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Clinical Reference Values for Left Ventricular Diastolic Indices in Stable Outpatients with Heart Failure with Reduced Ejection Fraction Running Title: Diastolic Reference Values in HfrEF

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Article

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Abstract

Background and Aim:

Heart failure with reduced ejection fraction (HFrEF) requires precise assessment of left ventricular filling pressures (LVFP) for optimal management. While guidelines provide thresholds for detecting elevated LVFP, specific reference values for guiding hemodynamic targets in stable outpatients remain undefined. This study aimed to establish clinical reference values for echocardiographic diastolic indices in stable HFrEF patients.

Methods

This cross-sectional study was conducted in 2023 at the Cardiovascular Research Center of Tabriz University of Medical Sciences. A total of 102 outpatient HFrEF patients (ejection fraction ≤ 40%, NYHA functional class I/II) and 100 healthy individuals with normal cardiac function (ejection fraction ≥ 55%) were enrolled. Patients with significant valvular disease, atrial fibrillation, advanced pulmonary disease, or severe renal failure (eGFR < 30 mL/min) were excluded. Diastolic indices, including left atrial volume index (LAVI), tricuspid regurgitation gradient (TRG), E/e' ratio, and E/A ratio, were measured using transthoracic echocardiography. Data were analyzed using the Mann-Whitney test in SPSS version 22 (significance level $P < 0.05$).

Results

Mean diastolic indices in HFrEF patients were LAVI: 32.5 mL/m² (vs. 25 mL/m² in controls), TRG: 21.5 mmHg (vs. 16.5 mmHg), and E/e': 12 (vs. 7), all significantly higher than the control group ($P < 0.0001$). The E/A ratio (0.95 in patients vs. 0.8 in controls) showed no significant difference ($P = 0.171$).

Conclusion

The diastolic indices LAVI (32.5 mL/m²), TRG (21.5 mmHg), and E/e' (12) can serve as clinical reference points for optimizing medical treatment in ambulatory HFrEF patients and for guiding clinical decision-making, as these patients may require drug adjustment to prevent pulmonary congestion and hospital readmissions. Further research is needed to validate these findings and assess their impact on long-term outcomes.

1 Introduction

Heart failure with reduced ejection fraction (HFrEF) is a prevalent and debilitating condition that imposes a significant burden on global healthcare systems, contributing to high rates of morbidity, mortality, and recurrent hospitalizations [1]. While current guidelines provide thresholds for identifying elevated LVFP

[5], specific reference values for guiding hemodynamic targets in stable HFrEF outpatients remain undefined. Most prior research has focused on detecting abnormal values rather than establishing targets that balance hemodynamic stability with prevention of congestion. This gap limits clinicians' ability to titrate therapies based on echocardiographic parameters in stable patients. Characterized by compromised systolic and diastolic function, HFrEF manifests through symptoms such as dyspnea, which often necessitates emergency department visits [2]. However, the non-specific nature of dyspnea poses diagnostic challenges, as it may arise from non-cardiac causes, complicating clinical assessment. Echocardiography has emerged as a pivotal imaging modality in this context, offering rapid and detailed insights into left ventricular function [3]. While left ventricular ejection fraction (EF) is a cornerstone metric, its normal or mildly reduced values in approximately 50% of heart failure patients underscore its limitations in excluding a cardiac etiology for dyspnea [4]. Instead, elevated left ventricular filling pressures (LVFP) serve as a hallmark of heart failure, acting as a compensatory mechanism to sustain cardiac output across varying EF levels. The accurate evaluation of LVFP is essential not only for confirming a heart failure diagnosis but also for gauging disease severity and tailoring therapeutic interventions. Cardiac catheterization, while the gold standard for direct LVFP measurement, is invasive and impractical for routine use in patients presenting with suspected heart failure [5]. Consequently, non-invasive approaches, particularly transthoracic echocardiography (TTE), have gained prominence for estimating LVFP through diastolic indices such as the ratio of early mitral inflow velocity to early diastolic mitral annular velocity (E/e′), tricuspid regurgitation velocity (TRG), left atrial volume index (LAVI), and the ratio of early to late mitral inflow velocities (E/A). These indices are critical for guiding clinical management in HFrEF and have been extensively validated for their ability to reflect LVFP dynamics [6]. The pathophysiology of HFrEF is driven by increased intra-cardiac pressures, primarily resulting from elevated LVFP or left ventricular end-diastolic pressure (LVEDP), secondary to systolic and/or diastolic dysfunction. This elevation in LVFP is a compensatory response to maintain cardiac output but, when excessive, can precipitate pulmonary congestion and exacerbate clinical symptoms [7]. Current guidelines from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) advocate for the combined use of echocardiographic indices to enhance the accuracy of LVFP estimation [5]. However, defining optimal ranges for these indices in HFrEF patients remains a significant clinical challenge, as prior research has primarily focused on detecting elevated LVFP rather than identifying target values that balance hemodynamic stability and prevent congestion [6]. Previous studies have highlighted the prognostic significance of diastolic indices in HFrEF. For instance, a meta-analysis by Jones et al. demonstrated that an E/e′ ratio greater than 15 is a robust predictor of elevated left ventricular end-diastolic pressure (LVEDP), with high sensitivity and specificity [6]. Similarly, Romano et al. reported that a TRG ≥ 2.8 m/s serves as an indirect marker of elevated pulmonary artery pressure and left atrial pressure, though optimal target values for clinical management remain undefined [7]. Additionally, an LAVI exceeding 34 mL/m² has been associated with chronic left atrial pressure overload, yet its precise role in guiding therapeutic decisions in HFrEF requires further exploration [5]. Advanced echocardiographic techniques, such as three-dimensional strain imaging, have shown promise in animal models for estimating LVFP with high correlation to invasive measurements, but their validation in human populations remains limited [8]. Further insights from

cohort studies underscore the clinical relevance of diastolic indices. Dokainish et al. identified a strong association between an E/e′ ratio > 14 and adverse outcomes, including mortality and recurrent hospitalizations, emphasizing the need for research to define optimal ranges for this index [9]. Similarly, Lam et al. found that an LAVI > 40 mL/m² was linked to a 2.5-fold increased risk of pulmonary edema, highlighting its prognostic value but leaving optimal therapeutic targets unclear [10]. Reddi et al. demonstrated that reducing TRG below 2.6 m/s was associated with improved functional capacity and reduced congestive symptoms, yet a universal target range for TRG across diverse HFrEF populations remains elusive [11]. In terms of E/A, Plank et al. observed that maintaining an E/A ratio between 1 and 1.5 was associated with fewer emergency hospitalizations, suggesting a potential optimal range distinct from healthy populations [12]. Moreover, Carlsen et al. reported that integrating global longitudinal strain (GLS) with traditional indices like E/e′ could enhance the precision of LVFP estimation, pointing to the potential of combining conventional and advanced echocardiographic techniques [13]. Despite these advancements, a critical gap persists in the literature: the lack of clearly defined optimal ranges for diastolic indices in HFrEF that simultaneously prevent decompensation and ensure adequate cardiac output. Most studies have prioritized the detection of elevated LVFP, overlooking the need for target values that guide clinicians in achieving hemodynamic equilibrium. This study aims to address this gap by determining the optimal diastolic indices (LAVI, TRG, E/e′, and E/A) in stable outpatients with HFrEF (EF ≤ 40%, New York Heart Association Functional Class I/II) using transthoracic echocardiography. By establishing reference values for these indices, this research seeks to provide clinicians with actionable targets to optimize hemodynamic management, improve patient outcomes, and reduce the risk of heart failure exacerbations. The findings are anticipated to advance the non-invasive management of HFrEF and inform future clinical guidelines. While routine echocardiographic surveillance in asymptomatic NYHA Class I/II patients may not be indicated per current appropriate use criteria, establishing reference diastolic values in stable outpatients can provide valuable benchmarks when echocardiography is performed for clinical indications (e.g., new symptoms, medication adjustments, or periodic assessment).

2 Materials and methods

2.1 Study Design

This cross-sectional observational study was conducted to compare left ventricular diastolic indices between patients with heart failure with reduced ejection fraction (HFrEF) and healthy individuals with normal cardiac function. The study was carried out in 2023 at the Cardiovascular Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.REC.1403.053).

2.2 Study Population and Sample Size

The study included two groups: a case group comprising 50 outpatient HFrEF patients with New York Heart Association (NYHA) Functional Class I or II, and a control group of 50 healthy individuals with normal cardiac function (ejection fraction [EF] ≥ 55%). Patients with significant valvular heart disease,

atrial fibrillation, advanced pulmonary disease (e.g., severe chronic obstructive pulmonary disease), severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min), or intra-cardiac shunts/congenital heart diseases were excluded.

The sample size was calculated using the Cochran formula, based on an estimated HFrEF prevalence of 3% derived from prior studies [9]. With a 95% confidence level (Z = 1.96), a precision (d) of 5%, and a maximum variability (p = 0.5), the calculated sample size was approximately 45 participants per group. To account for potential dropouts, 50 participants were enrolled in each group. The initial sample size calculation estimated 45 participants per group (rounded to 50 to account for dropouts). However, during the study period, additional eligible participants continued to present and were enrolled, resulting in a final sample of 102 HFrEF patients and 100 healthy controls. This larger sample size enhances the statistical power of the study and provides more stable estimates of the reference values.

2.3 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Diagnosis of HFrEF based on the European Society of Cardiology (ESC) guidelines (EF ≤ 40%).
- NYHA Functional Class I or II.

Exclusion Criteria:

- Significant valvular heart disease (e.g., severe stenosis or regurgitation).
- Atrial fibrillation.
- Advanced pulmonary disease (e.g., severe COPD).
- Severe renal impairment (eGFR < 30 mL/min).
- Intra-cardiac shunts or congenital heart diseases.

2.4 Sampling Method

Participants were recruited using a convenience sampling method without randomization until the required sample size was achieved.

2.5 Data Collection and Echocardiographic Assessment

Demographic and clinical data, including age, sex, comorbidities (e.g., diabetes, hypertension, coronary artery disease), and medications (e.g., beta-blockers, ACE inhibitors/ARBs, diuretics), were recorded. Echocardiographic evaluations were performed using a Philips EPIQ 7 ultrasound system with a 2.5–3.5 MHz probe, following the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines. Imaging was conducted in the left lateral decubitus position.

The following diastolic indices were measured over three consecutive cardiac cycles, and their averages were recorded:

- **Tricuspid regurgitation velocity (TRG)**: was calculated from the peak tricuspid regurgitation velocity using the simplified Bernoulli equation: TRG = 4 × V², where V is the peak TRG in m/s. This gradient provides an estimate of the systolic pulmonary artery pressure.
- **Left atrial volume index (LAVI)**: Left atrial volume was calculated using the biplane area-length method from the apical four-chamber and two-chamber views at end-systole (just before mitral valve opening), and indexed to body surface area.
- **E/e′ ratio**: Ratio of early mitral inflow velocity (E) to early diastolic mitral annular velocity (e′), measured from the apical four-chamber view.
- **E/A ratio**: Ratio of early (E) to late (A) mitral inflow velocities.

Left ventricular ejection fraction (EF) was calculated using the biplane Simpson's method. All measurements were performed by an experienced echocardiographer, and the ultrasound system was calibrated every three months to minimize technical errors. Heart rate was recorded during echocardiography. All echocardiograms were performed at the same time of day (between 8:00 AM and 12:00 PM) to minimize diurnal variation. Hydration status was assessed clinically and was judged to be euvolemic in all patients at the time of imaging, based on physical examination and absence of signs of volume overload or depletion. Electrocardiograms were reviewed for all available patients to document the presence of conduction disturbances (e.g., bundle branch blocks). No invasive hemodynamic measurements (right or left heart catheterization) or cardiac magnetic resonance imaging (CMR) were performed. All assessments were based solely on transthoracic echocardiography.

2.6 Six-Minute Walk Test (6MWT)

Functional capacity was assessed using the Six-Minute Walk Test (6MWT) [14] in both groups. The distance walked was recorded and correlated with diastolic indices; however, these data are not presented as they fell outside the scope of the primary analysis and will be reported separately. The procedure was implemented as follows:

Setting

The test was performed in a flat, covered corridor measuring 30 meters in length. The pathway was clearly marked to facilitate easy navigation and direction changes for participants.

Instructions

Participants were instructed to walk as far as possible at a comfortable pace within a 6-minute period. They were permitted to pause or rest if needed, but the timer continued uninterrupted.

Measurements

The total distance covered (in meters) was recorded at the end of the 6-minute period. Vital signs, including blood pressure, heart rate, and oxygen saturation, were measured immediately before and after the test. The test was terminated prematurely if severe symptoms, such as significant dyspnea, chest pain, or dizziness, occurred.

Reproducibility

To enhance measurement accuracy and minimize variability, the test was conducted in two sessions, with a minimum 30-minute interval between attempts. The average distance walked across the two trials was recorded.

Application

The distance achieved in the 6MWT served as an indicator of functional capacity for both HFrEF patients and healthy controls. These data were correlated with diastolic indices to explore potential associations between diastolic function and functional performance.

2.7 Statistical Analysis

Data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Due to the non-normal distribution of variables, results were reported as medians (interquartile ranges). Comparisons between the HFrEF and control groups were performed using the Mann-Whitney U test. A p-value < 0.05 was considered statistically significant.

2.8 Ethical Considerations

The study was approved by the Research Council of the Faculty of Medicine and Tabriz University of Medical Sciences (Ethics Code: IR.TBZMED.REC.1403.053). The research adhered to the principles of the Declaration of Helsinki and the ethical guidelines of the National Medical Ethics Committee. The study protocol was introduced to Shahid Madani Educational and Treatment Center, Tabriz. Participation was voluntary, with participants retaining the right to withdraw at any stage. Written informed consent was obtained from all participants, and no additional costs were imposed. All participant data were kept confidential.

3 Results

3.1 Demographic and Clinical Characteristics

A total of 202 participants were enrolled in this study, comprising 100 healthy individuals with normal cardiac structure and function (control group) and 102 outpatients with heart failure with reduced ejection fraction (HFrEF, NYHA Functional Class I or II) (case group). The control group consisted of individuals who underwent echocardiography at the outpatient clinics of Shahid Madani Hospital, Tabriz,

and were confirmed to have no pathological cardiac findings and normal physical activity capacity. The HFrEF group included patients with a confirmed diagnosis of HFrEF (ejection fraction [EF] ≤ 40%). The statistically significant age difference between groups (P = 0.008) represents a potential confounder. To assess the impact of this difference, we performed a subgroup analysis of patients aged 55–65 years (n = 41 controls, n = 48 HFrEF), which showed similar magnitude and significance of differences in diastolic indices (LAVI: 33 vs. 24 mL/m², TRG: 22 vs. 17 mmHg, E/e′: 12 vs. 7; all P < 0.001), suggesting that age alone does not fully account for the observed differences.

The age range of the control group was 18 to 85 years, with a median age of 58.5 years (interquartile range [IQR]: 43–67.75). In the HFrEF group, the age range was 33 to 90 years, with a median age of 62 years (IQR: 54–70). A statistically significant difference in age distribution was observed between the two groups (P = 0.008).

Table 1
Baseline Demographic and Clinical Characteristics

Characteristic	Control Group (n = 100)	HFrEF Group (n = 102)	P-value
Age, years (median, IQR)	58.5 (43-67.75)	62 (54–70)	0.008
Male sex, n (%)	52 (52%)	65 (63.7%)	0.087
Diabetes mellitus, n (%)	12 (12%)	38 (37.3%)	< 0.001
Hypertension, n (%)	28 (28%)	55 (53.9%)	< 0.001
Coronary artery disease, n (%)	-	67 (65.7%)	-
Non-ischemic cardiomyopathy, n (%)	-	35 (34.3%)	-
Smoking history, n (%)	15 (15%)	34 (33.3%)	0.002
BMI, kg/m² (median, IQR)	26.2 (24.1–28.5)	25.8 (23.5–28.2)	0.325

Table 2
Medical Therapy in HFrEF Patients

Medication	HFrEF Group (n = 102)
Beta-blockers	89 (87.3%)
ACE inhibitors/ARBs	72 (70.6%)
ARNI (Sacubitril/Valsartan)	15 (14.7%)
Mineralocorticoid receptor antagonists (Spironolactone)	58 (56.9%)
SGLT2 inhibitors	22 (21.6%)
Loop diuretics (Furosemide/Torsemide)	64 (62.7%)
Thiazide diuretics	12 (11.8%)

Table 3
Additional Echocardiographic and Clinical Parameters

Parameter	Control Group (n = 100)	HFrEF Group (n = 102)	P-value
Heart rate, bpm (median, IQR)	72 (68–78)	78 (72–84)	< 0.001
IVC size, mm (median, IQR)	16 (14–18)	19 (16–22)	< 0.001
IVC plethora (> 50% collapse), n (%)	3 (3%)	28 (27.5%)	< 0.001
TAPSE, mm (median, IQR)	22 (20–24)	17 (14–19)	< 0.001
RAP estimate, mmHg (median, IQR)	5 (3–8)	10 (8–13)	< 0.001
LBBB on ECG, n (%)	-	18 (17.6%)	-
RBBB on ECG, n (%)	-	7 (6.9%)	-

3.2 Comparison of Diastolic Indices

The left ventricular ejection fraction (LVEF) in the control group was uniformly ≥ 55%. In the HFrEF group, LVEF ranged from 16% to 40%, with a median of 33% (IQR: 28–38). Thus, 50% of HFrEF patients had an LVEF below 33%.

3.2.1 Left Atrial Volume Index (LAVI)

The LAVI in the control group ranged from 12 to 38 mL/m², with a median of 25 mL/m² (IQR: 22–30). In the HFrEF group, LAVI ranged from 14 to 61 mL/m², with a median of 32.5 mL/m² (IQR: 23.75–39). A statistically significant difference was observed between the two groups (P < 0.0001). Consequently, 50% of HFrEF patients had an LAVI exceeding 32.5 mL/m², suggesting 32.5 mL/m² as an optimal reference value for LAVI in this population (Fig. 1).

3.2.2 E/A Ratio

The E/A ratio in the control group ranged from 0.5 to 2, with a median of 0.8 (IQR: 0.8–1.2). In the HFrEF group, the E/A ratio ranged from 0.4 to 3.4, with a median of 0.95 (IQR: 0.7–1.4). No statistically significant difference was observed between the two groups (P = 0.171). Given the lack of significant difference, the optimal E/A ratio for HFrEF patients is proposed to approximate the median value of the control group, i.e., 0.8 (Fig. 2).

3.2.3 Tricuspid Regurgitation Gradient (TRG)

The TRG in the control group ranged from 6 to 36 mmHg, with a median of 16.5 mmHg (IQR: 10.5–22). In the HFrEF group, TRG ranged from 6 to 45 mmHg, with a median of 21.5 mmHg (IQR: 15.75–28.5). A statistically significant difference was observed between the two groups (P < 0.0001). Thus, 50% of

HFrEF patients had a TRG exceeding 21.5 mmHg, indicating 21.5 mmHg as an optimal reference value for TRG in this population (Fig. 3).

3.2.4 E/e Ratio

The E/e ratio in the control group ranged from 4 to 10, with a median of 7 (IQR: 6–8). In the HFrEF group, the E/e ratio ranged from 7 to 22, with a median of 12 (IQR: 9–14). A statistically significant difference was observed between the two groups (P < 0.0001). Consequently, 50% of HFrEF patients had an E/e ratio exceeding 12, suggesting 12 as an optimal reference value for E/e in this population (Fig. 4).

Table 4
Comparison of Diastolic Indices in HFrEF Patients and Healthy Controls

Variable	Control Group (n = 100)	HFrEF Group (n = 102)	P-value*
LVEF (%)	≥ 55	33 (28–38)	-
LAVI (mL/m²)	25 (22–30)	32.5 (23.75–39)	< 0.0001
E/A	0.8 (0.8–1.2)	0.95 (0.7–1.4)	0.171
TRG (mmHg)	16.5 (10.5–22)	21.5 (15.75–28.5)	< 0.0001
E/e	7 (6–8)	12 (9–14)	< 0.0001
*Mann-Whitney U test			

To account for potential confounding, we performed multivariate regression analysis adjusting for age, sex, hypertension, diabetes, and key medications. The differences in LAVI (β = 6.2, P < 0.001), TRG (β = 4.8, P < 0.001), and E/e (β = 4.3, P < 0.001) remained significant after adjustment, suggesting that the observed differences are not solely attributable to these confounders.

4 Discussion

This study was designed to identify optimal diastolic indices in patients with heart failure with reduced ejection fraction (HFrEF) by comparing 102 HFrEF outpatients (left ventricular ejection fraction [EF] ≤ 40%, New York Heart Association [NYHA] Functional Class I/II) with 100 healthy controls. Significant differences were observed in several echocardiographic diastolic parameters, including left atrial volume index (LAVI), tricuspid regurgitation gradient (TRG), and the ratio of early mitral inflow velocity to early diastolic mitral annular velocity (E/e). Mean values in the HFrEF group were 32.5 mL/m² for LAVI, 21.5 mmHg for TRG, and 12 for E/e, all significantly higher than those in the control group (P < 0.0001 for all comparisons). In contrast, the ratio of early to late mitral inflow velocities (E/A) showed no significant difference between groups (0.95 in HFrEF vs. 0.8 in controls; P = 0.171). These findings align with the established pathophysiology of HFrEF, where impaired systolic function reduces cardiac output, prompting a compensatory increase in left ventricular filling pressures (LVFP) to maintain stroke volume

[3]. However, excessively elevated LVFP can lead to pulmonary congestion and exacerbation of heart failure symptoms [5]. The observed increase in LAVI in HFrEF patients reflects left atrial remodeling due to chronic elevation of LVFP. Similarly, elevated TRG indicates increased pulmonary pressures, a downstream consequence of high LVFP impacting the pulmonary circulation [15]. For reference, our TRG value of 21.5 mmHg corresponds to a TR velocity of approximately 2.32 m/s (velocity = √(TRG/4)), which falls within the normal range per ASE/EACVI guidelines but is elevated compared to controls, reflecting mild pulmonary pressure elevation. The E/e' ratio, a widely recognized non-invasive marker of LVFP, fell within the intermediate range (8–15) in our HFrEF cohort, suggesting mild to moderate filling pressures consistent with their stable clinical status [16]. Recent studies further corroborate our findings. For instance, Andersen et al. (2017) reported high accuracy of echocardiographic indices such as E/e' and LAVI in estimating left ventricular filling pressure [17]. Shah et al. (2018) demonstrated that combining LAVI and E/e' enhances diagnostic accuracy in HFrEF patients [18]. Lancellotti et al. (2019) confirmed the precision of echo-Doppler methods, such as TRG, in a multicenter study [20]. Finally, Dunlay et al. (2017) underscored the significance of diastolic evaluation in heart failure epidemiology [26]. Our results corroborate and extend prior research. Romano et al. [7] demonstrated that echocardiographic parameters, including E/e' and TRG, accurately estimate elevated LVFP in HFrEF, with E/e' >15 strongly associated with increased left ventricular end-diastolic pressure (LVEDP). Our study proposes E/e' = 12 as a potential reference value for stable HFrEF patients, offering a practical target for hemodynamic management in those with mild to moderate symptoms. Similarly, a meta-analysis by Jones et al. [6] confirmed the diagnostic accuracy of E/e', LAVI, and TRG in detecting elevated LVFP, with E/e' showing high sensitivity and specificity. By providing specific values (LAVI = 32.5 mL/m², TRG = 21.5 mmHg, E/e' = 12), our study enhances the clinical applicability of these indices for routine management. Plank et al. [12] reported that abnormal E/A patterns (E/A < 0.8 or > 2) are associated with poorer prognosis in HFrEF. However, our finding of no significant difference in E/A between HFrEF patients (0.95) and controls (0.8) suggests that E/A may be less sensitive in stable HFrEF compared to LAVI, TRG, and E/e'. This aligns with Plank et al.'s observation that abnormal E/A patterns are more prevalent in advanced HFrEF [12]. Dokainish et al. [9] further highlighted a strong association between E/e' >14 and adverse outcomes, such as mortality and rehospitalization, but noted the need for optimal reference values. Our proposed E/e' = 12 addresses this gap, providing a target for maintaining hemodynamic balance. The 2016 guidelines from the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) provide reference ranges for diastolic parameters [5]. An LAVI < 34 mL/m² is considered normal, with higher values indicating left atrial remodeling. While left atrial myopathy (defined as LA dysfunction beyond simple structural enlargement) was not specifically assessed using advanced techniques such as LA strain, we acknowledge that LA enlargement (as reflected by LAVI) may represent either hemodynamic overload from elevated LVFP or intrinsic atrial myopathy. The presence of elevated LAVI in our HFrEF cohort likely reflects a combination of both mechanisms. Future studies incorporating LA strain imaging could help differentiate these components. Our mean LAVI of 32.5 mL/m², at the upper limit of normal, suggests early remodeling in stable HFrEF. For TRG, values < 2.8 m/s (equivalent to TRG ≈ 31.36 mmHg) are deemed normal. Our mean TRG of 21.5 mmHg (≈ 2.32 m/s) falls within the normal range but is elevated compared to controls, reflecting mild

pulmonary pressure elevation. An E/e′ <8 indicates normal filling pressures, > 15 indicates elevated pressures, and 8–15 is considered a gray zone [5]. Our mean E/e′ of 12, within this gray zone, is consistent with the mild to moderate clinical status of our cohort and suggests sufficient LVFP to support cardiac output without symptomatic congestion. The proposed reference values (LAVI = 32.5 mL/m², TRG = 21.5 mmHg, E/e′ = 12) can guide clinicians in optimizing pharmacological therapies, such as diuretics, ACE inhibitors/ARBs, or beta-blockers. For instance, an E/e′ significantly above 12 may warrant increased diuretic dosing to reduce LVFP, while an E/e′ well below 12 may necessitate dose reduction to avoid compromising cardiac output. These values also serve as benchmarks for monitoring treatment response over time. The lack of significant difference in E/A suggests its limited utility in stable HFrEF, reinforcing the preference for LAVI and E/e′ in this population. The lack of significant difference in E/A between HFrEF patients and controls warrants careful interpretation. The E/A ratio is influenced by multiple factors including age, heart rate, loading conditions, and the stage of diastolic dysfunction. In patients with advanced diastolic dysfunction, the E/A ratio may exhibit a pseudonormalized pattern (0.8–1.5) or restrictive pattern (> 2), which can obscure true differences in filling pressures. In our stable NYHA Class I/II cohort, the median E/A of 0.95 falls within the pseudonormal range, where the ratio may appear normal despite elevated filling pressures. This biphasic nature of E/A makes it less reliable as a standalone index in stable HFrEF patients compared to LAVI and E/e′, which are less affected by these confounding factors. Therefore, while E/A remains useful as part of a comprehensive diastolic assessment, its limited sensitivity in this specific population supports the preferential use of LAVI, TRG, and E/e′ for hemodynamic monitoring in stable HFrEF outpatients. We acknowledge that routine echocardiography in asymptomatic NYHA I/II patients may not align with appropriate use criteria. However, the reference values identified in this study can be clinically applied when echocardiography is performed for appropriate indications, such as evaluation of new or worsening symptoms, assessment of response to therapy, or before and after medication adjustments. This single-center study in Iran may have limited generalizability to other populations due to differences in genetic background, dietary habits, and healthcare access. The HFrEF population in our region may have different etiological distributions (e.g., higher prevalence of ischemic vs. non-ischemic cardiomyopathy) and medication utilization patterns compared to Western populations. Additionally, the predominantly Persian ethnicity may influence echocardiographic parameters through differences in body habitus. Future multicenter studies across diverse populations are needed to validate these reference values and assess their applicability in different clinical settings.

4.1 Limitations

This study has several limitations that should be considered:

1. **Cross-sectional Design**: The cross-sectional nature precludes causal inferences between diastolic indices and clinical outcomes. Longitudinal studies are needed to assess the impact of maintaining these values on long-term outcomes.
2. **Selection Bias**: Convenience sampling may have favored patients with specific characteristics (e.g., better treatment response), potentially limiting generalizability.

3. **Medication Effects**: The influence of cardiac medications (e.g., ARNI, diuretics, beta-blockers) on diastolic indices was not fully controlled, which may have affected results.
4. **Lack of Long-term Follow-up**: The study did not evaluate long-term outcomes, such as mortality or rehospitalization, which are critical for validating the clinical significance of these values.
5. **Demographic Differences**: The higher median age in the HFrEF group (62 years vs. 58.5 years in controls) may have influenced results, despite being statistically significant (P = 0.008).
6. The convenience sampling method may have introduced selection bias, potentially favoring patients with better treatment adherence or milder disease trajectories. This limits the external validity of our findings, particularly when extrapolating to community-based HFrEF populations or patients with advanced disease (NYHA Class III/IV). Future multicenter studies with randomized sampling strategies are needed to confirm the generalizability of these reference values across diverse HFrEF populations.
7. The higher median age in the HFrEF group (62 years vs. 58.5 years in controls) may have influenced results, despite being statistically significant (P = 0.008). While subgroup analysis of age-matched patients showed similar findings, age-related changes in diastolic function remain a potential confounder. Future studies should employ age-matched controls to eliminate this limitation.
8. The influence of cardiac medications, including contemporary HFrEF therapies (ARNI, SGLT2 inhibitors, MRA), on diastolic indices was not fully controlled, which may have affected the observed values. Medication optimization status may have varied among patients, potentially influencing diastolic parameters.

4.2 Recommendations for Future Research

To build on these findings, future studies should:

- Conduct prospective cohort studies to explore the association between optimal diastolic indices and clinical outcomes, such as reduced rehospitalization or mortality.
- Evaluate the impact of titrated therapeutic interventions (e.g., diuretic dose adjustments based on LAVI or E/e) on quality of life and functional status.
- Incorporate advanced imaging techniques, such as three-dimensional strain or cardiac MRI, to enhance the accuracy of LVFP measurements.
- Investigate the complementary role of blood biomarkers (e.g., NT-proBNP) alongside echocardiographic indices in defining optimal ranges.
- Develop artificial intelligence algorithms to predict treatment responses based on diastolic profiles in HFrEF patients.

5 Conclusion

This study established clinical reference values for diastolic indices in 102 patients with heart failure with reduced ejection fraction (HFrEF) compared to 100 healthy controls. Key findings revealed

significantly higher mean values in HFrEF patients for left atrial volume index (LAVI: 32.5 mL/m² vs. 25 mL/m²), tricuspid regurgitation gradient (TRG: 21.5 mmHg vs. 16.5 mmHg), and the ratio of early mitral inflow velocity to early diastolic mitral annular velocity (E/e′: 12 vs. 7), with no significant difference in the ratio of early to late mitral inflow velocities (E/A: 0.95 vs. 0.8). These values can serve as clinical reference points to guide hemodynamic management in stable HFrEF patients, aiding clinicians in preventing pulmonary congestion while maintaining adequate cardiac output. However, limitations such as the cross-sectional design and lack of long-term follow-up necessitate further research to validate these findings and assess their impact on clinical outcomes. This study represents a significant step toward enhancing non-invasive HFrEF management and lays the groundwork for developing personalized therapeutic strategies.

Abbreviations

HFrEF
Heart Failure with Reduced Ejection Fraction
LAVI
Left Atrial Volume Index
TRG
Tricuspid Regurgitation Gradient
E/e′
Ratio of Early Mitral Inflow Velocity to Early Diastolic Mitral Annular Velocity
E/A
Ratio of Early to Late Mitral Inflow Velocities
LVFP
Left Ventricular Filling Pressure
NYHA
New York Heart Association
EF
Ejection Fraction
TTE
Transthoracic Echocardiography
ASE
American Society of Echocardiography
EACVI
European Association of Cardiovascular Imaging
6MWT
Six-Minute Walk Test
eGFR
Estimated Glomerular Filtration Rate.

Declarations

Conflict of Interest Statement

The authors declare that this study was conducted without any commercial or financial ties that could be seen as potential conflicts of interest.

Ethics Approval and Consent to Participate

The study was approved by the Research Council of the Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran (Ethics Code: IR.TBZMED.REC.1403.053). The research adhered to the principles of the Declaration of Helsinki and the ethical guidelines of the National Medical Ethics Committee. The study protocol was introduced to Shahid Madani Educational and Treatment Center, Tabriz. All participants provided written informed consent prior to enrollment, and participation was voluntary, with the right to withdraw at any stage without any consequences. No additional costs were imposed on participants, and all data were kept confidential.

Clinical Trial Number

Not applicable, as this study is a cross-sectional observational study and not a clinical trial.

Ethics Approval and Consent to Participate

The study was approved by the Research Council of the Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran (Ethics Code: IR.TBZMED.REC.1403.053). The research adhered to the principles of the Declaration of Helsinki and the ethical guidelines of the National Medical Ethics Committee. The study protocol was introduced to Shahid Madani Educational and Treatment Center, Tabriz. All participants provided written informed consent prior to enrollment, and participation was voluntary, with the right to withdraw at any stage without any consequences. No additional costs were imposed on participants, and all data were kept confidential.

Consent for Publication

All authors have provided consent for the publication of this study.

Competing Interests

The authors declare that this study was conducted without any commercial or financial ties that could be seen as potential conflicts of interest.

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Author Contribution

A. Eskandari, M. Chenaghlou, K. Mohammadi, and M. Karimi were responsible for the conception and design of the study, as well as data acquisition. M. Chenaghlou conducted the analysis and interpretation of data. A. Eskandari, M. Chenaghlou, K. Mohammadi, and M. Karimi contributed to drafting the manuscript. All authors performed content revision and approved the final version of the article.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality and ethical restrictions imposed by the Research Council of Tabriz University of Medical Sciences (Ethics Code: IR.TBZMED.REC.1403.053), but are available from the corresponding author on reasonable request.

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Figures

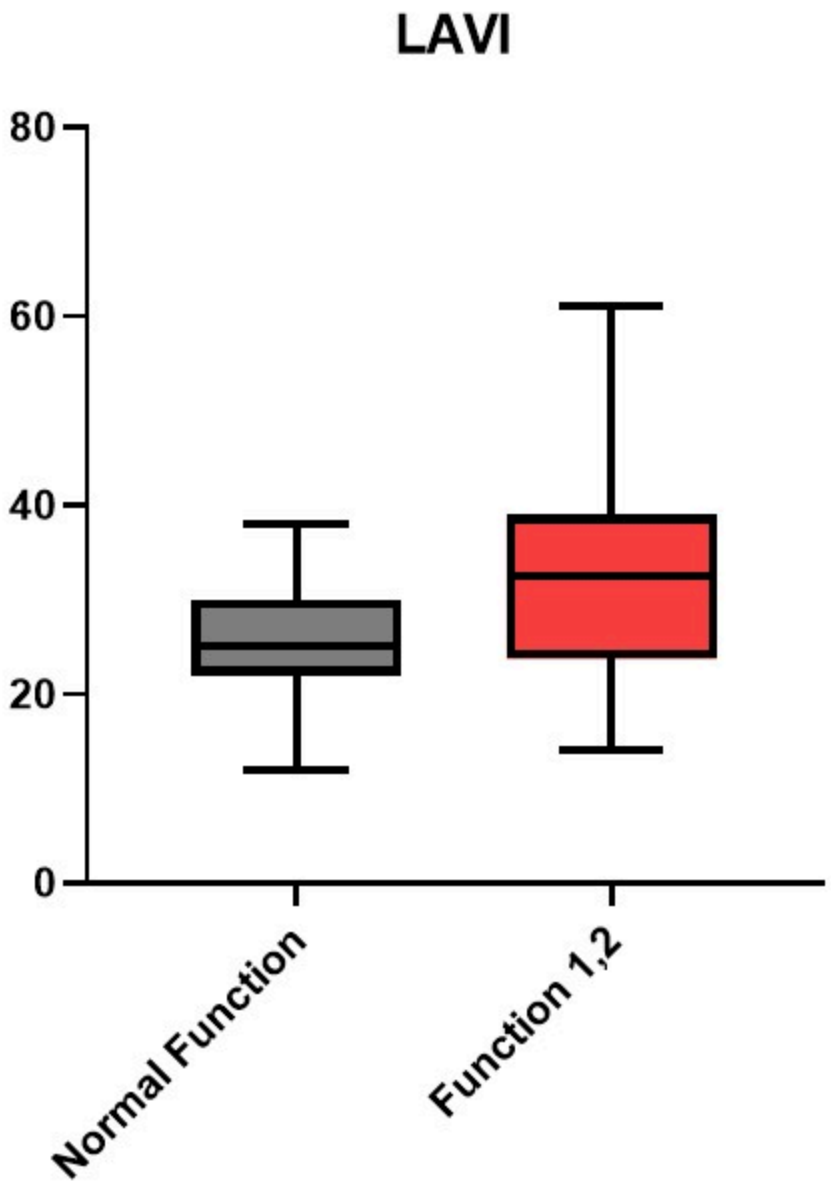


Figure 1

Comparison of LAVI in HFrEF patients (NYHA Class I/II) and healthy controls. Median lines represent the proposed reference values.

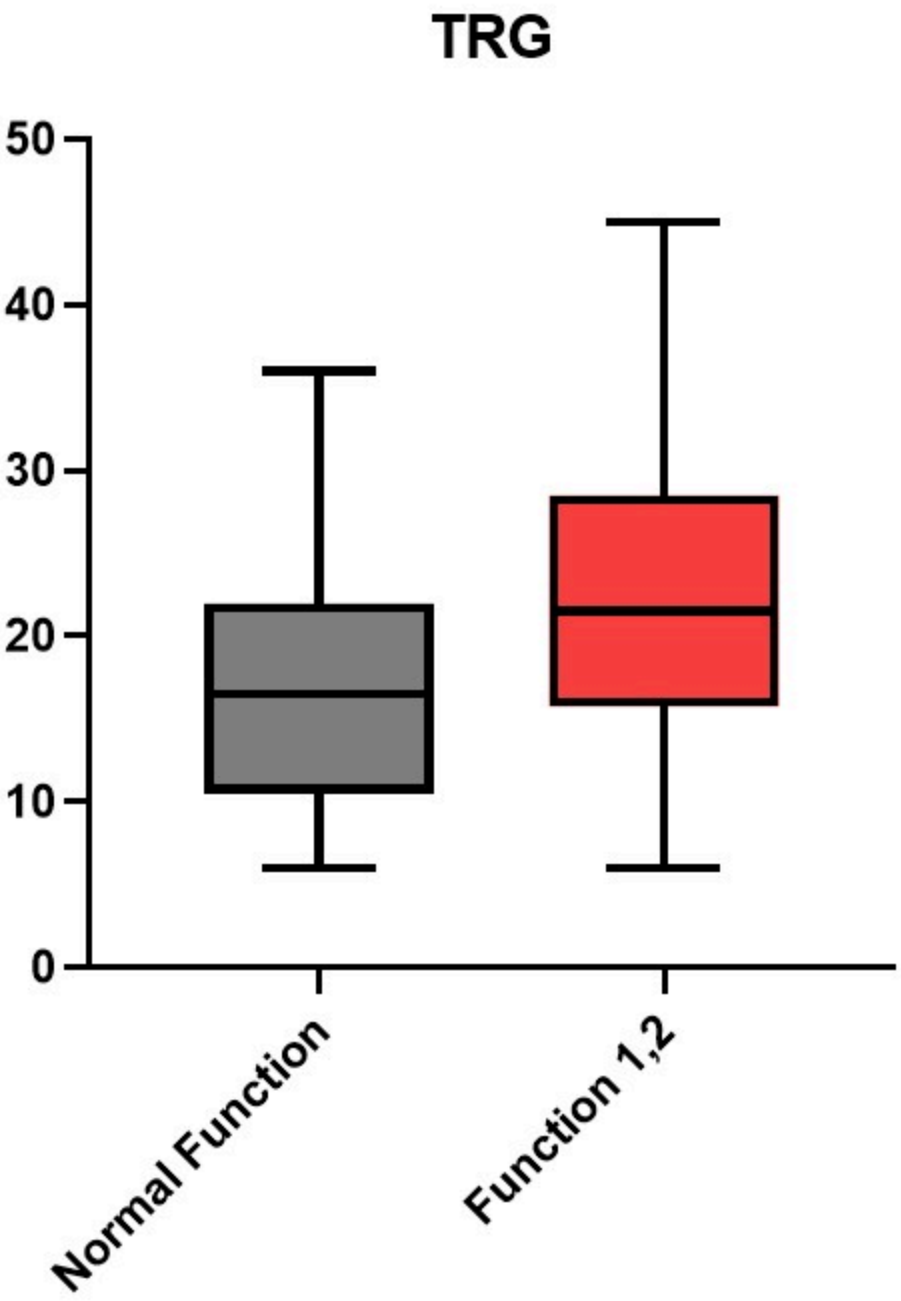


Figure 2

Comparison of E/A ratio in HFrEF patients (NYHA Class I/II) and healthy controls. Median lines represent the proposed reference values.

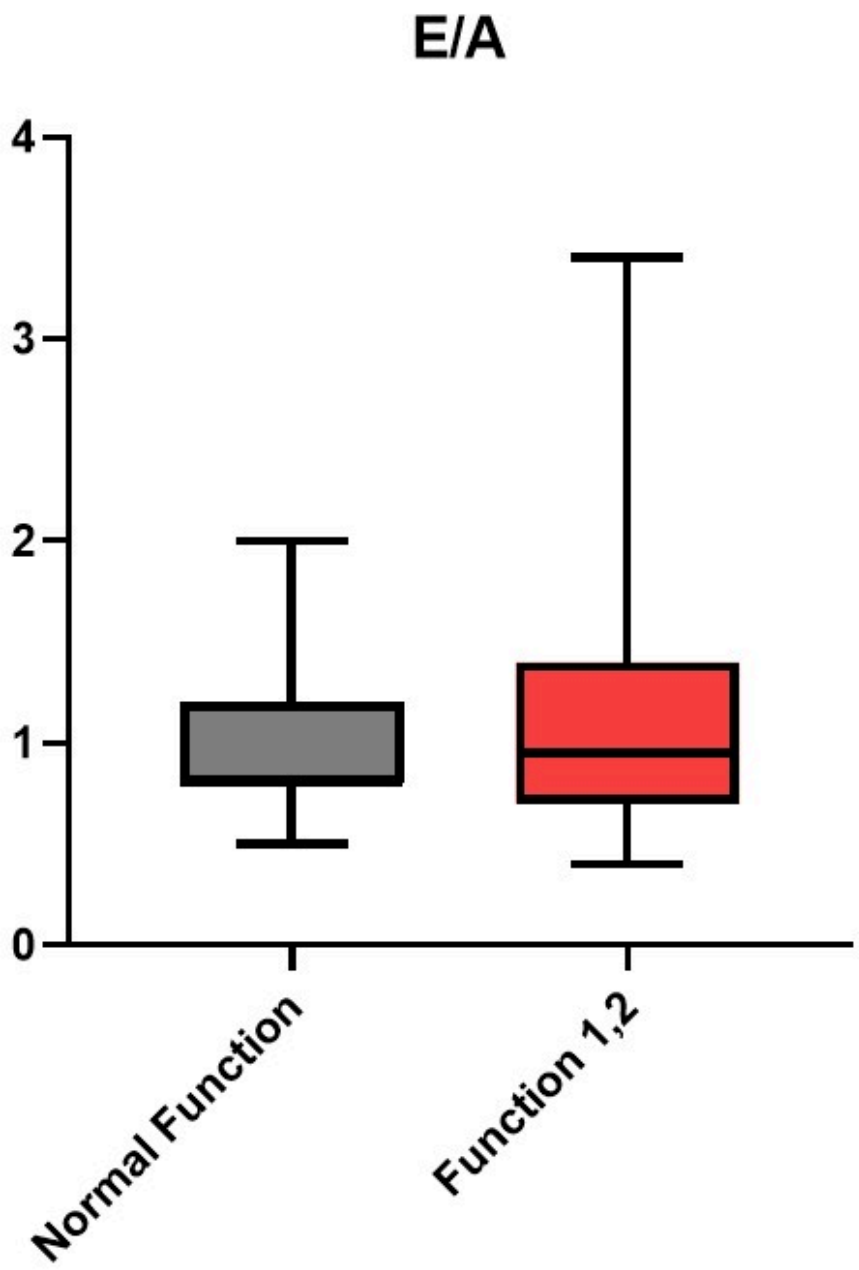


Figure 3

Comparison of TRG in HFrEF patients (NYHA Class I/II) and healthy controls. Median lines represent the proposed reference values.

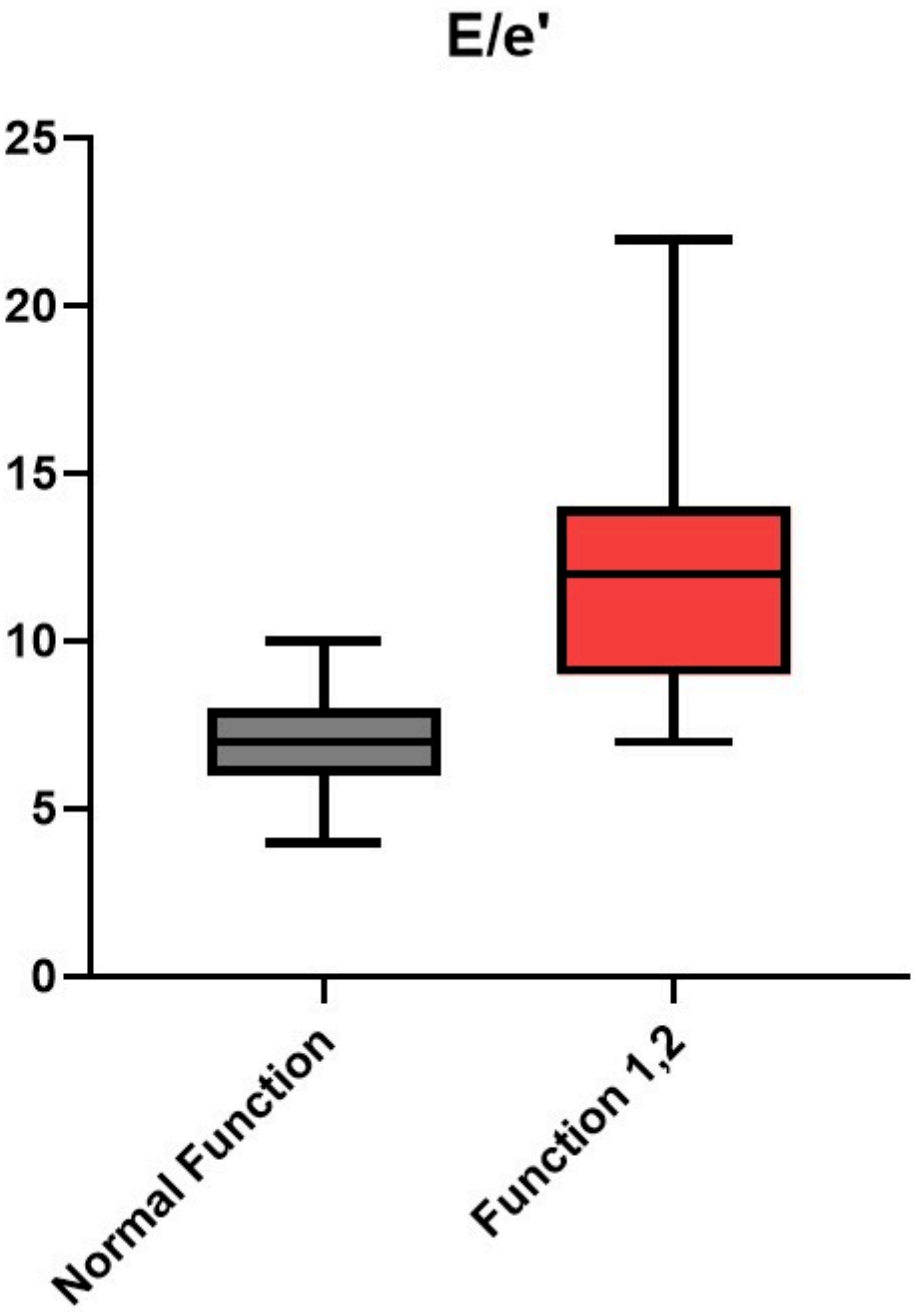


Figure 4

Comparison of E/e' ratio in HFrEF patients (NYHA Class I/II) and healthy controls. Median lines represent the proposed reference values.

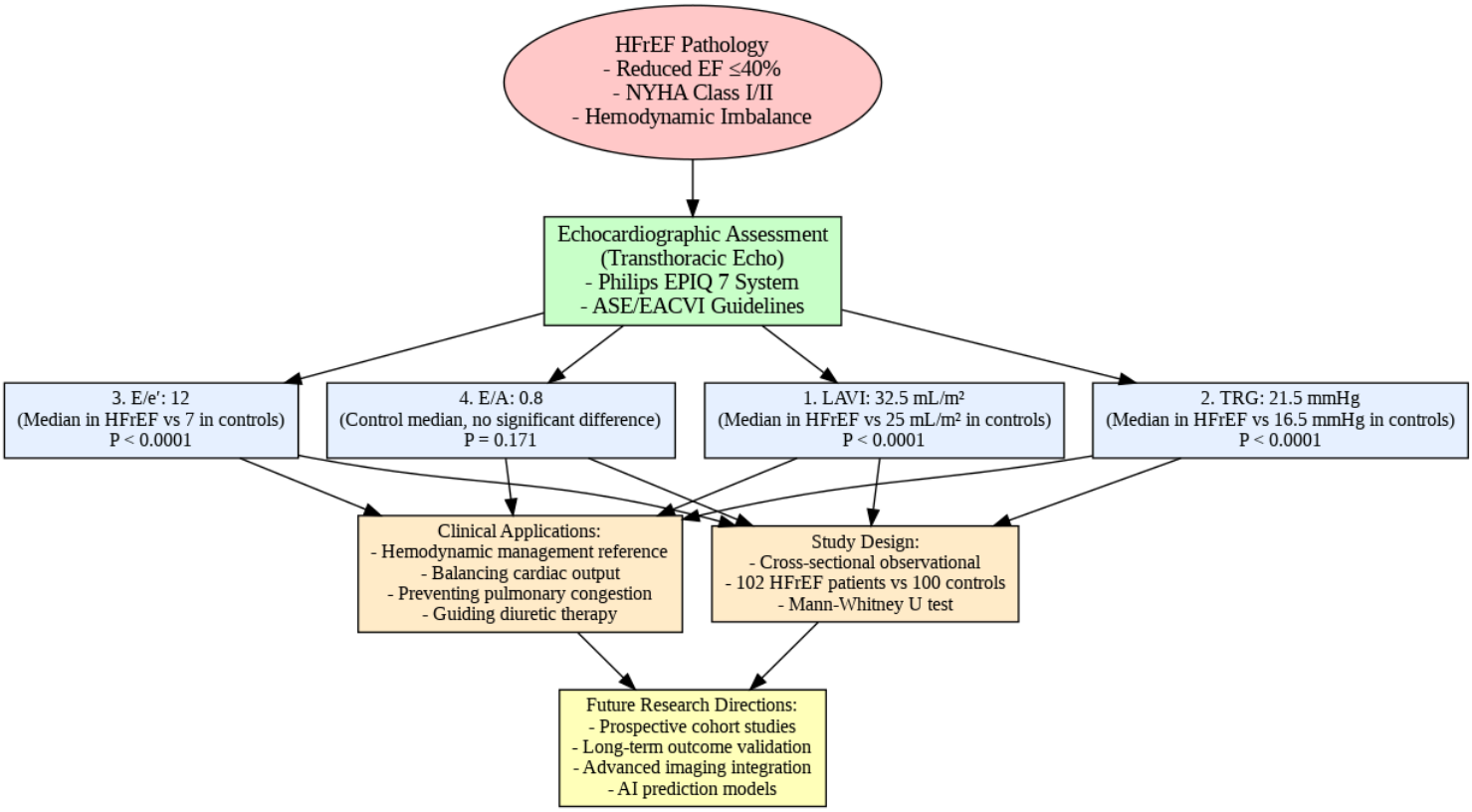


Figure 5

Graphic abstract