

Clinical Characteristics and Outcomes of Heart Failure with Preserved, Mildly Reduced, and Reduced Ejection Fraction: A 6-Month Follow-up Study

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Abstract

Background and Objective: Heart failure is a major public health problem with 64.3 million people affected all over the world, and it is an important cause for hospital admission and mortality. The aim of this study is to assess the clinical characteristics, frequency of hospitalization, and outcomes of heart failure with preserved, mildly reduced, and reduced ejection fraction. **Materials and Methods:** This is a prospective study of 91 patients aged more than 18 years of both genders with clinical features of heart failure supported by transthoracic echocardiography, who had been admitted to the Coronary Care Unit of Hawler Teaching Hospital for the period from October 2019 to February 2021. Heart failure patients were classified into preserved, mildly reduced, and reduced ejection fraction according to the European Society of Cardiology guidelines 2021 for the diagnosis of heart failure. The hospital outcomes, echocardiographic variables, the frequency of hospitalization, and mortality over 6 months were compared. **Results:** Among the 91 patients, the majority were females 48 (52.7%), the male: female ratio is 1:1.1, and the majority had heart failure with preserved ejection fraction 68 (75%). Ischemic heart disease 27 (30%) accounts for the majority of heart failure with preserved ejection fraction. Hyperlipidemia 17 (18.9%), orthopnea 15 (16.7%), paroxysmal nocturnal dyspnea 15 (16.5%), cardiovascular hospitalization 13 (14.3%), and mortality 6 (6.6%) were higher in heart failure with reduced ejection fraction. **Conclusion:** The high frequency rate of ischemic heart disease was reported in heart failure with preserved ejection fraction. Cardiovascular hospitalization and mortality rate were higher among heart failure patients with reduced ejection fraction.

Keywords: Heart Failure, HFpEF, HFmrEF, HFrEF

INTRODUCTION

Heart failure is an important cause of hospital admission and mortality,^[1] with 64.3 million people affected all over the world.^[2] The prevalence of heart failure in developed countries is generally estimated at 1–2% of the general adult population.^[3]

The European Society of Cardiology (ESC) guidelines 2021 classified heart failure into heart failure with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction <40%; heart failure with mildly reduced ejection fraction (HFmrEF) previously known as heart failure with mid-range ejection fraction, defined as left ventricular ejection fraction of 40–49%; and heart failure

with preserved ejection fraction (HFpEF), defined as left ventricular ejection fraction $\geq 50\%$.^[4]

There have been conflicting reports as to whether patients in HFpEF have a greater morbidity and mortality when compared with HFmrEF and HFrEF. The prevalence of comorbidities has previously been reported to be higher in patients with HFpEF when compared with HFrEF.^[5]

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A prospective multicenter longitudinal study in New Zealand and Singapore showed that the death rate was comparable in HFpEF and HFmrEF and lower than in HFrEF in contrary to a study done in western Saudi Arabia, which showed that the mortality rates among HFrEF, HFmrEF, and HFpEF were not significantly different.^[6,7]

No previous studies were carried out in Iraq to assess the differences in clinical characteristics, frequency of hospitalization, and outcomes among various types of heart failure.

This study aimed to assess the clinical characteristics, echocardiographic findings, frequency of hospitalization, and outcomes of patients diagnosed with HFpEF, HFmrEF, and HFrEF.

MATERIALS AND METHODS

This study is a prospective study of 91 consecutive patients of both genders aged 18 years or older with clinical features of heart failure (stages C and D) with New York Heart Association (NYHA) functional class II–IV supported by two-dimensional echocardiography who had been admitted for the first time to the Coronary Care Unit (CCU) or Medical Ward of Hawler Teaching Hospital for the period from October 2019 to February 2021. These patients were included in the study.

The patients with the following conditions were excluded from the study: NYHA class I, stage A and B heart failure, heart failure with more than one admission, heart failure with atrial fibrillation, congenital heart disease, peripartum cardiomyopathy, acute myocarditis, chronic kidney disease with glomerular filtration rate of less than 60%, patients on cardiac assist device, cardiac resynchronization therapy (RCT) or pacemaker, patients with advanced liver cirrhosis, portal hypertension, patients with history of COVID-19 of less than 3 months or COVID-19 vaccination of less than 1 month, patients on cytotoxic medications, patients with limited life expectancy, and heart failure patients with poor acoustic window.

Clinical evaluation had been done for each patient to assess the clinical presentation such as orthopnea, paroxysmal nocturnal dyspnea, and hospital mortality as well as to evaluate the risk factors for heart failure including hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemia, family history of ischemic heart disease or cardiomyopathies, smoking, alcohol consumption, and obesity defined as body mass index more than 30.

Hypertension is diagnosed with two average measurements of systolic blood pressure (BP) more than 130 mmHg and/or diastolic BP more than 85 mmHg or previously diagnosed with or without treatment.^[8]

Diabetes mellitus is diagnosed as patients already having and/or on treatments for diabetes mellitus, or recently diagnosed supported by clinical symptoms and two sample fasting blood sugar levels equal to or more than 126 mg/dL or two sample random blood sugar levels more than 200 mg/dL with or without HbA1C more than 6.5%.^[9] Hyperlipidemia is diagnosed as total cholesterol of ≥ 200 mg/dL and low-density lipoprotein of ≥ 100 mg/dL.^[10]

Transthoracic two-dimensional echocardiography had been performed for all patients within the first 3 days of hospital admission using Vivid E9 with X D clear Version 113 to assess the left ventricular systolic and diastolic functions, chamber size, wall thickness, mitral valve, aortic valve, pulmonary valve, tricuspid valve, and right ventricular function, according to the American College of Cardiology guidelines.

The patients were classified into heart failure with preserved, mildly reduced, and reduced ejection fraction according to the ESC 2021 guideline for the diagnosis and treatment of acute and chronic heart failure.^[4]

Heart failure with reduced ejection fraction is defined as clinical features of heart failure with ejection fraction of less than 40%, and heart failure with mildly reduced ejection fraction defined as clinical features of heart failure with ejection fraction of 40–49%. Heart failure with preserved ejection fraction is defined as clinical features of heart failure with ejection fraction equal to or more than 50% and left ventricular diastolic dysfunction by echocardiography.^[4]

Left ventricular systolic function is assessed by the Teicholz method. Two-dimensional directed M-mode echocardiography at the parasternal long-axis view with the linear measurement of the left ventricle at the level of mitral chordae is evaluated. Dilated left ventricular end-diastolic diameter (using the left parasternal long-axis view) is defined as equal to or more than 5.6 cm in men and equal to and more than 5.2 cm in women. Left atrial size is measured using two-dimensional M-mode echocardiography at the left parasternal long-axis view with the plane passing through the aortic valve. Left atrial enlargement is defined as left atrial diameter of more than 4 cm in men and 3.8 cm in women. Right ventricular systolic dysfunction is diagnosed by tricuspid annular plane systolic excursion (TAPSE) of less than 1.7 cm.^[11]

Left ventricular diastolic dysfunction is diagnosed by $E/A \leq 0.75$, $E/e' < 10$ (mild left ventricular diastolic dysfunction), $E/A < 2$, $E/e' \geq 10$ (moderate left ventricular diastolic dysfunction) and $E/A > 2$, $E/e' \geq 10$ (severe left ventricular diastolic dysfunction).^[11]

Pulmonary arterial hypertension (PAH) is diagnosed by 2D echocardiography as mild when maximum tricuspid regurgitation velocity is equal to 2.8 mm/s, moderate PAH

when maximum tricuspid regurgitation velocity equal to 2.9–3.4 mm/s, and severe PAH when maximum tricuspid regurgitation velocity ≥ 3.5 mm/s.^[12]

All recruited patients in each group of heart failure were followed after hospital discharge for 6 months by phone contact to assess the mortality and the frequency of hospital admission.

The clinical presentations, risk factors for heart failure, echocardiographic variables, mortality and frequency of hospitalization over 6 months after the first hospital discharge for each type of heart failure were compared.

Verbal and written consent was obtained from each patient, and this study is approved by the Ethics Committee of Kurdistan Board for Medical Specialization.

Data were analyzed using the Statistical Package for Social Sciences (version 22). The χ^2 test of association was used to compare between proportions of the study groups. Student's *t*-test of two independent samples was used to compare means of two groups. A *P*-value of ≤ 0.05 was considered statistically significant.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local Ethics Committee according to the document number 180 dated 3/2/2020 to get this approval.

RESULTS

The final total study group consisted of 91 patients with heart failure, the majority were female 48 (52.7%), and the male to female ratio equals 1:1.1. Majority of patients had HFpEF 68 (75%) followed by HFrEF 15 (16%) and HFmrEF 8 (9%) as shown in Figure 1.

The mean age was 62.46 ± 12.458 with no significant difference among the groups and female reported in the higher frequency rate among HFmrEF 5 (62.5%) vs. HFpEF 40 (58.8%) and HFrEF 3 (20%), whereas males reported in higher frequency rate among HFrEF 12 (80%) vs. HFpEF 28 (41.2%) and HFmrEF 3 (37.5%) (*P*-value 0.017).

The high frequency rate of orthopnea 15 (16.7%) and paroxysmal nocturnal dyspnea 15 (16.6%) were recorded among patients with HFrEF when compared with HFpEF 11 (12.2%), 11 (12.09%) and HFmrEF 4 (4.4%) and 4 (4.4%), respectively (*P* < 0.001). Most of the patients with HFpEF presented with obesity 31 (38.3%) when compared with HFrEF 5 (6.17%) and HFmrEF 1 (1.23%) but without statistical significance.

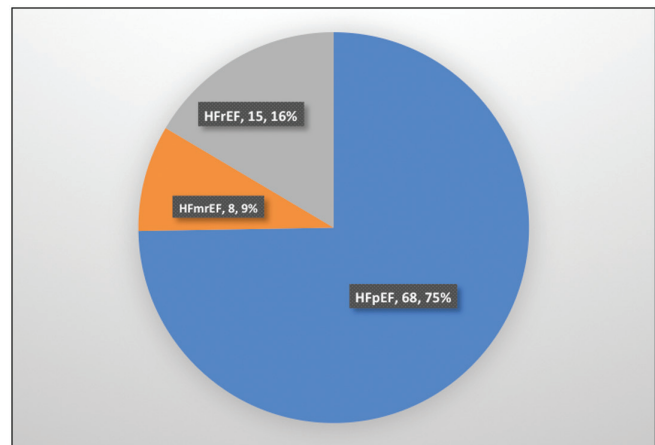


Figure 1: Frequency of distribution of heart failure with preserved, mildly reduced, and reduced ejection fraction

Ischemic heart disease was more frequently encountered among HFpEF 27 (30%) than among HFrEF 11 (12.2%) and HFmrEF 3 (3.3%) (*P*-value 0.05). High frequency rate of hyperlipidemia reported among HFrEF 17 (18.9%) than among HFpEF 1 (1.1%) and HFmrEF 0 (0%) (*P* = 0.033). There was no statistical difference among various types of heart failures in relation to hypertension, diabetes mellitus, smoking and family history of ischemic heart disease, chronic obstructive pulmonary disease and stage I and II chronic kidney disease, as shown in Table 1.

Twenty-five patients (27.5%) with heart failure were admitted to the hospital during the 6-month follow-up study due to cardiovascular symptoms; 13 patients (14.3%) had HFrEF versus HFpEF 10 (11%) and HFmrEF 2 (2.2%) (*P* < 0.001). Nine patients (9.9%) with heart failure were admitted for non-cardiovascular causes over the six-month follow-up period without statistical significance, as shown in Table 2.

A high frequency rate of cardiovascular mortality is reported among patients with HFrEF 6 (6.6%) when compared with HFpEF 1 (1.1%) and HFmrEF 0 (0%) (*P* < 0.001) whereas there is no significant difference among various types of heart failure reported in relation to non-cardiovascular mortality over a six-month follow-up study, as shown in Table 2.

The results of the two-dimensional transthoracic echocardiography study show that dilated left atrium was found in 47 (51.6%) patients with HFpEF and in 14 (15.4%) and 8 (8.8%) in patients with HFrEF and HFmrEF, respectively (*P* < 0.001). Dilated left ventricular diameter in end diastole is reported in 14 (15.6%) patients with HFrEF when compared with HFmrEF 4 (4.4%) and HFpEF 2 (2.2%) (*P* < 0.001). The majority of patients with HFrEF were having dilated right atrium 7 (8%) when compared with 3 (3.4%) and HFmrEF 2 (2.3%) (*P* < 0.001), as shown in Table 3. High incidence of mild left ventricular hypertrophy is recorded by echocardiographic examination among

Table 1: Characteristics of the patients at baseline

Characteristics		HFpEF N=68	HFmrEF N=8	HFrEF N=15	P-value
Age		63.38 ± 12.41	59.25 ± 10.01	63.27 ± 13.07	0.669
Male		28 (41.2%)	3 (37.5%)	12 (80%)	0.017*
Female		40 (58.8%)	5 (62.5%)	3 (20%)	
Orthopnea		11 (12.22%)	4 (4.44%)	15 (16.7%)	<0.001*
PND		11 (12.09%)	4 (4.4%)	15 (16.5%)	
BMI	Underweight	0 (0%)	0 (0%)	0 (0%)	0.335
	Normal	9 (11.1%)	1 (1.23%)	4 (4.94%)	
	Overweight	21 (25.9%)	4 (4.94%)	5 (6.17%)	
	Obese	31 (38.3%)	1 (1.23%)	5 (6.17%)	
Family history		21 (23.1%)	1 (1.1%)	7 (7.69%)	0.232
Smoking		7 (7.7%)	2 (2.2%)	6 (6.59%)	<0.05*
Hypertension		49 (53.8%)	5 (5.49%)	7 (7.69%)	0.16
Diabetes mellitus		33 (36.3%)	5 (5.49%)	6 (6.59%)	0.588
IHD		27 (30%)	3 (3.3%)	11 (12.2%)	0.05*
Hyperlipidemia		1 (1.1%)	0 (0.0%)	17 (18.9%)	0.033*
COPD		1 (1.1%)	1 (1.1%)	2 (2.2%)	0.064
Stage I and II CKD		3 (3.3%)	0 (0%)	1 (1.1%)	0.759

*Statistically significant P-value

HFpEF=heart failure with preserved ejection fraction, HFmrEF=heart failure with mildly reduced ejection fraction, HFrEF=heart failure with reduced ejection fraction, PND=paroxysmal nocturnal dyspnea, BMI=body mass index, IH = ischemic heart disease, COPD = chronic obstructive pulmonary disease, CKD = chronic kidney disease

Table 2: Cardiovascular outcomes among heart failure with preserved, mildly reduced, and reduced ejection fraction

Cardiovascular outcomes	HFpEF N=68	HFmrEF N=8	HFrEF N=15	P-value
CV hospitalization	10 (11%)	2 (2.2%)	13 (14.3%)	<0.001*
Non-CV hospitalization	8 (8.8%)	0 (0%)	1 (1.1%)	0.347
CVS mortality	1 (1.1%)			<0.001*
		0 (0%)	6 (6.6%)	
Non-CVS mortality				0.554
	2 (2.2%)	0 (0%)	0 (0%)	

*In-hospital mortality and mortality over 6 months' follow-up after hospital discharge

*Statistically significant P-value

HFpEF=heart failure with preserved ejection fraction, HFmrEF=heart failure with mildly reduced ejection fraction, HFrEF=heart failure with reduced ejection fraction, CV=cardiovascular

patients with HFpEF 28 (30.8%) when compared with HFmrEF 4 (4.4%) and HFrEF 0 (0%) and 1 (1.1%), and high incidence of moderate left ventricular hypertrophy is reported among patients with HFpEF 8 (8.8%) vs. HFrEF 1 (1.1%) and HFmrEF 0 (0%), respectively, P-value <0.001, as shown in Table 3.

Mild and moderate functional mitral regurgitation (MR) diagnosed by 2D-transthoracic echocardiography was more frequent among patients with HFpEF 15 (16.7%) and 3 (3.3%), compared with HFrEF 4 (4.4%) and 2 (2.2%) and HFmrEF 4 (4.4%) and 1 (1.1%). Severe functional MR was more frequent among patients with HFrEF 5 (5.6%), compared with HFpEF 3 (3.3%) and HFmrEF 0 (0%), P < 0.001, as shown in Table 3.

The echocardiographic incidence of mild and moderate pulmonary arterial hypertension was higher among

patients with HFpEF 14 (15.5%) and 6 (6.6%) vs. HFrEF 2 (2.2%) and 5 (5.5%) and HFmrEF 0 (0%) and 2 (2.2%), respectively, whereas severe pulmonary hypertension was higher among patients with HFrEF 5 (5.5%) vs. HFpEF 4 (4.4%) and HFmrEF 1 (1.1%) with highly significant P-value <0.001, as shown in Table 3.

DISCUSSION

Up to our knowledge, this is the first prospective study in Iraq reporting clinical characteristics, outcomes, clinical presentation, co-morbidities, and mortality rates, through conveying 6 months of follow-up of patients with HF among all the three groups, namely, heart failure with preserved, mildly reduced, and reduced EF in Iraq.

A hospital-based study does not give us the exact epidemiology of the illness of the whole community. In this

Table 3: Two-dimensional transthoracic echocardiographic abnormalities among heart failure with preserved, mildly reduced, and reduced ejection fraction

Echocardiographic abnormalities		HFpEF N=68	HFmrEF N=8	HFrEF N=15	P-value
Dilated LA		47 (51.6%)	8 (8.8%)	14 (15.4%)	<0.001*
Dilated LVDD		2 (2.2%)	4 (4.4%)	14 (15.6%)	
Dilated RA		3 (3.4%)	2 (2.3%)	7 (8%)	
MR					<0.001*
	Mild	15 (16.7%)	4 (4.4%)	4 (4.4%)	
	Moderate	3 (3.3%)	1 (1.1%)	2 (2.2%)	
	Severe	3 (3.3%)	0 (0%)	5 (5.6%)	0.183
AR					
	Mild	6 (6.7%)	0 (0%)	0 (0%)	
	Moderate	2 (2.2%)	1 (1.1%)	3 (3.3%)	<0.001*
	Severe	1 (1.1%)	0 (0%)	0 (0%)	
LVH					
	Mild	28 (30.8%)	4 (4.4%)	0 (0%)	<0.001*
	Moderate	8 (8.8%)	0 (0.0%)	1 (1.1%)	
PAH					
	Mild	14 (15.4%)	0 (0%)	2 (2.2%)	<0.001*
	Moderate	6 (6.6%)	2 (2.2%)	5 (5.5%)	
	Severe	4 (4.4%)	1 (1.1%)	5 (5.5%)	

*Statistically significant P-value

HFpEF = heart failure with preserved ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFrEF = heart failure with reduced ejection fraction, LA = left atrium, LVDD = left ventricular diameter in diastole, RA = right atrium, MR = mitral regurgitation, AR = aortic regurgitation, LVH = left ventricular hypertrophy, PAH = pulmonary arterial hypertension

study, 75% of the cases had HFpEF followed by the HFrEF (16%) and HFmrEF (9%), supported by the study of Shiga *et al.*^[13] from Japan but contrary to the results of Farré *et al.*^[14] and Choincel *et al.*^[15] in which heart failure was more prevalent in patients with HFrEF followed by HFmrEF and the lower frequency rate reported among HFpEF.

The mean age of our patients was 62.46 ± 12.458 years without significant difference among the groups, similar to the study in Nigeria (57.6 ± 15.9 years) but less than that from Japan (70.0 ± 12 years).^[16,17] This difference may be explained by longer survival and better therapeutic outcomes of patients with heart failure in Japan compared to Iraq and Nigeria.

Females accounted for the majority of HFmrEF followed by HFpEF and HFrEF, whereas a study done in Japan found that the majority of HFpEF cases were females, followed by HFmrEF and HFrEF patients. Our results are in contrast to the studies of Kapoor *et al.*^[18] and Hsu *et al.*^[19] Ischemic heart disease was more frequent among HFpEF compared with HFmrEF and HFrEF supported by studies done in Tanzania and Saudi Arabia while another study from Korea stated that the ischemic heart disease was more frequent in HFmrEF.^[20-22]

Dilated left ventricular diameter in end diastole was reported in 14 patients with HFrEF when compared with HFmrEF 4 and HFpEF 2 ($P < 0.001$), and the majority of patients with HFrEF were having dilated right atrium followed by HFpEF and lastly HFmrEF, consistent with the study of Lyu *et al.*^[23]

High incidence of mild and moderate left ventricular hypertrophy was recorded by echocardiographic examination among patients with HFpEF 28 (30.8%), 8 (8.8%) versus HFmrEF 4 (4.4%), 0 (0%), and HFrEF 0 (0%), 1 (1.1%), respectively P -value < 0.001 ; our results are comparable to a study done in Saudi Arabia.^[21] Our study reports high prevalence of functional MR in HFrEF when compared with HFpEF and HFmrEF in agreement with Goliash *et al.*^[24]

The echocardiographic incidence of mild and moderate pulmonary arterial hypertension was higher among patients with HFpEF vs. HFrEF and HFmrEF, respectively, supported by a study of Lyu *et al.*^[23] in contrast to a Bulgarian study in which pulmonary hypertension was higher in HFrEF.^[25]

The rate of hospitalization due to CVS events during the 6-month follow-up study was significantly higher in cases with HFrEF (14.3%) vs. HFpEF (11%) and HFmrEF (2.2%); it is parallel to the study of Choincel *et al.*^[15]

The cardiovascular mortality was higher in patients with HFrEF (6.6%) vs. HFpEF (1.1%) and HFmrEF (0%) ($P < 0.001$), in agreement with Grundy *et al.*^[10] whereas some former studies showed to be higher in HFpEF.^[3,26] The mortality rate was also higher in HFrEF than in HFmrEF and HFpEF in the OPTIMIZ-HF trial.^[27]

Limitations of this study included the small number size explained by the impact of COVID-19 on hospital admission during the study period and short duration of follow-up as well as the unavailability of N-terminal

pro-B-type natriuretic peptide or B-type natriuretic peptide for proper assessment of HFpEF.

A larger scale study with longer follow-up is recommended for better understanding of the prognosis and the outcomes of HFpEF, HFmrEF, and HFrEF in Iraq.

CONCLUSION

High frequency rates of ischemic heart disease are reported among HF patients with preserved EF. Cardiovascular hospitalization and cardiovascular mortality rate were higher among HF patients with reduced EF. More therapeutic efforts and closer follow-up should be directed toward HFrEF to improve the cardiovascular outcomes and the prognosis of these patients.

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Conflicts of interest

The authors report no conflicts of interest.

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