reduced early diastolic (E′) velocities (mean: 6.1 cm/s). Structural abnormalities, including increased left atrial volume index (mean: 45 mL/m²) and LV hypertrophy (32.3%), were evident. These findings are consistent with prior studies by Shah et al. (2019) and Obokata et al. (2019), highlighting the importance of echocardiography in identifying diastolic dysfunction and elevated filling pressures.[16,18] Additionally, elevated pulmonary artery pressures (mean RVSP: 40 mmHg) and mild right ventricular dysfunction (mean TAPSE: 15.5 mm) were observed, reflecting the multifaceted nature of HFpEF.

The mean NT-proBNP level in the study population was 1471 pg/mL, correlating significantly with echocardiographic markers such as the E/e′ ratio ($r = 0.72$) and left atrial volume index ($r = 0.68$). These findings are consistent with the diagnostic and prognostic value of NT-proBNP emphasized in studies by Wang et al. (2022) and Chrysohoou et al. (2024).[14,17] However, NT-proBNP levels showed limited association with certain clinical symptoms and comorbidities, such as BMI and hypertension, reflecting the biomarker's specificity for cardiac stress rather than systemic risk factors.[19]

The results reinforce the utility of combining imaging findings and biomarker data to improve HFpEF diagnosis and risk stratification.[20] The strong correlation between NT-proBNP levels and key echocardiographic parameters underscores its role as a robust marker of myocardial stress and diastolic dysfunction. However, its limited association with non-cardiac symptoms and comorbidities suggests that a comprehensive approach, integrating clinical, imaging, and laboratory data, is essential for effective HFpEF management.

CONCLUSION

This study highlights the role of NT-ProBNP and echocardiographic parameters in assessing HFpEF severity, emphasizing its prognostic value. Echocardiography, particularly tissue Doppler imaging, proved essential for identifying diastolic dysfunction, left atrial enlargement, and PASP. The significant burden of comorbidities, especially hypertension and diabetes, underscores the need for aggressive management. However, limitations such as a single-center design, cross-sectional nature, and lack of long-term follow-up affect generalizability. Future research should include multicenter, longitudinal studies with larger cohorts, advanced imaging, and additional biomarkers to refine risk stratification, explore personalized treatment approaches, and improve HFpEF management through targeted intervention trials.

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