International Journal of Research in Medical Sciences
Waneshwari M et al. Int J Res Med Sci. 2026 Jun;14(6):2316-2322
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20261670

Original Research Article

Heart failure with reduced and mid-range ejection fraction: laboratory and instrumental profile

Murugaiya Waneshwari, Alao Clara Tomisin*, Liudmila Kalatsei

Department of Internal Medicine, Grodno State Medical University, Grodno, Belarus

Received: 17 April 2026
Revised: 15 May 2026
Accepted: 19 May 2026

***Correspondence:**
Dr. Alao Clara Tomisin,
E-mail: alaoclara99@gmail.com

ABSTRACT

Background: Since the publication of the European Society of Cardiology Guidelines for the Diagnosis and Treatment of Heart Failure in 2016, a new class of HF has been defined - HF with mid-range ejection fraction (HFmrEF). Aim of the study was to establish clinical, anamnestic, laboratory and echocardiographic differences in patients with HF with reduced left ventricular ejection fraction (HFrEF) and HFmrEF.
Methods: The retrospective single-center study included 92 patients with HF who were admitted to the Grodno Regional Clinical Cardiological Center for treatment from January 2023 to June 2025. Group 1 included 48 patients with HFrEF (LVEF<40%), while Group 2 included 44 patients with HFmrEF (LVEF 41-49%). We analyzed demographics, comorbidities, treatment, laboratory results, and echocardiographic data.
Results: HFmrEF and HFrEF shared similar age, sex, and major comorbidities ($p>0.05$), yet displayed distinct clinical and instrumental profiles. HFmrEF showed a milder presentation better NYHA class, fewer pleural effusions, smaller chambers, and markedly lower NT-proBNP whereas HFrEF exhibited advanced remodeling (larger LA/LV dimensions and volumes), more wall-motion abnormalities, thinner systolic septum suggestive of a dilated/ischemic phenotype, higher NT-proBNP, and greater congestion. NT-proBNP level had significant correlations with echocardiographic parameters, including LVEF ($R=-0.49$, $p<0.001$).
Conclusions: These findings support: systemic phenotyping of HFmrEF to individualize therapy, broader adoption of SGLT2 inhibitors alongside ARNI optimization and prospective studies to define trajectories, subphenotype-specific responses (e.g. obesity-, ischemia-, AF- driven), and multimodal risk stratification.

Keywords: Grey zone heart failure, Left ventricular ejection fraction, Mid-range, NT-proBNP, Quadruple therapy

INTRODUCTION

Chronic heart failure (HF) is the end stage of the cardiovascular continuum and is characterized by a significant increase in the risk of all-cause and cardiovascular mortality.[1] Despite advances in the treatment and prevention of cardiovascular diseases in recent years, the prevalence of HF remains quite high. Experts predict that by 2030, the prevalence of HF could increase to 46%, affecting up to 80 million adults worldwide. This already places this condition among the largest epidemics of modern times.[2,3]

Until recently, two main types of HF were distinguished: HF with reduced left ventricular ejection fraction (HFrEF), also known as systolic HF; and HF with preserved ejection fraction (HFpEF), also known as diastolic HF. Since the publication of the European Society of Cardiology Guidelines for the Diagnosis and Treatment of Heart Failure in 2016, a new class of HF has been defined HF with mid-range ejection fraction (HFmrEF).[2] It should be

noted that previously, patients with an EF of 41-49% were either completely excluded from studies or divided into two groups: preserved and reduced EF. Consequently, defining the clinical profile of the population with intermediate EF was quite difficult.[4]

Distinguishing instrumental phenotypes within HF syndrome with preserved, mid-range, and reduced ejection fraction allows us to rank the evidence base and identify patient groups with preferred drug intervention strategies aimed at reducing mortality for HF.[5] HFpEF and HFrEF are currently well described; however, the determinants and outcomes of HFmrEF remain unclear. HFmrEF is a heterogeneous syndrome with various pathogenesis mechanisms and a limited list of prognosis-modifying drugs with a solid evidence base.[6,7] Furthermore, data on the phenotypic characteristics of HFmrEF patients are inconsistent, and their clinical and hemodynamic profiles, as well as biomarker levels, have been insufficiently studied.[8-10]

Following a series of studies launched by identifying a «gray zone» an unstudied cohort of patients with moderately reduced EF there remain highly conflicting opinions on a number of issues. According to some publications, the HFmrEF group occupies an intermediate position in its clinical and demographic characteristics between HFrEF and HFpEF.[1,7,8] At the same time, the available literature includes the results of a number of other studies that present a somewhat different «portrait» of a patient with CHF and an LVEF of 41-49%. Delepaul et al and Kapoor et al argue that the clinical profile of this HF phenotype is more similar to that of patients with HFpEF.[9,10] Given the above-mentioned evidence, further cohort studies are needed in this area to better manage patients with HFmrEF. Aim of the study was to establish clinical, anamnestic, laboratory and echocardiographic differences in patients with HFrEF and HFmrEF.

METHODS

Study design and patient selection

The retrospective single-center study included 92 patients with HF who were admitted to the Grodno Regional Clinical Cardiological Center for treatment from January 2023 to June 2025. Group 1 included 48 patients with HFrEF (LVEF<40%), while Group 2 included 44 patients with HFmrEF (LVEF 41-49%).

Exclusion criteria from the study were age <18 years, acute coronary syndrome, chronic rheumatic heart disease, valvular pathology of the heart requiring surgical correction, infective endocarditis, myocarditis, hypertrophic cardiomyopathy, channelopathies, oncological diseases, severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2) and other severe concomitant extracardiac pathology.

Clinical and demographic data, the results of basic laboratory tests, medical history of comorbidities were collected for all patients from the hospital electronic database (4D Client).

Echocardiographic assessment

Transthoracic echocardiography was performed on Phillips iE33 device with a multi-frequency sensor (frequency 2.5-5.0 MHz). The examination was performed with the patient lying on his left side with his back to the researcher or on his back. The study protocol included the following parameters: left atrium (LA) and right atrium (RA) diameter in 2-chamber and 4-chamber mode, end-systolic diameter and end-diastolic diameter (mm) of the left ventricle (LV), LV ejection fraction (LVEF); assessment of the state of the valvular apparatus of the heart, degree of regurgitation on the valves.

Statistical analysis

Statistical analysis was performed using the STATISTICA 12.0 computer software. Data distribution was assessed for normality via histogram analysis. Sets of quantitative indicators whose distribution deviated from normal were described using median (Me) values and lower and upper quartiles (Q1; Q3). Nominal data were described using absolute values and percentages. Given that most quantitative variables were not normally distributed, non-parametric methods were applied. Differences between two independent groups were evaluated by Mann-Whitney test, alongside a p-value of less than 0.05 considered statistically significant. To assess the correlation relationships between the studied parameters, Spearman's rank correlation coefficient was used.

Ethical consideration

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

RESULTS

Clinical characteristics of the patients are presented in Table 1.

Patients in both groups were comparable in age (63.9 [58; 70] vs 65.4 [59; 70], p>0.05) and gender, with male sex predominant in both groups (77.1% vs.84.1%), p>0.05). The study found no statistically significant differences between the groups in the prevalence of hypertension (p>0.05). However, its incidence was extremely high: 79.5% and 81.8%, respectively. There were no significant intergroup differences in the prevalence of such comorbidities as atrial fibrillation (both paroxysmal and persistent), atrial flutter, and diabetes mellitus (p>0.05).

It is interesting that patients with HFmrEF had a higher prevalence of obesity (44.4% vs. 22.9%, p=0.023) in comparison with patients with HFrEF. In both groups there was rather high number of patients with stable angina (41.7% vs. 34.1%, p>0.05), but patients with HFrEF more often had CCS class 3 (14.6%) vs. 2.3%), p=0.037). Thus, stable angina was more severe in patients with HFrEF. Also, the ejection fraction reduction correlated with HF NYHA Class, with Class 2 being the most common in HFmrEF patients (61.4% vs. 18.8%, p<0.001) and Class 3 prevalent in HFrEF (70.7% vs. 29.5%, p<0.001).

Table 1: Clinical characteristics of patients.

Parameters	Group 1 HFrEF (n=48)	Group 2 HFmrEF (n=44)	P value
Male gender, N (%)	37 (77.1)	37 (84.1)	>0.05
Age, years, Me [Q1; Q3]	63.9 [58; 70]	65.4 [59; 70]	>0.05
Obesity, N (%)	11 (22.9)	20 (44.4)	0.023*
Hypertension, N (%)	38 (79.5)	36 (81.8)	>0.05
Stage 1, N (%)	8 (16.7)	5 (11.4)	>0.05
Stage 2, N (%)	30 (62.5)	29 (65.9)	>0.05
Stage 3, N (%)	-	2 (4.5)	>0.05
Stable angina, N (%)	20 (41.7)	15 (34.1)	>0.05
Class 1, N (%)	1 (2.1)	2 (4.5)	>0.05
Class 2, N (%)	12 (25)	12 (27.3)	>0.05
Class 3, N (%)	7 (14.6)	1 (2.3)	0.037*
Diabetes mellitus, N (%)	11 (22.9)	11 (25)	>0.05
Atrial fibrillation, N (%)	30 (62.5)	26 (59.1)	>0.05
Paroxysmal AF, N (%)	9 (18.8)	3 (6.8)	>0.05
Persistent AF, N (%)	21 (43.8)	23 (52.3)	>0.05
Atrial flutter, N (%)	2 (4.2)	1 (2.3)	>0.05
Heart failure NYHA class			
Class 1, N (%)	1 (2.1)	4 (9.1)	>0.05
Class 2, N (%)	9 (18.8)	27 (61.4)	<0.001*
Class 3, N (%)	34 (70.7)	13 (29.5)	<0.001*
Class 4, N (%)	4 (8.4)	-	<0.001*

Note: Me-Median value; Q1-Lower quartile; Q3-Upper quartile; AF-Atrial fibrillation; NYHA-New York Heart Association. *Statistically significant

Laboratory parameters of patients are presented in Table 2.

When comparing patients with HFmrEF and HFrEF, it was found that patients with reduced ejection fraction had both higher D-dimers level (977.9 [266; 993.1] vs. 564.8 [190; 520.8] ng/mL, p=0.021) and higher NT-proBNP levels (5949.8 [1748; 8083.5] vs. 1731.8 [711; 2143.8] pg/mL, p=0.003), clearly indicating that elevated circulating plasma NT-proBNP levels correlate with the severity of HF.

In biochemical blood test patients with HFmrEF were characterized by higher eGFR (83.6 [64.5; 98.5] vs 75.6 [54; 91.5] ml/min/1.73m^2, p=0.047), however their urea and creatinine levels showed no differences (p>0.05).

Other parameters, including renal function tests, liver enzymes, and electrolytes showed no differences.

Table 2: Laboratory parameters of patients.

Parameters	Group 1 HFrEF (n=48) Me [Q1; Q3]	Group 2 HFmrEF (n=44) Me [Q1; Q3]	P value
RBC, 10^{12}/L	4.6 [4.2; 5.1]	4.7 [4.3; 5.2]	>0.05
Hemoglobin, g/L	141.2 [130; 153]	147.1 [135; 159]	>0.05
WBC, 10^9/L	7.4 [6.4; 8.6]	7.2 [6.3; 8.1]	>0.05
ESR, mm/h	12.3 [4; 18.5]	12 [5; 15]	>0.05
Platelets, 10^3/L	195.1 [152.5; 229]	205.9 [179; 235.5]	>0.05
Urea, mmol/L	8.4 [5.7; 9.7]	7.0 [5.4; 7.9]	>0.05
Creatinine, µmol/L	112.0 [90.3; 122]	98.1 [86.7; 109]	>0.05
eGFR, ml/min/1.73m^2	75.6 [54; 91.5]	83.6 [64.5; 98.5]	0.047*
Total cholesterol, mmol/L	4.1 [3.1; 4.8]	4.0 [3.1; 4.6]	>0.05

Continued.

Parameters	Group 1 HFrEF (n=48) Me [Q1; Q3]	Group 2 HFmrEF (n=44) Me [Q1; Q3]	P value
AST, IU/L	30.5 [21; 43.2]	32.5 [21; 35.3]	>0.05
ALT, IU/L	32.3 [20; 53.8]	42.6 [22.3; 62.1]	>0.05
Glucose, mmol/L	7.2 [5.1; 6.5]	6.9 [5.4; 8.0]	>0.05
Sodium, mEq/L	141.6 [138; 143]	141.5 [140; 143.8]	>0.05
Potassium, mEq/L	4.5 [4.2; 4.8]	4.5 [4.2; 4.8]	>0.05
NT-proBNP, pg/mL	5949.8 [1748; 8083.5]	1731.8 [711; 2143.8]	0.003*
D-dimer, ng/mL	977.9 [266; 993.1]	564.8 [190; 520.8]	0.021*

Note: Me-Median value; Q1-Lower quartile; Q3-Upper quartile; RBC-Red blood cells; WBC-White blood cells; ESR-Erythrocyte sedimentation rate; eGFR-Estimated glomerular filtration rate; AST-Aspartate aminotranferase; ALT-Alanin aminotranferase; NT-proBNP-N-terminal pro-B-type natriuretic peptide; *Statistically significant

Echocardiographic parameters of the patients are presented in Table 3.

According to the results of transthorasic echocardiography, patients of the studied groups had significant differences in the linear and volumetric parameters of left atrium and both ventricles (p<0.05), which demonstrated undeniable correlation between LVEF and other heart diameters and volumes. Only right atrium sizes were comparable between the groups (p>0.05)

It is interesting that patients with HFrEF had lower systolic septal thickness than patients with HFmrEF (15.1 [13.8; 16.3] vs. 16.8 [15.8; 18.3] mm, p=0.002), indicating formation of dilated cardiomyopathy in patients with HFrEF, however, there were no such differences present in the systolic posterior wall thickness (p>0.05). Diastolic thickness of both interventricular septum and posterior wall of the left ventricle didn't show significant intergroup differences either (p>0.05).

Three quarters of the patients with HFrEF and more than a half of patients with HFmrEF had areas of hypokinesis (p=0.024), with contractility index being higher in HFrEF (1.8 [1.5; 2.1] vs. 1.3 [1; 1.4], p>0.05). Incidence of pleural effusion was also almost three times higher in HRrEF group (45.8 vs. 18.2%, p=0.006), indicating formation of decompensated congestive HF. However, incidence of pericardial effusion in each group was rather low, and demonstrated no statistically significant differences (p>0.05).

Table 3: Echocardiographic parameters of patients.

Parameter	Group 1 HFrEF (n=48) Me [Q1; Q3]	Group 2 HFmrEF (n=44) Me [Q1; Q3]	P value
LA diameter (2 chamber), mm	47.5 [44; 51]	44.8 [40; 49]	0.033*
LA diameter (medial to lateral), mm	47.5 [45; 50]	44.0 [41.8; 47.5]	0.003*
LA diameter (front to back), mm	65.5 [63; 70]	61.3 [57.8; 67]	0.002*
RA diameter (medial to lateral), mm	44.1 [40.8; 47]	42.8 [38; 46]	>0.05
RA diameter (front to back), mm	61.0 [57.8; 64.2]	58.4 [52.8; 63]	>0.05
LV ESD, mm	52.5 [47.8; 58]	43.2 [39.8; 47]	<0.001*
LV EDD, mm	62.8 [57; 67]	57.4 [55; 60.1]	<0.001*
M-mode		-	-
LV ESV, ml	142.1 [108; 168.5]	90.6 [78; 103]	<0.001*
LV EDV, ml	206.7 [163.5; 236.5]	167.5 [149; 181]	<0.001*
LVEF, %	33.1 [29; 39.5]	46.1 [45; 48]	<0.001*
B-mode		-	-
LV ESV, ml	133.4 [88.3; 165]	86.5 [64; 106]	<0.001*
LV EDV, ml	196.2 [137.5; 243.3]	153.8 [113.8; 186.8]	0.006*
LVEF, %	33.5 [29; 37.8]	45.6 [43; 48]	<0.001*
Septal thickness (systolic), mm	15.1 [13.8; 16.3]	16.8 [15.8; 18.3]	0.002*
Septal thickness (diastolic), mm	12.8 [12; 14]	13.5 [15.8; 18.3]	>0.05
Posterior wall thickness (systolic), mm	15.4 [14; 17]	15.9 [15; 17]	>0.05
Posterior wall thickness (diastolic), mm	11.8 [10.8; 13]	12.0 [11; 13]	>0.05
Right ventricle diameter, mm	30.5 [27.5; 34]	27.9 [26; 30.1]	0.012*
TAPSE, mm	15 [14; 16.75]	13.3 [8.5; 16.5]	>0.05
Contractility index	1.8 [1.5; 2.1]	1.3 [1; 1.4]	<0.001*
Hypokinesis areas, N (%)	36 (75)	23 (52.3)	0. 024*
Akinesis areas, N (%)	18 (37.5)	4 (9.1)	0.002*

Continued.

Parameter	Group 1 HFrEF (n=48) Me [Q1; Q3]	Group 2 HFmrEF (n=44) Me [Q1; Q3]	P value
Pleural effusion, N (%)	22 (45.8)	8 (18.2)	0.006*
Pericardial effusion, N (%)	3 (6.3)	3 (6.8)	>0.05

Note: Me-Median value; Q1-Lower quartile; Q3-Upper quartile; LA-Left atrium; RA-Right atrium; LV-Left ventricle; ESD-End-systolic diameter; EDD-End-diastolic diameter; ESV-End-systolic volume; EDV-End-diastolic volume; LVEF-Left ventricular ejection fraction; *Statistically significant

When conducting a correlation analysis, it was found that NT-proBNP level had significant correlations with echocardiographic parameters, including LVEF in both M-mode (R=-0.34, p<0.001) and B-modes (R=-0.49, p<0.001) (see Figure 1).

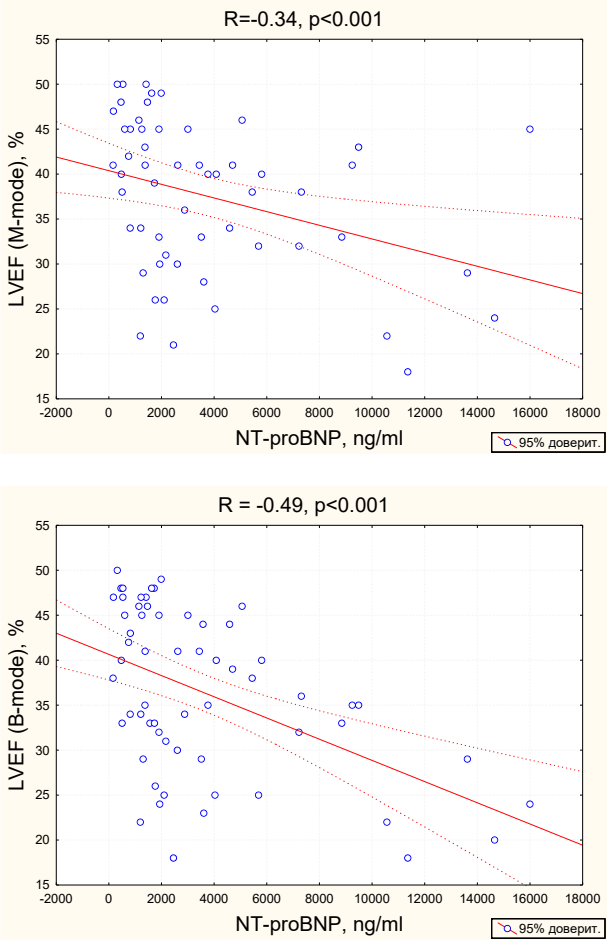

Figure 1: Results of correlation analysis of NT-proBNP and LVEF.

Other correlations between NTproBNP and echocardiographic parameters included LA diameter (R=0.26, p=0.035), LV end-systolic diameter (R=0.27, p=0.029), as well as LV end-systolic volume (R=0.30, p=0.018) and LV contractility index (R=0.27, p=0.045).

The foundation of medical therapy for both HFrEF and HFmrEF centers on the inhibition of the renin-angiotensin-aldosterone system with the use of angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist (MRA), the inhibition of the sympathetic nervous system with beta-blockers, and the more recent addition of sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

Analysis of pharmacological therapy of the studied patient groups is presented in Table 4.

Table 4: Pharmacological therapy of the patients.

Parameters	Group 1 HFrEF (n=48)	Group 2 HFmrEF (n=44)	P value
Beta-blocker, N (%)	48 (100)	48 (100)	>0.05
ACE inhibitor, N (%)	14 (29.17)	20 (45.45)	>0.05
Angiotensin II receptor blocker, N (%)	11 (22,92)	13 (31.82)	>0.05
ARNI, N (%)	16 (33.33)	6 (13.6)	0.027*
Mineralocorticoid receptor antagonist, N (%)	40 (83.33)	35 (84.09)	>0.05
SGLT2 inhibitor, N (%)	23 (47.92)	18 (40.91%)	>0.05
Loop diuretic, N (%)	42 (91.30)	21 (52.27)	<0.001*

Note: ACE-Angiotensin-converting enzyme; ARNI-Angiotensin receptor/neprilysin inhibitors; SGLT2-Sodium-glucose cotransporter-2; *Statistically significant

In the both groups, 100% patients were treated with beta-blockers, and the majority of patients received MRAs (83.3% vs. 84%, p>0.05). Overall, majority of patients in both groups were treated with ACEi/ARB/ARNI (85.4% vs. 88.6%) However; among the HFrEF group, 16 (33.3%) patients were on ARNI, while in HFmrEF this class of medications was significantly less common (13,6%), p<0.001. The prescription rate for SGLT2 inhibitors was comparable between groups, and didn't reach 50% of all study participants. Loop diuretics were significantly more common among HFrEF group of patients (p<0.001), indicating severity of clinical symptoms in this phenotype of HF.

DISCUSSION

HFmrEF was first proposed by Lam and Solomon in 2014, and listed as a new subtype of heart failure (HF) in 2016 European Society of Cardiology guidelines.[2,12] Recognition of HFmrEF as presented it as a distinct, previously under-studied «grey zone» unit with heterogenous features. Clinical positioning of HFmrEF between HFrEF and HFpEF: HFmrEF group looks milder than HFrEF (small chambers, lower NT-proBNP, fewer

effusions and better NYHA class), which aligns with the idea that HFmrEF can show intermediate or mixed features.

There is a higher NT-proBNP in HFrEF and its negative correlation with LVEF is consistent with established literature.[11,13] Our findings are consistent with those of other researchers, who have demonstrated that NT-proBNP levels, along with other factors, depend on the degree of LV dysfunction.[11] Other authors have found a weak positive correlation between the functional class of HF and NT-proBNP levels, which is also consistent with our findings.[15] According to literature data, the leading stimulus for the release of natriuretic peptide by cardiomyocytes is an increase in the extensibility of individual areas of the myocardium, including due to an increase in pressure in the chambers of the heart.[16]

There is also a greater level of obesity in HFmrEF. Prior broader literature often associates higher BMI with HFpEF.[14] Numerous studies have identified obesity as a significant risk factor for hypertension, cardiovascular disease, and left ventricular hypertrophy, which in turn are important risk factors for the onset and progression of HF. Obesity has been shown to be a risk factor for the development of HF, but is potentially a greater risk factor for the development of HFpEF than HFrEF.[14] However, to date, the complex pathogenetic mechanisms underlying the interaction between obesity and the progression of HF remain incompletely understood.[6] This article's HFmrEF obesity enrichment fits a phenotype leaning somewhat toward HFrEF-like comorbidity pattern in this unit.

There is a clear structural distinction (larger LA/LV, more wall-motion abnormalities, lower septal systolic thickness) in HFrEF; comparatively thicker septum in HFmrEF. This offers concrete instrumental differences that other findings describe more generally as «heterogenous».[2,3,8,13] Pleural effusion and NT-proBNP levels were also higher in HFrEF, supporting greater stage of decompensation.

Both groups received contemporary RAAS inhibition, beta-blockers, and MRAs; however, the low percentage of SGLT2 inhibitors represents a clear, actionable treatment gap given their proven benefits across EF ranges. Overall, HFmrEF emerges as a clinically relevant, generally milder phenotype than HFrEF but with meaningful overlap.

Studies investigating HFmrEF have answered a number of questions, but the data remain largely sparse and contradictory.[2,3,11,15] We can currently conclude that this category of patients represents an intermediate state in terms of epidemiology, etiology, clinical characteristics, and assessment. However, it is difficult to definitively compare the prognosis of patients with different categories of HF. Many studies, which are the basis for these conclusions, demonstrate that patients with CHFrEF are often grouped together with CHFpEF or CHFrEF in clinical trials, particularly when combining syndromic phenotypes, which are not always accurate. This work helps to fill the knowledge gap in understanding the epidemiology of various HF phenotypes. It highlights that these subgroups include patients with dynamic LVEF whose therapeutic profiles are currently unclear because we were limited by the dichotomous design of clinical trials for LVEF.

Methodical considerations strengths would be the use of detailed echo phenotyping; biomarker correlations; clear inclusion/exclusion; contemporary tracking database capture.

Limitations would be use of single-center, retrospective; modest sample; cross-sectional EF snapshot; no HFpEF arm for full tri-phenotype comparison.

CONCLUSION

HFmrEF and HFrEF shared similar age, sex, and major comorbidities, yet displayed distinct clinical and instrumental profiles. HFmrEF showed a milder presentation – better NYHA class, fewer pleural effusions, smaller chambers, and markedly lower NT-proBNP – whereas HFrEF exhibited advanced remodeling (larger LA/LV dimensions and volumes), more wall-motion abnormalities, thinner systolic septum suggestive of a dilated/ischemic phenotype, higher NT-proBNP, and greater congestion.

HFmrEF was enriched for obesity, aligning with a HFpEF-like comorbidity pattern and supporting HFmrEF as a heterogenous «grey zone» with intermediate or mixed features. NT-proBNP correlated negatively with LVEF and positively with adverse structural indices (LA size, LV ESD/ESV, lower contractility), reinforcing its role as an integrative severity marker across EF levels. Renal function by eGFR was modestly better in HFmrEF, consistent with less decompensation.

These findings support: systemic phenotyping of HFmrEF to individualize therapy, broader adoption of SGLT2 inhibitors alongside ARNI optimization and prospective studies to define trajectories, subphenotype-specific responses (e.g. obesity-, ischemia-, AF- driven), and multimodal risk stratification.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Katsi V, Georgiopoulos G, Laina A, Koutli E, Parissis J, Tsioufis C, et al. Left ventricular ejection fraction as therapeutic target: is it the ideal marker? Heart Fail Rev. 2017;22(6):641-55.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart

failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;74(10):1037-147.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-3726.
4. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol. 2022;19(2):100-16.
5. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail. 2017;19(12):1624-1634.
6. Tromp J, Khan MAF, Mentz RJ, O'Connor CM, Metra M, Dittrich HC, et al. Biomarker profiles of acute heart failure patients with a mid-range ejection fraction. JACC Heart Fail. 2017;5(7):507-517.
7. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and oneyear outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(12):1574-85.
8. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail. 2017;19(10):1258-69.
9. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, et al. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? ESC Heart Fail. 2017;4(2):99-104.
10. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail. 2016;4(6):464-72.
11. Srivastava PK, Hsu JJ, Ziaeian B, Fonarow GC. Heart failure with mid-range ejection fraction. Curr Heart Fail Rep. 2020;17(1):1-8.
12. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%) Eur J Heart Fail. 2014;16:1049-55.
13. Lopatin Y. Heart failure with mid-range ejection fraction and how to treat it. Card Fail Rev. 2018;4(1):9-13.
14. Ebong IA, Goff DC Jr, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. Obes Res Clin Pract. 2014;8(6):e540-8.
15. Virani SS, Alonso A, Benjamin EJ. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139-e596.
16. Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest. 1991;87(4):1402-12.

Cite this article as: Waneshwari M, Alao CT, Kalatsei L. Heart failure with reduced and mid-range ejection fraction: laboratory and instrumental profile. Int J Res Med Sci 2026;14:2316-22.