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Original Research Article

# Comparative Analysis of Clinical, Echocardiographic, and Prognostic Profiles Across Heart Failure Phenotypes

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**Abstract:**

**Background:** Heart failure (HF) is a heterogeneous syndrome classified into three main phenotypes based on left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF). These phenotypes differ not only in pathophysiology but also in their clinical presentation, echocardiographic profile, and overall prognosis.

**Objectives:** This study aimed to compare the clinical characteristics, echocardiographic parameters, and short-term outcomes among patients with HFrEF, HFmrEF, and HFpEF.

**Methods:** A prospective observational study was conducted at a tertiary cardiac center over 24 months. A total of 250 patients with confirmed heart failure were enrolled and categorized based on LVEF. Comprehensive clinical evaluations and two-dimensional echocardiography were performed at baseline and at 12-month follow-up. Statistical analysis was performed using SPSS version 23.0, with significance set at $p<0.05$.

**Results:** Of 250 patients, 98 (39.2%) had HFrEF, 72 (28.8%) had HFmrEF, and 80 (32.0%) had HFpEF. HFpEF patients were significantly older (67.8±9.4 vs. 62.1±10.8 vs. 58.4±11.2 years; $p<0.001$) with a higher proportion of females and greater burden of hypertension and atrial fibrillation. HFrEF patients had significantly larger left ventricular dimensions, lower LVEF, and higher NT-proBNP. Worse functional class and higher cardiovascular event rates were observed in HFrEF patients over 12 months of follow-up.

**Conclusion:** The three phenotypes of heart failure exhibit distinct clinical and echocardiographic signatures. HFrEF carries the greatest hemodynamic burden while HFpEF demonstrates a unique comorbidity-driven profile. These differences underscore the importance of phenotype-specific diagnostic and management strategies.

**Keywords:** Heart Failure Phenotypes; HFrEF; HFmrEF; HFpEF; Echocardiography; Left Ventricular Ejection Fraction; Diastolic Dysfunction; Clinical Outcomes.

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## Introduction

Heart failure (HF) is a complex clinical syndrome that continues to impose a substantial global burden, affecting more than 64 million individuals worldwide, with escalating rates of hospitalization and mortality across all age groups.[1] Despite considerable advances in cardiovascular medicine over the past two decades, HF remains one of the leading causes of morbidity and premature death, particularly in patients aged 65 years and above. The syndrome is defined by structural or functional cardiac abnormalities that result in the heart's inability to supply adequate cardiac output to meet the metabolic demands of peripheral tissues, or to do so only at the cost of elevated filling pressures.[2]

The classification of HF based on left ventricular ejection fraction (LVEF) has gained wide clinical acceptance because it reflects distinct underlying pathophysiology and guides therapeutic decision-making. Three principal phenotypes are now recognized: HF with reduced ejection fraction (HFrEF, LVEF <40%), HF with mid-range ejection fraction (HFmrEF, LVEF 40–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%).[3] Historically, HFrEF received the greatest research attention and benefited from an

expanding array of evidence-based therapies, including neurohormonal blockade with angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists.[4]

HFpEF has emerged as a clinically distinct and increasingly prevalent phenotype, now accounting for approximately 50% of all HF cases in community-based studies.[5] Unlike HFrEF, HFpEF predominantly affects elderly women with multiple non-cardiac comorbidities, including hypertension, obesity, diabetes mellitus, and atrial fibrillation. The pathophysiological basis of HFpEF centers on impaired myocardial relaxation, increased ventricular stiffness, and abnormal ventricular-arterial coupling, which collectively result in elevated filling pressures despite preserved systolic function.[6]

HFmrEF was formally recognized as a distinct category by the 2016 European Society of Cardiology (ESC) Heart Failure Guidelines, with the primary purpose of characterizing this intermediate group more precisely and stimulating dedicated research.[7] Emerging evidence suggests that HFmrEF may represent a dynamic transitional phenotype, with some patients improving to HFpEF range and others declining toward HFrEF, thereby necessitating longitudinal echocardiographic surveillance.[8]

Echocardiography remains the cornerstone diagnostic tool for phenotyping HF due to its wide availability, safety, and ability to provide comprehensive information on cardiac structure and function. Key parameters—including LVEF, left ventricular dimensions, wall thickness, diastolic function indices such as the E/A and E/e' ratios, left atrial volume index, and right ventricular systolic pressure—permit differentiation of HF phenotypes and carry independent prognostic value.[9]

Despite a growing body of literature, comparative studies simultaneously evaluating all three HF phenotypes using standardized echocardiographic protocols and clinical assessments are relatively limited, particularly in indian populations where comorbidity profiles may differ from Western cohorts. Available registries, such as the CHARM programme and the I-PRESERVE trial, have provided important insights into HFpEF, yet their findings may not be universally generalizable.[10] Understanding the distinct clinical and echocardiographic signatures of each phenotype is fundamental to individualized patient care, risk stratification, and the development of novel therapeutic strategies. In this context, the present study was designed to comprehensively characterize and compare the clinical features, echocardiographic parameters, and short-term outcomes among patients with HFrEF, HFmrEF, and HFpEF presenting to a tertiary cardiac referral center.

## Materials and Methods

**Study Design and Setting:** This was a prospective, single-center, observational study conducted at the Department of Cardiology of our tertiary care hospital, over a period of 24 consecutive months (January 2015 to December 2016). Ethical approval was obtained from the Institutional Review Board, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

**Patient Selection:** Adult patients aged ≥18 years presenting with a confirmed diagnosis of heart failure—established on the basis of clinical symptoms, physical examination findings, elevated natriuretic peptide levels, and supportive echocardiographic evidence—were considered for enrollment. Exclusion criteria included acute myocardial infarction within the preceding three months, severe valvular heart disease requiring intervention, constrictive pericarditis, hypertrophic or restrictive cardiomyopathy, end-stage renal disease on dialysis, active malignancy, pregnancy, and inability to obtain interpretable echocardiographic images.

**Sample Size Calculation:** The sample size was estimated using G*Power version 3.1 for one-way ANOVA comparing three independent groups. Assuming an effect size of 0.25, a two-sided alpha error of 5%, and 80% power, the minimum required sample size was 220 participants. After accounting for a 10% attrition rate, a target sample size of 242 was determined. Ultimately, 250 eligible patients were enrolled.

**Phenotype Classification:** Patients were classified into three groups based on LVEF as measured by two-dimensional echocardiography using the modified Simpson's biplane method: HFrEF (LVEF <40%), HFmrEF (LVEF 40–49%), and HFpEF (LVEF ≥50%). All echocardiograms were reported by two experienced cardiologists blinded to clinical data, and discordant readings were resolved by a third reviewer.

**Clinical Assessment:** A standardized proforma was used to capture demographic information, comorbidities, NYHA functional class, pharmacological history, vital signs, and relevant laboratory parameters at the time of enrollment. Functional capacity was further assessed using the six-minute walk test (6MWT) and health-related quality of life was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ).

**Echocardiographic Protocol:** Transthoracic echocardiography was performed using a Philips EPIQ 7 ultrasound system with a 3.5 MHz phased-array transducer according to the American Society of Echocardiography (ASE) guidelines. Parameters recorded included: LVEF, left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter (LVESd), interventricular septal thickness in diastole (IVSd), left atrial diameter, E/A ratio, E/e' ratio, right ventricular systolic pressure (RVSP), and the degree of mitral regurgitation (MR).

**Statistical Analysis:** Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate, and compared using one-way ANOVA or Kruskal-Wallis test. Categorical variables were reported as frequencies and percentages and compared with the chi-square test or Fisher's exact test. Post-hoc pairwise comparisons were performed using Bonferroni correction. All statistical tests were two-tailed and significance was defined as $p<0.05$. Analyses were conducted using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA).

## Results

**Participant Enrollment:** A total of 284 consecutive patients with heart failure were screened, of whom 250 met the eligibility criteria and were enrolled. Of these, 98 (39.2%) were classified as HFrEF, 72 (28.8%) as HFmrEF, and 80 (32.0%) as HFpEF.

**Table 1: Baseline Clinical and Demographic Characteristics of Study Participants by Heart Failure Phenotype**

| Variable | HFrEF (n=98) | HFmrEF (n=72) | HFpEF (n=80) | p-value |
|---|---|---|---|---|
| **Age (years), mean±SD** | 58.4±11.2 | 62.1±10.8 | 67.8±9.4 | <0.001 |
| **Male sex, n (%)** | 72 (73.5) | 46 (63.9) | 38 (47.5) | 0.003 |
| **BMI (kg/m²), mean±SD** | 26.8±4.6 | 28.4±5.1 | 30.2±5.8 | 0.008 |
| **Hypertension, n (%)** | 54 (55.1) | 48 (66.7) | 66 (82.5) | <0.001 |
| **Diabetes mellitus, n (%)** | 38 (38.8) | 34 (47.2) | 42 (52.5) | 0.04 |
| **Atrial fibrillation, n (%)** | 32 (32.7) | 28 (38.9) | 46 (57.5) | 0.001 |
| **CAD, n (%)** | 62 (63.3) | 40 (55.6) | 28 (35.0) | <0.001 |
| **NYHA Class III/IV, n (%)** | 74 (75.5) | 44 (61.1) | 36 (45.0) | <0.001 |
| **NT-proBNP (pg/mL), median** | 3120 | 1850 | 980 | <0.001 |

Table 1 presents the baseline demographic and clinical profile of the study population stratified by HF phenotype. Patients with HFpEF were significantly older (mean age 67.8±9.4 years) compared to HFmrEF (62.1±10.8 years) and HFrEF (58.4±11.2 years; $p<0.001$). The proportion of male patients was highest in the HFrEF group (73.5%) and lowest in the HFpEF group (47.5%), consistent with the known female predominance in preserved ejection fraction heart failure. Hypertension was more prevalent in HFpEF (82.5%) compared to HFrEF (55.1%), while coronary artery disease was most frequent in HFrEF (63.3%). NT-proBNP levels were highest in HFrEF patients, and higher NYHA class III/IV prevalence reflected greater functional impairment in this group.

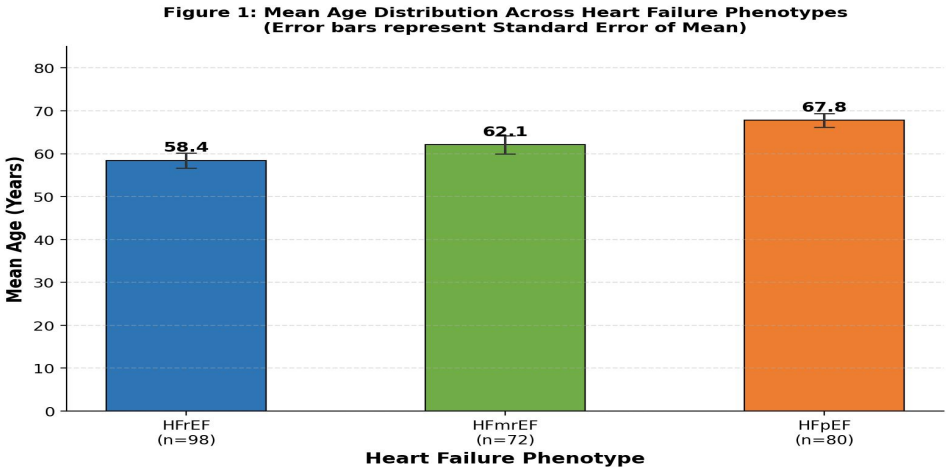


**Figure 1: Mean age distribution across the three heart failure phenotypes (HFrEF, HFmrEF, HFpEF). Error bars denote standard error of the mean. HFpEF patients were significantly older than both HFmrEF and HFrEF counterparts ($p<0.001$).**

**Table 2: Echocardiographic Parameters by Heart Failure Phenotype**

| Parameter | HFrEF (n=98) | HFmrEF (n=72) | HFpEF (n=80) | p-value |
|---|---|---|---|---|
| **LVEF (%)** | 30.6±6.4 | 44.2±2.8 | 59.8±6.2 | <0.001 |
| **LVEDd (mm)** | 64.8±8.2 | 55.4±6.6 | 48.6±5.8 | <0.001 |
| **LVESd (mm)** | 52.4±8.6 | 41.8±6.2 | 31.2±5.4 | <0.001 |
| **IVSd (mm)** | 9.2±1.8 | 10.8±2.2 | 12.6±2.4 | <0.001 |
| **LA diameter (mm)** | 44.2±6.8 | 46.8±5.4 | 48.4±6.2 | 0.006 |
| **E/A ratio** | 1.8±0.6 | 1.2±0.4 | 0.8±0.3 | <0.001 |
| **E/e' ratio** | 18.4±4.6 | 14.8±3.8 | 13.2±3.4 | <0.001 |
| **MR (moderate/severe)** | 44 (44.9%) | 26 (36.1%) | 16 (20.0%) | 0.002 |
| **RVSP (mmHg)** | 46.8±12.4 | 40.2±10.8 | 36.4±9.6 | <0.001 |

Table 2 summarizes the echocardiographic parameters across the three HF phenotypes. As expected by definition, LVEF was markedly lower in HFrEF (30.6±6.4%) compared to HFmrEF (44.2±2.8%) and HFpEF (59.8±6.2%; p<0.001). LV cavity dimensions were significantly larger in HFrEF, with LVEDd of 64.8±8.2 mm, compared to HFpEF patients (48.6±5.8 mm). In contrast, interventricular septal thickness was greatest in HFpEF (12.6±2.4 mm), reflecting concentric hypertrophy typical of this phenotype. Diastolic function indices showed worsening E/A and E/e' ratios in HFrEF, consistent with pseudonormal or restrictive filling patterns. RVSP and functional MR were also most prominent in the HFrEF group.

**Table 3: Clinical Outcomes at 12-Month Follow-Up by Heart Failure Phenotype**

| Outcome | HFrEF (n=98) | HFmrEF (n=72) | HFpEF (n=80) | p-value |
|---|---|---|---|---|
| **All-cause mortality, n (%)** | 22 (22.4) | 12 (16.7) | 10 (12.5) | 0.12 |
| **CV hospitalization, n (%)** | 54 (55.1) | 30 (41.7) | 28 (35.0) | 0.02 |
| **Composite endpoint, n (%)** | 62 (63.3) | 38 (52.8) | 34 (42.5) | 0.03 |
| **NYHA improvement ≥1 class, n (%)** | 42 (42.9) | 38 (52.8) | 48 (60.0) | 0.04 |
| **New-onset AF, n (%)** | 18 (18.4) | 14 (19.4) | 22 (27.5) | 0.22 |
| **Acute kidney injury, n (%)** | 24 (24.5) | 14 (19.4) | 10 (12.5) | 0.09 |
| **6MWT distance (m), mean±SD** | 284±68 | 318±72 | 346±80 | <0.001 |
| **QoL score (KCCQ), mean±SD** | 42.6±14.8 | 48.4±13.6 | 52.8±15.4 | 0.003 |

Table 3 depicts the 12-month clinical outcomes stratified by HF phenotype. While all-cause mortality did not reach statistical significance across groups (p=0.12), cardiovascular hospitalization was significantly more frequent in HFrEF patients (55.1%) compared to HFmrEF (41.7%) and HFpEF (35.0%; p=0.02). The composite endpoint of death or CV hospitalization was reached by 63.3% of HFrEF, 52.8% of HFmrEF, and 42.5% of HFpEF patients (p=0.03). Conversely, NYHA functional class improvement of at least one grade was most frequently observed in HFpEF (60.0%). Six-minute walk test distance and KCCQ quality of life scores were significantly better in HFpEF patients, highlighting differences in functional recovery across phenotypes.

## Discussion

The findings of this study provide a comprehensive and contemporaneous characterization of the three principal heart failure phenotypes in a tertiary care population. Our results confirm and extend the existing literature by demonstrating significant differences in age, sex distribution, comorbidity burden, echocardiographic profile, and 12-month outcomes across HFrEF, HFmrEF, and HFpEF phenotypes.

The significantly older age of HFpEF patients observed in our cohort (mean 67.8 years) aligns with established epidemiological data suggesting that HFpEF predominantly afflicts the elderly, with each decade of age associated with progressively impaired ventricular relaxation and increased arterial stiffness.[5] In Olmsted County data, persons developing HFpEF were on average six years older than those developing HFrEF, a finding closely mirrored in our study. The female predominance in HFpEF (52.5% female) is also consistent with observations from large registry data, where women are known to develop concentric remodeling and impaired diastolic function more readily than men in response to common risk factor exposures such as hypertension.[6]

The higher burden of hypertension in HFpEF patients (82.5%) versus HFrEF (55.1%) in our cohort is consistent with the pathophysiological framework of HFpEF, where chronic pressure overload induces maladaptive concentric hypertrophy, myocardial fibrosis, and progressive diastolic stiffness. Similarly, the higher prevalence of atrial fibrillation in HFpEF (57.5%) is well recognized, given that loss of atrial contribution to ventricular filling is particularly detrimental in a

non-compliant ventricle.[9] In contrast, coronary artery disease was most prevalent in HFrEF (63.3%), reflecting the predominance of ischemic etiology in this phenotype, a finding consistent with data from major HFrEF registries worldwide.[4]

Echocardiographically, HFrEF patients exhibited classical features of dilated cardiomyopathy—markedly enlarged LV cavity, globally impaired systolic function, and elevated filling pressures—consistent with patterns reported in the CHARM-Reduced and Val-HeFT trials.[10] In HFpEF, the characteristic findings of increased wall thickness (IVSd 12.6 mm) alongside relatively preserved chamber dimensions and impaired relaxation (E/A 0.8, E/e' 13.2) reflect the compensated concentric hypertrophy phenotype. The intermediate echocardiographic profile of HFmrEF patients—sharing features with both extremes—supports the notion that HFmrEF is a transitional and potentially heterogeneous phenotype.[8]

With respect to clinical outcomes, although all-cause mortality did not differ significantly between groups during 12 months of follow-up—a finding likely attributable to the relatively short observation window and the well-optimized pharmacological therapy in HFrEF—the significantly higher cardiovascular hospitalization rate in HFrEF patients underscores the substantial healthcare resource utilization associated with this phenotype. This observation mirrors data from the ESC Heart Failure Long-Term Registry and other real-world HF datasets.[3] Interestingly, HFpEF patients achieved greater functional class improvement and performed better on the 6MWT, possibly reflecting the impact of diuretic optimization and comorbidity management in this group, where the primary hemodynamic disturbance is less severe at rest.[7] These findings are consistent with the EMPEROR-Preserved trial, which demonstrated that empagliflozin significantly reduced the risk of cardiovascular death or hospitalization for heart failure in patients with HFpEF.[a]

Our study adds to a growing literature emphasizing that a one-size-fits-all therapeutic approach to HF is inadequate. While neurohormonal blockade remains the cornerstone of HFrEF management with proven mortality benefit, no comparable pharmacological strategy exists for HFpEF, where ongoing trials are investigating novel agents targeting myocardial energetics, collagen turnover, and inflammatory pathways. The intermediate group of HFmrEF may benefit from strategies effective in HFrEF, particularly when echocardiographic monitoring reveals progressive systolic deterioration over time.[2] From a diagnostic standpoint, our findings reinforce the value of echocardiography as an indispensable tool in phenotyping HF, capable of guiding both prognosis and therapy. Particularly, tissue Doppler-derived E/e' ratio and wall thickness measurements provide non-invasive surrogates of filling pressure and myocardial remodeling that distinguish HFpEF from the other phenotypes in a clinically meaningful way.[9]

## Limitation

This study has several limitations. Being a single-center design, findings may not be fully generalizable to other populations with differing cardiovascular risk profiles. The observational nature precludes causal inferences. The 12-month follow-up duration may not capture long-term mortality differences across phenotypes. Furthermore, invasive hemodynamic data were not obtained, and cardiac magnetic resonance imaging—which provides superior tissue characterization—was not routinely performed. Larger multi-center longitudinal studies are warranted to validate and extend our findings.

## Conclusion

Patients with HFrEF, HFmrEF, and HFpEF exhibit clinically and echocardiographically distinct profiles. HFpEF disproportionately affects older women with hypertension and atrial fibrillation and demonstrates a concentric remodeling pattern on echocardiography. HFrEF carries a greater hemodynamic burden, reflected in larger cavity dimensions, lower LVEF, higher NT-proBNP, and more frequent cardiovascular hospitalizations. HFmrEF occupies an intermediate position. Recognition of these phenotype-specific features is essential for accurate diagnosis, risk stratification, and individualized management of heart failure patients.

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