RESEARCH PAPER

Beyond Ejection Fraction: Synergistic Role of NT-proBNP and The Heart Failure Echocardiographic Index in Phenotyping Structural and Functional Burden in Heart Failure

Dr. Vinod Kumar[1*], Dr. Monisha Ganesh[2], Lavanya Damodaran[3], Jaisri Sankar[4], Dr. Hari Lalith Kovvuria[5], Dr. Rajasekaran Namakkal Soorappan[6], Dr. Preetam Krishnamurthya[7], Dr. Balasubramaniyan Jayanthy Venkataa[8], Dr. Sandhya Sundaram[9], Dr. Ramesh Sankarana[10]

[1*]Associate Professor, Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: vinodkumar.b@sriramachandra.edu.in. B, MD, DM (Cardio) Fellowship in intravascular imaging (South Korea) FESC; FSCAI; FACC, Sr. Consultant Interventional Cardiologist, Associate Professor, Department of Cardiology, SRIHER. Managing Trustee & Director: C3 Research Foundation, Chennai Cardiac Care

[2]Associate Professor, Department of Cardiovascular Technology, Faculty of Allied Health Sciences, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: kgmonisha12@sriramachandra.edu.in

[3]Associate Professor, Department of Cardiovascular Technology, Faculty of Allied Health Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Chennai, Tamil Nadu, India. Email: francelavs7@gmail.com

[4]Associate Professor, Department of Cardiovascular Technology, Faculty of Allied Health Sciences, Mahatma Gandhi Medical College and Research Institute, Puducherry, India. Email: jaisrisankar1330@gmail.com

[5]Senior Resident, Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: lalith.kovvuri95@gmail.com

[6]Associate Professor, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, United States. Email: rnamakkalsoorappan@uabmc.edu

[7]Associate Professor, Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: k.preetam@sriramachandra.edu.in

[8]Associate Professor, Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: drjvbala@gmail.com

[9]Professor, Department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: sandhyas@sriramachandra.edu.in

[10]Professor, Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. Email: rameshsankaran39@gmail.com

ABSTRACT

Background: Heart failure (HF) is a multifactorial disorder with a rising global burden, and classification based solely on left ventricular ejection fraction (LVEF) fails to capture the full spectrum of pathophysiological changes, particularly in patients with preserved or mid-range ejection fraction. This study aims to evaluate the combined diagnostic and prognostic utility of N-terminal pro-brain natriuretic peptide (NT-proBNP) and the Heart Failure Echocardiographic Index score criteria (HFEI) in characterizing structural and functional alterations across the HF spectrum.

Methods: This prospective observational study included 90 patients with chronic HF were categorised into three groups: HFrEF (EF <40%), HFmEF (EF 40–49%), and HFpEF (EF ≥50%). Comprehensive echocardiographic assessments and NT-proBNP measurements have been performed. Diastolic dysfunction was graded, and HFEI scores were calculated using an integrative scoring system encompassing systolic function, diastolic parameters, pulmonary pressures, atrioventricular remodeling, and valvular pathology. Statistical comparisons, correlation analyses, and linear regression were conducted to evaluate associations among EF categories, NT-proBNP levels, diastolic dysfunction, and HFEI.

Results: NT-proBNP levels differed significantly among EF categories ($p < 0.0001$), being highest in HFrEF and lowest in HFpEF. NT-proBNP levels also rose significantly with worsening diastolic dysfunction within HFrEF ($p = 0.044$) and HFpEF ($p = 0.030$). HFEI scores showed a strong inverse relationship with LVEF, with median scores of 6 in HFrEF, 4 in HFmEF, and 1 in HFpEF ($p < 0.0001$). Linear regression confirmed HFEI as a robust indicator of structural disease severity across all EF groups. Diastolic dysfunction was most advanced in HFrEF (Grade III: 46.6%) and mildest in HFpEF (Grade I: 60%).

Conclusion: NT-proBNP and HFEI provide complementary insights into the hemodynamic and structural burden of HF beyond LVEF. Their integration into routine evaluation may enhance phenotyping accuracy, support individualized

treatment strategies, and refine prognostic stratification in patients across the HF spectrum. This study reinforces the need for a multiparametric approach to modern HF assessment.

How to cite this article: Kumar V, Ganesh M, Damodaran L, Sankar J, Kovvuria HL, Soorappan RN, Krishnamurthya P, Venkataa BJ, Sundaram S, Sankarana R. Beyond Ejection Fraction: Synergistic Role of NT-proBNP and The Heart Failure Echocardiographic Index in Phenotyping Structural and Functional Burden in Heart Failure. Int J Drug Deliv Technol. 2026;16(16s): 56-64. DOI: 10.25258/ijddt.16.16s.7

INTRODUCTION

Heart failure (hf) is still among the most resilient challenges in modern healthcare, presenting in more than 26 million patients and as a common endpoint pathway for multiple cardiovascular diseases [1]. Its increasing incidence, particularly within aging populations, has amplified the need for timely and accurate diagnostic strategies and meaningful prognostic markers [1]. As much as the therapeutic approach is evolving, hf still carries increased morbidity, mortality, and health expenditure burdens [1].

In the past, physicians have primarily relied on left ventricular diastolic filling (lvdf) and left ventricular ejection fraction (lvef) to assess cardiac function. Lvef, an index of systolic function, has informed the classification and treatment of hf for decades [2]. Yet, lvef is not adequate to describe the complex and multifaceted pathophysiology of hf, especially in patients with preserved (hfpef) or mid-range (hfmref) ejection fraction [3]. These patients can have severe symptoms and poor consequences despite apparently intact systolic function. Therefore, the shortcomings of single-parameter diagnostic tests have challenged the necessity of more comprehensive, integrative diagnosis [4].

The heart failure echocardiographic index (hfei) offers a solution in this regard by combining a range of echocardiographic variables—encompassing systolic and diastolic function, pulmonary arterial pressure, valvular function, and structural remodelling—into a single, overall score [5]. Unlike the subjective classifications such as the new york heart association (nyha) functional class, hfei offers an objective, quantitative image of overall cardiac function. Moreover, hfei has demonstrated a strong correlation with invasive hemodynamic measures, further increasing its value as a non-invasive diagnostic and prognostic tool [3].

Concurrently, biomarkers such as n-terminal pro-brain natriuretic peptide (nt-probnp) have become more important in the diagnosis of hf [6]. Myocardial wall strain and volume overload are indicators of nt-probnp, which has been well demonstrated to be a reliable predictive biomarker [7]. Its specificity is, however, lower in comorbid illness such as renal failure or pulmonary disease. Thus, an overall strategy that uses both structural-functional imaging and biochemical markers can give a better overall and more accurate estimation of the severity of hf [8].

To further refine the diagnostic profile, the heart failure association of the european society of cardiology (hfa–esc) introduced the hfa–peff score a systematic, evidence-based diagnostic algorithm specifically for hfpef [9]. The hfa–peff model employs a stepwise approach that integrates clinical features, echocardiographic markers (e.g., e/e′ ratio, la volume index, lv mass index), and natriuretic peptide levels [9]. Each category—functional, morphological, and biochemical is assigned weighted scores as 1 point and 2 points with a total score that classifies patients as likely (≥5) for hfref and hfmef, unlikely (≤1), or intermediate (2–4) for hfpef.

The hfa–peff framework highlights the necessity of multidomain integration in the diagnosis of hfpef, especially given the limitations of lvef and standalone biomarkers [9]. It reinforces the concept that no single parameter is sufficient to capture the heterogeneity of hfpef, and instead promotes a probabilistic, phenotype-based assessment using a combination of imaging and laboratory findings [9].

Our study aims to investigate the utility of hfesi in conjunction with nt-probnp across the full hf spectrum, including hfref, hfmref, and hfpef. By examining how these tools correlate with disease severity, diastolic dysfunction, and adverse clinical outcomes, we aim to establish an integrated model for comprehensive risk stratification in chronic heart failure. Such a model could significantly enhance clinical decision-making, facilitate early therapeutic interventions, and improve patient outcomes.

Overall, this research advocates for a paradigm shift from reliance on isolated diagnostic markers toward a multifactorial, precision-based strategy in hf evaluation. Through robust validation of hfei alongside nt-probnp and in comparison, to established models like the hfa-peff score, we seek to lay the groundwork for a more accurate and actionable assessment framework in modern heart failure care [5].

METHODS

Study Design and Population

This prospective observational study was conducted at the Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research (SRIHER), over months from December 2024 to March 2025. Ninety individuals with a diagnosis of heart failure (HF) were progressively enrolled. According to the 2016 European Society of Cardiology (ESC) recommendations, the diagnosis of heart failure was made and independently verified by two cardiologists. According to these guidelines, patients were categorized into heart failure with reduced ejection fraction (HFrEF), mid-range ejection fraction (HFmrEF), or preserved ejection fraction (HFpEF). Patients were eligible for inclusion if they had a confirmed diagnosis of HF and comprehensive clinical and echocardiographic data were available. Individuals were excluded if they had significant renal or hepatic dysfunction, a history of malignancy, or underlying neurological disorders. All patients provided informed written consent prior to enrollment. The study protocol was reviewed and approved by the institutional ethics committee of SRIHER.

Clinical Data Collection

Baseline clinical data were recorded at the time of hospital admission. This included demographic details, comorbid conditions, and relevant medical history. Blood samples were collected within 24 hours of admission and analyzed in the hospital's central laboratory. Laboratory investigations included complete blood count, biochemical profile, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. All data entries were documented by a designated physician and subsequently reviewed for accuracy by a second independent investigator.

Echocardiographic Assessment

All patients underwent comprehensive transthoracic echocardiography using a GE Vivid T8, E9, E95 and Philips affinity ultrasound system with a probe frequency of 3.5 MHz Measurements were performed by an experienced sonographer and averaged across three consecutive cardiac cycles to minimize variability.

Echocardiographic measurements included

Cardiac structure: Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left atrial diameter (LAD), left atrial volume index (LAVi), and relative wall thickness (RWT = 2 × LVPWT / LVEDD).

Cardiac function: Early (E) and late (A) mitral inflow velocities, E/A ratio, early diastolic mitral annular velocity (e′), E/e′ ratio, pulmonary artery systolic pressure (PASP), deceleration time (DT).

Heart Failure Echocardiographic Index Score Criteria (HFEI)

HFEI was calculated using a composite scoring system derived from five echocardiographic indices: left ventricular systolic function, diastolic function, pulmonary arterial pressure, atrioventricular remodeling, and valvular pathology each of which reflects important aspects of cardiac performance and structural remodeling [5].

Left ventricular systolic function is primarily assessed by measuring the left ventricular ejection fraction (LVEF). Patients with an LVEF of 30% to 45% or regional wall motion abnormalities receive 1 point, indicating mild to moderate systolic impairment. Severe systolic impairment, such as with an LVEF of less than 30%, receives 2 points, indicating severe myocardial dysfunction [5].

Left ventricular Diastolic function is quantified by Doppler measures like the E/A ratio, deceleration time (DT), and pulmonary venous flow pattern (D/S ratio). Mild diastolic dysfunction, as defined by an E/A ratio of <0.5, DT of >220 ms, or a D/S ratio of <1, is given 1 point. Severe diastolic dysfunction or restrictive filling pattern, as indicated by an E/A ratio of >2, DT of <150 ms, or a D/S ratio of >1, is given 2 points, indicating increased left ventricular filling pressures [5].

Pulmonary arterial systolic pressure (PASP)

is used as an indirect indicator of pulmonary hypertension, which often accompanies worsening left heart function. A PASP between 35 mmHg and 50 mmHg is scored as 1 point, while pressures exceeding 50 mmHg suggestive of significant pulmonary vascular involvement are given 2 points [5].

Atrioventricular remodeling

is assessed through measurements such as the left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), and left atrial diameter (LAD). When LVEDD is between 56 mm and 66 mm or when there is moderate left atrial or ventricular wall thickening (e.g., IVST or LVPWT ≥13 mm, LAD >45 mm), the score is 1 point. However, marked remodelling (LVEDD ≥66 mm) or the presence of right ventricular dysfunction indicates more advanced structural changes and warrants 2 points [5,10].

Lastly, valvular regurgitation or stenosis is included to account for the impact of valve disease on cardiac function. Moderate valvular lesions contribute 1 point to the total score, while severe (serious) valvular pathology contributes 2 points, recognizing their role in exacerbating cardiac workload and dysfunction [5,11].

Overall, this echocardiographic scoring system provides a quantitative framework for integrating multiple dimensions of cardiac structure and function, allowing clinicians to stratify patients with heart failure according to the severity of their echocardiographic abnormalities. Higher cumulative scores indicate more advanced disease and may be useful in guiding treatment decisions and predicting outcomes

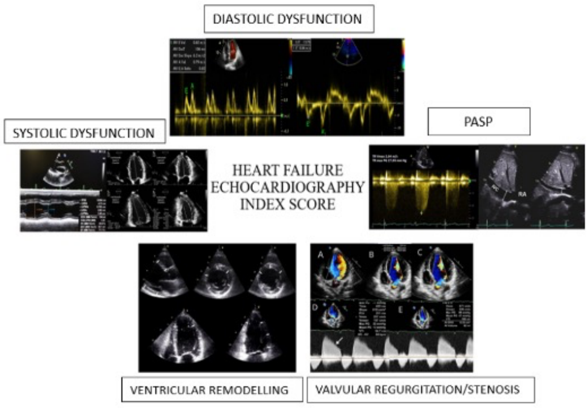

Figure 1. Heart Failure Echocardiographic Index Score Criteria (HFEI).

Table 1. Heart Failure Echocardiographic Index Score Criteria (HFEI).

Domain	Criteria	Score
Left Ventricular Systolic Function	LVEF 30%–45% or regional wall motion abnormality	1 point
	LVEF < 30%	2 points
Left Ventricular Diastolic Function	E/A < 0.5, DT > 220 ms, D/S < 1	1 point
	E/A > 2, DT < 150 ms, D/S > 1 or restrictive filling pattern	2 points
Pulmonary Arterial Systolic Pressure (PASP)	PASP 35–50 mmHg	1 point
	PASP ≥ 50 mmHg	2 points
Atrioventricular Remodeling	LVEDD 56–66 mm, IVST or LVPWT ≥13 mm, LAD > 45 mm	1 point
	LVEDD ≥ 66 mm or right ventricular dysfunction	2 points
Valvular Regurgitation or Stenosis	Moderate valvular regurgitation or stenosis	1 point
	Severe valvular regurgitation or stenosis	2 points

(DT early diastolic mitral flow deceleration time, D/S pulmonary venous flow (S peak systolic wave velocity and D peak diastolic wave velocity), E/A peak velocity during early filing(E), late filling from atrial contraction (A), IVST interventricular septal thickness, LVEF left ventricular ejection fraction, LVEDD left ventricular end diastolic diameter, PASP pulmonary arterial systolic pressure, LVPWT left ventricular posterior wall thickness)

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. Descriptive statistics were used to analyse baseline demographic, laboratory, and echocardiographic variables. Continuous variables were expressed as a median with interquartile range (IQR) and sample t-tests were used to compare means between groups. A correlation matrix was employed to examine the relationships between the presence and severity grades of diastolic dysfunction with NT-proBNP levels in the study group. Additionally, a linear regression analysis was conducted to explore the predictive association between NT-proBNP levels and the Heart Failure Echocardiographic Index (HFEI), quantifying the strength and significance of this relationship. Statistical significance was defined as a two-tailed p-value of less than 0.05 for all analyses.

RESULTS

Baseline Clinical Characteristics

A total of 90 participants were stratified into three groups based on left ventricular ejection fraction (LVEF): Heart Failure with Reduced Ejection Fraction (HFrEF, n = 30), Mid-range Ejection Fraction (HFmEF, n = 30), and Preserved Ejection Fraction (HFpEF, n = 30). The clinical and demographic characteristics of these groups are presented in Table 2. The age distribution was similar across the groups, with median values of 68.5 years in HFrEF, 68 years in HFmEF, and 65 years in HFpEF (p = 0.435). This suggests that age did not significantly influence the categorization of heart failure by LVEF in this cohort. In contrast, body surface area (BSA) showed a significant difference (p = 0.025), with HFmEF patients having the lowest median BSA (1.6 m²), which may reflect distinct body composition patterns or metabolic profiles associated with mid-range cardiac function.

There were no statistically significant differences in heart rate (p = 0.270), systolic blood pressure (p = 0.245), or diastolic blood pressure (p = 0.405) across the groups. Although the HFrEF and HFpEF groups shared a higher median heart rate (90 bpm) compared to HFmEF (83 bpm), this was not statistically meaningful.

Laboratory investigations—including white blood cell (WBC) and red blood cell (RBC) counts, blood urea nitrogen (BUN), and serum creatinine—were not significantly different among the three groups. However, NT-proBNP levels differed markedly ($p < 0.0001$), with the highest median observed in HFrEF (16,304 pg/mL), followed by HFmEF (5,382 pg/mL), and the lowest in HFpEF (955 pg/mL). This progressive increase reflects neurohormonal activation in proportion to the degree of systolic impairment and underscores NT-proBNP' s diagnostic and prognostic utility in heart failure classification.

Table 2. Baseline clinical characteristics of study participants categorized by ejection fraction groups. Data are presented as median (interquartile range, IQR). Comparisons were made using the T-test; p-values < 0.05 were considered statistically significant.

Parameters	Group 1 (Reduced Ejection Fraction) - median (IQR)	Group 2 (Mid Ejection Fraction) - median (IQR)	Group 3 (Preserved Ejection Fraction) - median (IQR)	P-value
AGE	68.5 (58.25-70)	68 (57-70)	65 (58-70)	0.435
BSA	1.75 (1.6-1.8)	1.6 (1.5-1.7)	1.7 (1.6-1.8)	**0.025**
HEART RATE	90 (86.25-97)	83 (72.5-95.75)	90 (80.5-98)	0.270
SBP	120 (110-130)	135 (120-140)	130 (120-150)	0.245
DBP	70 (70-80)	80 (70-80)	80 (70-90)	0.405
WBC	9060 (7585-10987.5)	9695 (7782.5-12060)	9400 (8425-11445)	0.929
RBC	4.185 (3.5-4.5975)	3.925 (3.3025-4.185)	4.025 (3.6675-4.5175)	0.262
BUN	16.5 (13-19.75)	15 (12.25-19)	16.5 (14-19)	0.610
CR	1.1 (0.9-1.2)	1.05 (0.825-1.2)	1 (0.8-1.1)	0.134
NT PRO BNP	16304 (11687 ±23649)	5382(4389±8740)	955 (838 ±1085)	**<.0001**

Echocardiographic Structural and Functional Characteristics

Comprehensive echocardiographic assessment revealed significant and progressive remodelling of cardiac structure and function across the LVEF groups, detailed in Table 3. Patients in the HFrEF group exhibited pronounced ventricular remodelling, evidenced by significantly larger interventricular septal thickness (diastolic and systolic), posterior wall thickness, and left ventricular internal diameter in diastole (LVIDD). Median LVIDD was 54 mm in HFrEF, 48.5 mm in HFmEF, and 44 mm in HFpEF ($p < 0.001$). Similarly, left ventricular end-diastolic volume (LVEDV) was highest in HFrEF (133 mL) and lowest in HFpEF (90.5 mL), consistent with a dilated phenotype in systolic dysfunction.

As expected, LVEF was significantly lower in HFrEF (30%) and increased across groups to 42% in HFmEF and 55.5% in HFpEF ($p < 0.001$). TAPSE, a surrogate for right ventricular systolic function, was significantly reduced in HFrEF (1.6 cm), compared to 1.8 cm in both HFmEF and HFpEF groups ($p = 0.001$), reflecting early right heart involvement in advanced systolic dysfunction.

Markers of diastolic performance varied significantly. The E/e′ ratio, indicative of left ventricular filling pressure, was highest in HFrEF (18.61), followed by HFmEF (15.435), and lowest in HFpEF (13.585; $p < 0.001$). Deceleration time (DT) followed an inverse trend, being shortest in HFrEF (112 ms) and longest in HFpEF (180 ms; $p < 0.001$). These results reinforce the progressive impairment of both systolic and diastolic function as heart failure severity increases.

Interestingly, left atrial size and volume indices including LA diameter, LA volume, and LAVI did not differ significantly between groups ($p > 0.3$), suggesting that atrial remodeling may not directly correspond to ejection fraction categories alone and could be influenced by arrhythmia history or chronic volume load.

Table 3. Echocardiographic parameters across groups with different ejection fraction categories. Measurements include septal thickness, LV dimensions, EF, atrial size, and diastolic markers. Data are shown as median (IQR). Comparisons were made using the T-test; p-values reflect intergroup differences.

Parameters	Group 1 (Reduced Ejection Fraction) - median (IQR)	Group 2 (Mid Ejection Fraction) - median (IQR)	Group 3 (Preserved Ejection Fraction) - median (IQR)	P-value
IVSD	9 (8.25-10)	10 (9-11.75)	12 (11-13.75)	**<.001**

IVSS	10 (9.25-11)	11 (10-13)	14 (12-15)	**<.001**
PWD	10 (8.25-11)	10 (9-11.75)	12 (11-13.75)	**<.001**
PWS	11 (10.25-12)	11 (10-13)	13.5 (12-14)	**<.001**
LVIDD	54 (48-57.75)	48.5 (48-52.5)	44 (42-48)	**<.001**
LVEDV	133 (117.25-161.75)	119 (109-130.5)	90.5 (79.25-104.25)	**<.001**
LVEF%	30 (28.5-32)	42 (40-45)	55.5 (55-58)	**<.001**
LA Diameter	42 (34.25-44)	38 (33.25-42)	36.5 (33-42.75)	0.339
LA Volume	50 (37.025-62)	48 (40.25-58.5)	40.5 (34.25-61.5)	0.989
LAVI	29.565 (20.15-34.2)	27.85 (24.6-34.825)	23.65 (20.125-36.9475)	0.741
TAPSE	1.6 (1.3-1.7)	1.8 (1.7-1.9)	1.8 (1.625-1.9)	**0.001**
E/A	0.865 (0.62-1.545)	0.985 (0.8025-1.5775)	0.87 (0.73-1.0725)	0.156
E/e'	18.61 (13.905-21.445)	15.435 (12.235-19.2375)	13.585 (11.1225-16.145)	**<.001**
DT	112 (105.5-144.25)	147.5 (102.25-177.75)	180 (144.75-197)	**<.001**
PASP	42 (27.5-53)	35.5 (26-52.75)	33 (21.5-47.5)	0.608
HFESSI	6 (6-8)	4 (3-4.75)	1 (0-2)	**<.0001**

Distribution of Diastolic Dysfunction Grades

The severity of diastolic dysfunction, categorized into Grades I to Grade III, demonstrated a statistically significant relationship with ejection fraction phenotype (Table 4; p = 0.027). Among patients with HFrEF, nearly half (46.6%) exhibited Grade III diastolic dysfunction, while the remaining individuals were equally distributed between Grades I and II. In contrast, HFpEF patients predominantly had milder dysfunction, with 60% showing Grade I and only 13.3% with Grade III. The HFmEF group had a relatively even distribution across all grades, supporting its role as a pathophysiological intermediate category encompassing elements of both systolic and diastolic impairment**.**

Table 4. Distribution of diastolic dysfunction grades across LVEF categories. The statistical significance of the relationship between diastolic grade and EF classification was assessed using correlation.

Group	Diastolic Dysfunction (Grade)			
	Grade I	**Grade II**	**Grade III**	**P value**
Reduced Ejection Fraction	8 (26.7%)	8 (26.7%)	14 (46.6%)	0.027
Mid Ejection Fraction	9 (30%)	10 (33.3%)	11 (36.7%)	
Preserved Ejection Fraction	18 (60%)	8 (26.7%)	4 (13.3%)	

Relationship Between NT-proBNP and Diastolic Dysfunction Severity within each LV ejection fraction groups

To further examine the role of NT-proBNP as a marker of combined systolic and diastolic burden, values were compared across diastolic dysfunction grades within each LVEF group (Table 5). In the HFrEF group, NT-proBNP levels increased significantly from Grade I to Grade III (median values: 12,013 → 16,339 → 21,350 pg/mL; p = 0.044), underscoring additive neurohormonal stress with worsening diastolic impairment in already compromised systolic function. In the HFmEF group, although NT-proBNP showed an increasing trend (Grade I: 4,740 → Grade III: 7,203 pg/mL), the change was not statistically significant (p = 0.419). This may reflect overlapping systolic and diastolic influences, which together contribute variably to biomarker levels. Remarkably, in the HFpEF group, NT-proBNP levels rose significantly across dysfunction grades (p = 0.030), from 932 pg/ml in Grade I to 1,660 pg/mL in Grade III. These findings highlight NT-proBNP' s diagnostic value in identifying occult hemodynamic burden, even when systolic performance remains preserved.

Table 5. NT-proBNP concentrations stratified by diastolic dysfunction grade within each ejection fraction group was assessed using correlation. Data are presented as median (IQR); p-values reflect intragroup differences.

Group	Diastolic Dysfunction			P value
	Grade I	Grade II	Grade III	
Reduced Ejection Fraction	12013 (10734-17375)	16339 (11822-21225)	21350 (15020-25882)	0.044
Mid Ejection Fraction	4740 (3485-5117)	6915 (4624-9302)	7203 (4627-8997)	0.039
Preserved Ejection Fraction	932 (837-1073)	905 (776-1004)	1660 (1658-1667)	0.030

Relationship Between HFEI and NT Pro Level

The analysis demonstrated a progressive increase in NT-proBNP levels with rising HFESI scores, highlighting a strong positive association between echocardiographic BnP burden of heart failure and circulating biomarker levels. Patients with a HFESI of 0 had a mean NT-proBNP of 805.31 ± 193.29 pg/mL. As the HFESI increased, NT-proBNP concentrations rose incrementally: 1092 ± 261.49 pg/mL (score 1), 2549.5 ± 1406.67 pg/mL (score 2), and 3523.11 ± 2059.80 pg/mL (score 3). A substantial elevation was observed at HFESI 4, with a mean NT-proBNP of 4727.59 ± 2624.78 pg/mL.

Marked elevations occurred in the mid and high HFESI range. At score 5, the NT-proBNP level increased to 10,598.6 ± 1301.30 pg/mL, reaching 14,487.4 ± 4828.84 pg/mL at score 6 and 17,012.25 ± 7607.61 pg/mL at score 7. The highest levels were seen in patients with HFESI scores of 8–10, where NT-proBNP exceeded 20,000 pg/mL, peaking at 31,207 pg/mL for a score of 10.

Based on these distributions, three distinct categories were defined: low HFESI (1–4) associated with NT-proBNP <6000 pg/mL, intermediate HFESI (5–7) corresponding to NT-proBNP levels between 10,000–20,000 pg/mL, and high HFESI (8–10) aligning with NT-proBNP values >20,000 pg/mL.

The present findings highlight that NT-proBNP levels closely correlate with echocardiographic severity as quantified by the Heart Failure Echocardiographic Index score (HFEI), reflecting complementary aspects of the hemodynamic and structural burden of heart failure beyond conventional left ventricular ejection fraction (LVEF) assessment. Integration of both NT-proBNP and HFEI offers complementary assessment of hemodynamic stress and structural remodeling beyond LVEF. Adopting a multiparametric strategy may enhance phenotyping, guide individualized therapy, and improve prognostic precision across the heart failure spectrum.

Table 6. Illustrate the mean NT pro-BNP concentrations (pg/ml) with standard deviation across progressive heart failure score index scores 0 to 10.

NT PRO-BNP (MEAN±SD)	HFESI
805.31 + 193.29	0
1092 + 261.49	1
2549.5 + 1406.67	2
3523.11 + 2059.80	3
4727.59 + 2624.78	4
10598.6 + 1301.30	5
14487.4 + 4828.84	6
17012.25 + 7607.61	7
25309 + 4839.99	8
22941 + 1416	9
31207	10

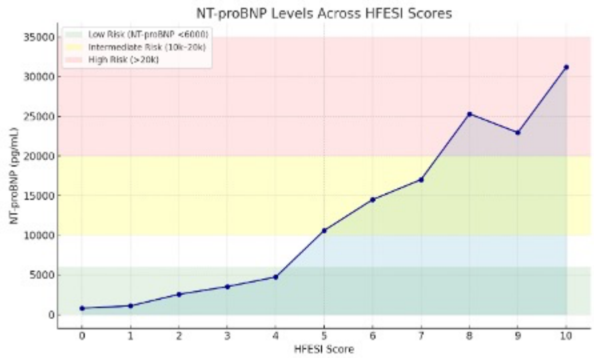

Figure 3. NT pro-BNP levels across HFEI score (0-10).

Association Between HFEI and Ejection Fraction Phenotypes

To integrate structural findings into a single risk stratification tool, the Heart Failure Echocardiographic Index score criteria (HFEI) was applied to all participants. This composite index reflected cumulative burden from echocardiographic abnormalities and showed a robust association with ejection fraction categories (Table 7).

Median HFEI scores were highest in HFrEF (6; IQR 6–8), moderate in HFmEF (4; IQR 3–4.75), and lowest in HFpEF (1; IQR 0–2). Linear regression analysis confirmed statistically significant associations in all three groups (HFrEF: p = 0.000; HFmEF: p < 0.0001; HFpEF: p < 0.0001), suggesting that HFEI effectively captures disease severity gradients across the heart failure spectrum.

Clinically, HFEI could be a useful supplement to LVEF in the classification of structural heart failure, providing detailed information about subclinical remodeling and potentially guiding personalized therapeutic strategies.

Table 7. Linear regression analysis of HFEI scores across heart failure phenotypes (7.aHFrEF, 7.bHFmEF, 7.cHFpEF) with respective NT-proBNP levels. P-values denote the significance of the correlation between structural severity and EF classification.

Table 7. a:

	HFrEF		
HFESI	**ESTIMATE**	**SE**	**P**
	3741	680	0.000

Table 7. b:

	HFmEF		
HFESI	**ESTIMATE**	**SE**	**P**
	1744	251	<0.001

Table 7. c:

	HFpEF		
HFESI	**ESTIMATE**	**SE**	**P**
	788	458	<0.0001

DISCUSSION

The present study comprehensively analysed the clinical, biochemical, and echocardiographic profiles of heart failure (HF) patients classified by ejection fraction into Reduced (HFrEF), Mid-range (HFmEF), and Preserved (HFpEF) categories. Our results underscore the complexity and heterogeneity of heart failure and emphasise that ejection fraction (EF), while a central metric, provides only a partial snapshot of cardiac pathophysiology. Through integrated analysis of diastolic dysfunction grades, NT-proBNP levels, and structural remodelling indices notably the Heart Failure Echocardiographic Index score criteria (HFEI) our findings highlight the value of multiparametric evaluation for risk stratification and individualized management [15,17].

Ejection Fraction Alone is Insufficient for Phenotyping Heart Failure

While LVEF remains the most used measure for classifying HF patients, its limitations have long been recognized. In line with prior studies, our findings confirm that similar clinical presentations can arise in patients with drastically different EF values, emphasizing the syndrome's multidimensional nature [17].

Age, previously described as a strong predictor of the development of HF, did not significantly differ between groups within our population. This indicates that HF development throughout the range of EF is less due to age and more due to the interplay between comorbidities, myocardial remodelling, and hemodynamic burden [14].

NT-proBNP: A Window into Hemodynamic Stress and Ventricular Dysfunction

The gradient of NT-proBNP levels we observed across the EF categories (highest in HFrEF, intermediate in HFmEF, lowest in HFpEF) reaffirms the biomarker's strong correlation with myocardial wall stress. Our observation states that NT-proBNP levels also rose in proportion to diastolic dysfunction severity, especially in HFpEF patients [16].

Interestingly, even within the HFpEF group, NT-proBNP values provided diagnostic and prognostic cues, reinforcing its critical role in assessing diastolic dysfunction in structurally preserved hearts, as previously described by Seferovic et al. [12] and Kasner et al. [13]. Our findings also support the suggestion by Tschope et al. [14] that NT-proBNP should be embedded in diagnostic algorithms for HFpEF, rather than treated as a secondary marker.

The diagnostic relevance of NT-proBNP extends to therapeutic decisions as well. Several landmark trials have used NT-proBNP for patient enrichment and risk stratification in heart failure, both in preserved and reduced EF categories [14]. Given our observation of consistent peptide elevation with advancing diastolic dysfunction, we support the position that NT-proBNP should remain a cornerstone in both diagnosis and treatment monitoring.

Echocardiographic Findings: Structural and Functional Divergence

Our echocardiographic findings complement the biochemical data and reinforce the concept of phenotype-specific remodelling in heart failure (HF). As expected, patients in the HFrEF group demonstrated significantly dilated ventricles, increased wall thickness, and larger end-diastolic volumes and the classic geometric hallmarks of chronic volume overload and maladaptive eccentric remodelling. These patterns are well described in the pathophysiology of systolic failure, where myocardial contractility declines and compensatory chamber dilation ensues [15].

Conversely, the HFpEF cohort presented relatively normal left ventricular sizes but displayed significant abnormalities in diastolic function markers, particularly E/e′ ratio and deceleration time. This finding highlights the distinction between systolic and diastolic heart failure and mirrors the description of HFpEF as a syndrome driven primarily by ventricular stiffness, impaired relaxation, and altered extracellular matrix composition [17,18].

Diastolic Dysfunction Grades: Clinical Implications

Diastolic dysfunction is an integral component of heart failure, systolic or preserved, and grading of diastolic dysfunction gives critical information about disease severity and course. Our study simulated the expected pattern of distribution wherein the most frequent severe diastolic dysfunction (Grade III) occurred in the HFrEF group and the HFpEF group had Grade I dysfunction. This is consistent with the natural progression of ventricular dysfunction, in which deteriorating systolic function is preceded by severe diastolic impairment [19].

The HFmEF cohort was evenly distributed across all grades of diastolic dysfunction, enhancing its highly valued heterogeneity. This is consistent with new evidence that HFmEF is not simply an intermediate along the spectrum between HFpEF and HFrEF, but may have unique pathophysiologic phenotypes, some related to recovery from low EF and others related to progression from preserved EF [21]. This supports the need for a personalized approach to diagnosis and treatment of HFmEF, as suggested by Wessler et al. [20].

HFEI: A Composite Structural Predictor Beyond Ejection Fraction

A particularly novel finding in our study is the significant correlation between the Heart Failure Echocardiographic Index score criteria (HFEI) and the LVEF categories. HFEI provides an integrated score that reflects not only systolic and diastolic dysfunction but also geometric remodelling and chamber dimensions, offering a comprehensive summary of cardiac structural health.

Our results are consistent with Al Saikhan et al. (2020), who demonstrated that composite echocardiographic indices improve risk prediction compared to isolated metrics like LVEF or NT-proBNP alone. HFEI's ability to stratify risk across all EF categories, including HFpEF and HFmEF, suggests it could address the gaps left by LVEF-centric classification systems.

Given that both HFpEF and HFmEF present therapeutic challenges, particularly as standard HFrEF treatments do not always translate into benefit, HFESSI could support more accurate phenotyping, thereby improving patient selection for clinical trials and targeted therapies [19].

Study Strengths and Limitations

A key strength of this study lies in its integrated, real-world evaluation of HF patients using accessible clinical tools. The use of HFESSI provides a scalable, non-invasive measure of structural heart disease, while the inclusion of NT-proBNP and diastolic grading enhances diagnostic granularity [16]. However, several limitations must be acknowledged. The cross-sectional design precludes temporal or prognostic inference. The sample size, though sufficient for statistical comparison, may limit generalizability. Future longitudinal studies incorporating serial measurements of NT-proBNP and HFESSI are necessary to confirm their long-term prognostic value and to assess their predictive and therapeutic value [21].

CONCLUSION

In conclusion, this study underscores the distinct clinical, biochemical, and structural profiles that define heart failure subgroups across the preserved, mid-range, and reduced ejection fraction spectrum. Our findings demonstrate that integrating NT-proBNP levels and the Heart Failure Echocardiographic Index score criteria (HFEI) with diastolic dysfunction grading offers a more comprehensive and accurate evaluation of disease severity and progression than reliance on ejection fraction or diastolic markers alone. Incorporating these indices into routine clinical evaluation has the potential to enhance diagnostic precision, personalize therapeutic strategies, and improve prognostic accuracy in this increasingly diverse and complex patient population. Such an integrated strategy not only strengthens the foundation for individualized, evidence-driven care but also marks a critical step toward advancing precision medicine in heart failure management.

REFERENCE

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3(1):7-11. doi:10.15420/cfr.2016:25:2
2. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;23(3):352-380. doi:10.1002/ejhf.2115
3. Branca, L., Sbolli, M., Metra, M., and Fudim, M. (2020) Heart failure with mid-range ejection fraction: pro and cons of the new classification of Heart Failure by European Society of Cardiology guidelines. *ESC Heart Failure*, 7: 381–399. https://doi.org/10.1002/ehf2.12586.
4. Kim IC, Yoo BS. Multidimensional Approach of Heart Failure Diagnosis and Prognostication Utilizing Cardiac Imaging with Biomarkers. *Diagnostics (Basel)*. 2022;12(6):1366. Published 2022 Jun 1. doi:10.3390/diagnostics12061366
5. Chen JS, Pei Y, Li CE, Li NY, Guo T, Yu J. Prognostic value of heart failure echocardiography index in HF patients with preserved, mid-ranged and

reduced ejection fraction. *BMC Cardiovasc Disord*. 2020;20(1):351. Published 2020 Jul 29. doi:10.1186/s12872-020-01635-6

6. McKie PM, Burnett JC Jr. NT-proBNP: The Gold Standard Biomarker in Heart Failure. *J Am Coll Cardiol*. 2016;68(22):2437-2439. doi:10.1016/j.jacc.2016.10.001
7. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347(3):161-167. doi:10.1056/NEJMoa020233
8. Moura B, Aimo A, Al-Mohammad A, et al. Integration of imaging and circulating biomarkers in heart failure: a consensus document by the Biomarkers and Imaging Study Groups of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2021;23(10):1577-1596. doi:10.1002/ejhf.2339
9. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2020;22(3):391-412. doi:10.1002/ejhf.1741
10. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32(1):1-64. doi:10.1016/j.echo.2018.06.004
11. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70(2):252-289. doi:10.1016/j.jacc.2017.03.011
12. Januzzi JL Jr, Prescott MF, Butler J, et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA*. 2019;322(11):1085-1095. doi:10.1001/jama.2019.12821
13. Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation*. 2007;116(6):637-647. doi:10.1161/CIRCULATIONAHA.106.661983
14. Savarese G, Orsini N, Hage C, et al. Utilizing NT-proBNP for Eligibility and Enrichment in Trials in HFpEF, HFmrEF, and HFrEF. *JACC Heart Fail*. 2018;6(3):246-256. doi:10.1016/j.jchf.2017.12.014
15. Al Saikhan, M. A., et al. (2020). Prognostic value of heart failure echocardiography index in HF patients with preserved, mid-ranged, and reduced ejection fraction. *BMC Cardiovascular Disorders*. https://doi.org/10.1186/s12872-020-01635-6
16. McMurray, J. J. V., et al. (2019). Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *European Journal of Heart Failure*, *21*(10), 1343-1354. https://doi.org/10.1002/ejhf.1494
17. Pieske, B., et al. (2019). How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *European Heart Journal*, *40*(39), 3297-3317. https://doi.org/10.1093/eurheartj/ehz641
18. Pieske, B., et al. (2020). Prognosis and NT-pro BNP in heart failure patients with preserved versus reduced ejection fraction. *Heart*, *105*(13), 1033-1039. https://doi.org/10.1136/heartjnl-2018-314173
19. Ponikowski, P., et al. (2019). Estimating left ventricular filling pressure by echocardiography. *Journal of the American College of Cardiology*, *69*(5), 634-651. http://dx.doi.org/10.1016/j.jacc.2017.01.058
20. Wessler, J. D., et al. (2019). Natriuretic peptides in heart failure with preserved left ventricular ejection fraction: From molecular evidences to clinical implications. *International Journal of Molecular Sciences*, *20*(11), 2629. https://doi.org/10.3390/ijms20112629
21. Zile, M. R., et al. (2020). The predictivity of N-terminal pro b-type natriuretic peptide for all-cause mortality in various follow-up periods among heart failure patients. *Journal of Clinical Medicine*, *8*(3), 357. https://doi.org/10.3390/jcm8030357