Dissimilarities in Females Having Heart Failure with Mildly Reduced Ejection Fraction

ABSTRACT

Background: The clinical features, epidemiology, pathogenesis & management of heart failure with mildly reduced ejection fraction (HFmrEF) differ in gender-specific dissimilarities like hormonal impact, anthropometry, pregnancy-related changes, comorbidities, specific diseases in women (incidence of HFpEFis higher in females whereas HFrEF is more common in males). This study aims to identify gender differences with meaningful clinical implications in females diagnosed with heart failure with HFmrEF.

Methodology: This study was done in 130 patients with HFmrEF patients aged more than 18 years without any evidence of sepsis were included in this study.

Results: Females patients were 26% (35 patients) of the study population having mean age of 64 years and belonged to upper-middle SES. Mean BMI was 25.6 (class I obesity), NYHA class II & III noted in 58% & 37% respectively. CAD was seen in 57%,mean haemoglobin & NT-proBNP were 10.8 gm% & 11145pg/ml respectively. Patients had mean EF of 44% and moderate PH was noted in 35%. Readmission rates were 28% in 1 year (17% in males). Around 90 % were on anti-platelets, statins and beta-blocker therapy. Diuretics/MRA's were used in <40% (compared to 31% in males), while SGLT2I & ARNI used in 30% & 16% respectively (42% & 20 % males). An improvement in left ventricular function was noted in 30% and AKI, CKD, ADHF & UTI were the major deterrents for initiating core HF therapy.

Conclusion: This study addressed the under-represented female population with HFmrEF sharing similar clinical features as their gender counterparts but with a higher proportional prevalence of anaemia, PH, CKD, readmission rates, and inadequate core HF treatment.

Keywords: Heart failure; ejection fraction; phenotypes; gender differences.

ABBREVIATIONS

HF : Heart failure
HFmrEF : Heart failure with mildly reduced ejection fraction
HFpEF : Heart failure with preserved ejection fraction
HFrEF : Heart failure with reduced ejection fraction
SES : Socioeconomic class
AKI : Acute kidney injury
CKD : Chronic kidney disease
CAD : Coronary artery disease
PH : Pulmonary hypertension

1. INTRODUCTION

Heart failure is likely to be a significant cause of death and disability in developing countries & along with the increased incidence of vascular diseases and the persistence of pre-transitional diseases such as Rheumatic heart disease (RHD) and cardiomyopathy [1]. Heart failure is a clinical syndrome characterized by typical

symptoms such as breathlessness, leg swelling, and easy fatiguability, which may be accompanied by signs such as raised jugular venous pressure (JVP), pulmonary crackles, and peripheral oedema caused by structural and functional cardiac abnormalities, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [2].

Heart failure affects approximately 26 million people worldwide. In the United States, heart failure was responsible for an estimated $13 billion in health expenditure in 2012 (more than 10% of total CVD health expenditure [3]. Heart failure is a major health issue in India, with demographic projections estimating an alarming rise in the prevalence of heart failure in India, ranging from 1.3 to 23 million [4]. Coronary artery disease (CAD) & Rheumatic heart disease (RHD) are the two major causes of heart failure in India, according to research from Trivandrum and hospital-based studies [5].

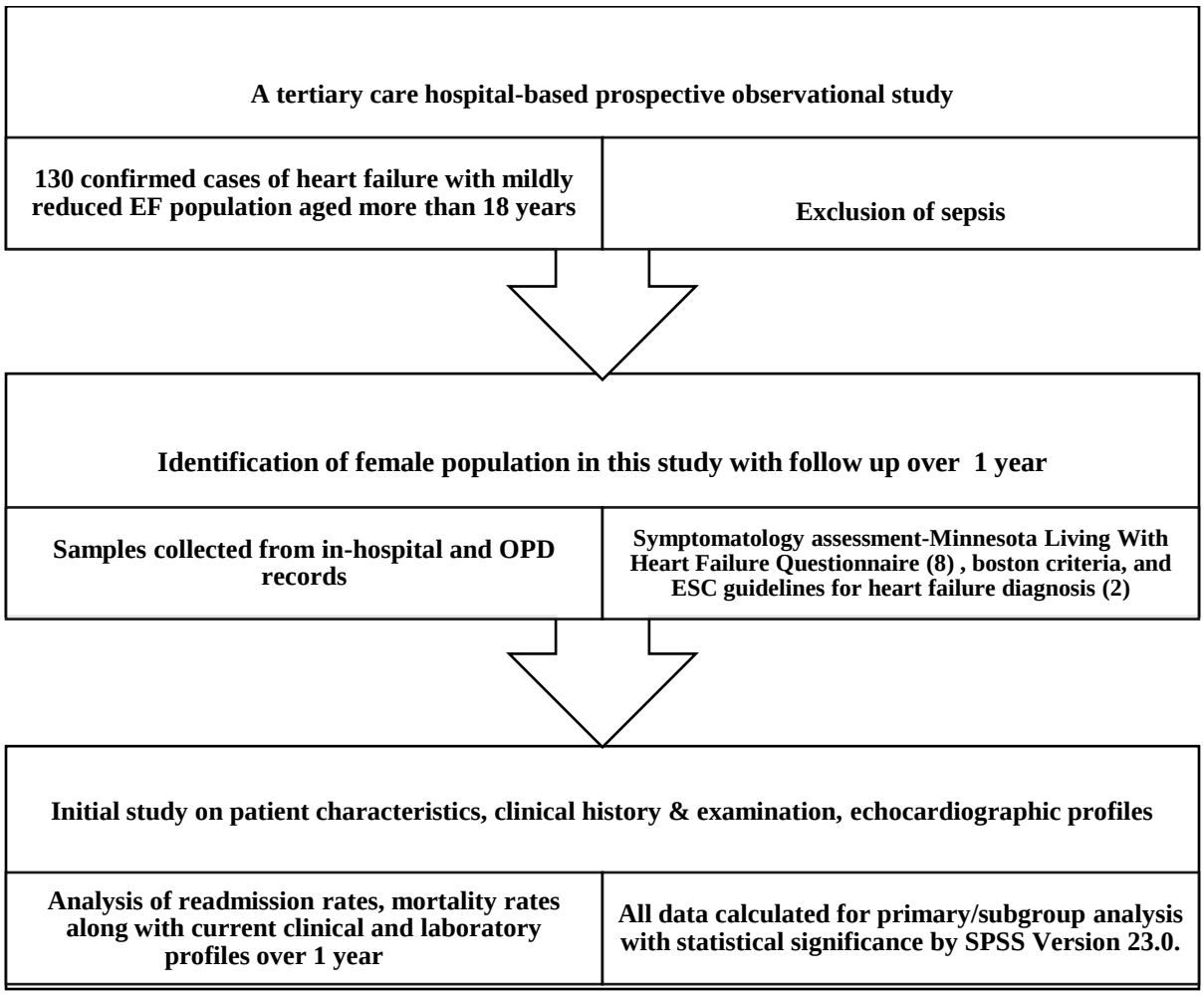
The 2016 European Society of Cardiology Heart failure guidelines defined a new category of HF with 40–49% EF as heart failure with mid-range EF (HFmrEF) [2]. Its overall prevalence in the Heart failure spectrum is 10–25% [6]. Heart failure with mid-range EF is a milder variety compared to Heart failure with reduced EF but the cardiovascular risk is less like Heart failure with preserved EF. Even though ejection fraction is a continuous variable, its importance in classification of distinct phenotypes of heart failure has led to the revision of heart failure with midrange ejection fraction to heart failure with mildly reduced ejection fraction [7].

The Trivandrum Heart Failure Registry, India (THFR) enrolled 1205 patients, while another research from the All India Institute of Medical Sciences (AIIMS) tested 10,163 individuals from six villages in Northern India for HF [5]. These are the two biggest studies that have lately been released in India, where HF with preserved and reduced EF was discussed in both studies. However, neither study considered mildly reduced EF.

2. METHODOLOGY

This study is a tertiary care hospital-based prospective observational study with 130 confirmed cases of heart failure with mildly reduced ejection fraction population over 18 years after excluding sepsis. This study population was aimed at female subsets with a study duration of 1 year. Samples were collected from in-hospital and OPD records of heart failure patients. Symptomatology was assessed by Minnesota Living With Heart Failure Questionnaire [8], Boston criteria, and ESC guidelines for heart failure diagnosis [2]. Patient characteristics, clinical history & examination, and echocardiographic profiles were initially studied. They were followed during a hospital stay while readmission rates, mortality rates over a period of 12 months along with clinical profile, available laboratory parameters like CBC, LFT, RFT, iron studies, NT-pro BNP, TSH,

Table 1. Methodology and study flow



echocardiographic assessment of ejection fraction using modified Simpson's method, angiographic evidence for heart failure worsening were analyzed as shown in Table 1. All data were instilled chronologically and were calculated statistically by SPSS Version 23.0. Subgroup analysis was done for statistical significance.

2.1 Statistical Analysis

All categorical variables are expressed as percentages. All continuous variables are expressed as mean+ SD if they are normally distributed. Comparison of those variables was done either by independent sample t-test. All other variables with no normal distribution will be expressed as median (interquartile range). A comparison of those was made by Mann Whitney U or Kruskal Wallis H tests. The Chi-square test is used for comparing categorical variables. Data entry is done in an MS Excel spreadsheet. Data analysis was carried out by SPSS Version 23.0. All analyses will be significant statistically when all P values <0.05.

3. RESULTS

After taking informed consent from a total of 130 patients with HFmrEF and their calculated LVEF ranging from 41-49 %. They were enrolled in our study between July 2021 to December 2022. This study's total population of females was 35 patients (26%, as shown in Fig. 1) with a mean age of around 64 years.

They belonged to upper-middle socioeconomic status and had increased awareness about their illness. The mean BMI noted was 25.6 as compared to 27 in males. Even though the general observation of more comorbid illnesses associated with obesity with regards to more hypoventilation disease, sleep disorders, and poor metabolic control there was limited significance in comparing HF episodes and

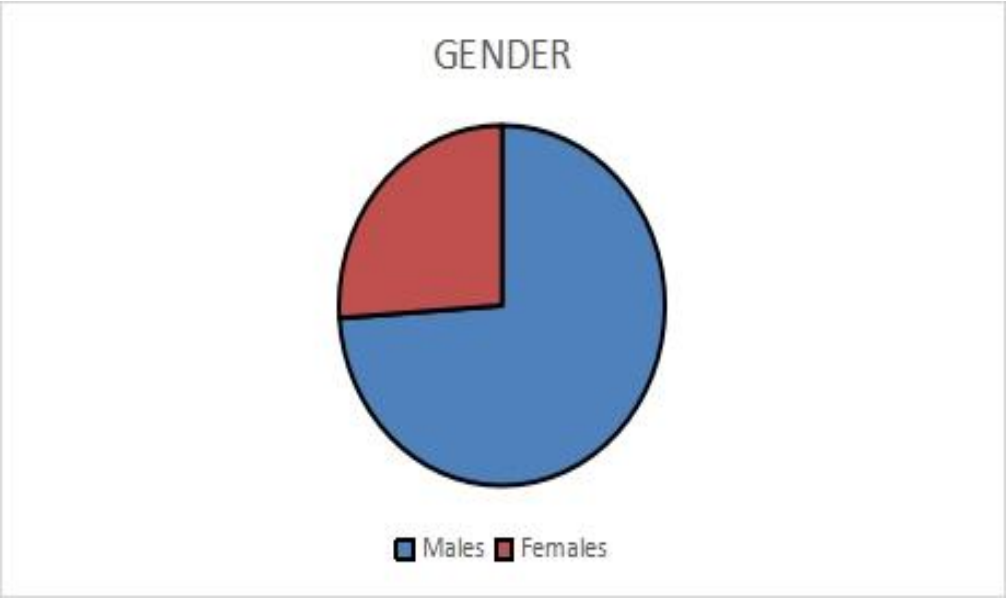


Fig. 1. Gender proportion of HFmrEF patients under study

pulmonary hypertension. The overweight class of patients had more than mild and moderate PAH. But NYHA class and increasing BMI scale had more statistical significance.

The average values of hemoglobin in this group of patients was 10.8 gm%, urea-40 mg %, creatinine -1.2mg%, sodium-135.6mEQ/L, mean potassium-4.3mEQ/L, median HbA1C recorded was 5.4%. Around 89% patients had TSH values of which 96% were euthyroid, 8% were hypothyroid & 3 % were hyperthyroid. There was statistical significance in comparing the anemia severity with number of prior HF admission (P value < 0.05).

On analyzing the reasons to avoid core drugs such as beta blockers were ADHF, recent ACS causing subnormal heart rate, and associated bronchial asthma/COPD/ peripheral artery disease. However, beta-blockers were initiated pre-discharge. However, ACEi/ARB and MRA's were not started or withheld in view of AKI/acute on chronic kidney disease /CKD (21 patients) & dyselectrolytemia in 8 patients. SGLT2i was initiated in only 30% of female patients either due to worsening CKD and mild symptomatic/asymptomatic status. Other insignificant reasons such as sleep disorders, contrast-induced AKI, immediate postoperative period, awaiting a surgical/ intervention, and aortic valve pathology have played a minor role.

CAD as a causative factor was noted in 57% of the study population and 40% of them underwent revascularization in the past. Around 85 % of them had their LIMA grafted to LAD & the remainder were grafted with saphenovenous graft to LAD. Very few were grafted with radial artery graft. Total arterial revascularization was attempted in 10 % of patients.

On comparing the NYHA class and CKD patients, it was found that CKD patients were more in the NYHA class IV than non CKD patients and it was statistically significant. Also CKD patients had more frequent heart failure hospitalization. Other detailed results of this study are given in Table 2.

4. DISCUSSION

Heart failure (HF) is a global pandemic [4] with its prevalence increasing on the scale of the growing population as suggested by Conrad et al. [9]. The most important triggers are the ageing population, better survival after suffering myocardial infarction & improved treatment, and survival of patients with HF [10]. Despite all advances in cardiac disease management, Heart failure prognosis could not be improved due to revascularization dependency in Heart failure patients. The presence of Heart failure with normal EF was recognized as a reason for this diagnostic delay. Then recognition of HFpEF has greatly aided in the increased diagnosis of Heart failure.

Table 2. Results of the study representing female versus male patients having heart failure with mildly reduced ejection fraction

Baseline Characteristics (n-130)	Prevalence (Females)	Prevalence (Males)
Total female population	26 % (35 female patients)	74% (105 male patients)
Mean age (in years)	64	67
Socio-economic status	Upper middle > lower middle	No difference
Type 2 diabetes mellitus	65%	70%
Systemic hypertension	68%	76%
Mean BMI	25.6	
Mean Hb (in grams %)	10.8 vs. 12.6	27
Mean NTproBNP (pg/mL)	11145	9899
Atrial arrhythmia	<3% of patients	7%
Hypothyroidism	15%	No difference
CAD	57%	66%
AKI/CKD	30%	35%
NYHA class II	58%	49%
NYHA class III	37%	40%
Mean EF	44%	45%
Moderate PH	35%	22%
Readmission rates in 1 year*	28%	17 %
Treatment-Related Differences		
Antiplatelets	90%	92%
Beta-blockers	86%	84%
Loop diuretics	40%	30%
Mineralocorticoid receptor antagonists	40%	28%
Nitrates, other vasodilators, other antianginals	18%	21%
ARNI (Angiotensin receptor blocker + neprilysin inhibitor)	16%	20%
SGLT2i (sodium-glucose-like transporter 2 inhibitors)	30%	42%
Prognosis		
Improving LVEF	28%	35%
Compliance with medical treatment	90%	92%
HF-related death*	2.85%	4.6%

**The factors significantly associated with Gender (P-value <0.05)*

In the 2016 European Society of Cardiology Heart failure guidelines [2], Heart failure with mid-range EF was an additional entry with separate clinical characteristics. This update was made for ongoing HF studies with an attempt to categorize patients, as studies were lacking compared for Heart failure with reduced EF (EF <40%) and Heart failure with preserved EF (EF ≥50%). Extensive contemporary research supports the evidence that Heart failure with midrange EF, as an intermediate category between Heart failure with reduced EF and Heart failure with preserved EF, shares distinct similarities & the term Heart failure with 'mildly reduced' EF was also proposed by authors over the past 2 years [7].

Our study was aimed at identifying the phenotypic characteristics of an unexplored subset of heart failure, i.e., Heart failure with mildly reduced ejection fraction, thereby identifying the triggers, gender differences, treatment aspects, and prognosis. Analysis of our study results and comparison with other relevant studies are discussed below.

4.1 Biochemical Aspects

Biochemical analysis revealed that most of the patients had euthyroid status. Their mean haemoglobin was in lower normal range (10.8gm%), mean creatinine was 1.6mg%. Mean NTpro-BNP was 11145pg/mL. Other blood parameters were within normal range.

Table 3. Shows the strength, limitations, and recommendations of this study

Components	Comments
Strength	• This HFmrEF study compares the female Asian population and their outcomes amongst poor scientific data. • This study helps in identification of reversible risk factors which are more common in females, such as BMI, anaemia & non-adherence to GDMT that can prevent deterioration in HFmrEF [9].
Limitations	• Recruitment bias is possible if patients were transitioning across various ejection fraction range. • Misclassification could not have occurred due to unstandardized operator variability, lack of core lab &of availability of single operator. • Restricted access for follow up of patients after index HF event due to cross referrals, initiation of HF device therapy, arrhythmia treatment and other non cardiac procedures. • Financial constraints in using cardiac biomarkers for HF. • Lack of prolonged follow-up period for better prognostication.
Recommendations	• There is a need for a multi-centric study in India to reduce heart failure mortality, worsening more rapidly than cancer mortality. • Long-term follow-up is needed for developing a structured protocol in heart failure management across major centers in India. • Serial echocardiographic follow-up with CPET (cardiopulmonary exercise testing) can be used to identify the subset of patients who had improved ejection fraction.

4.2 Echocardiographic Aspects

On analyzing the study population of 35 female patients over 12 months, 28% patients had improvement in left ventricular ejection fraction (Heart failure with preserved Ejection fraction/Heart failure with an improved EF category), while 23% had reduction in left ventricular ejection fraction with the transition to heart failure with reduced EF/heart failure with mildly reduced EF - Deteriorated. Nearly 49% of patients were still in heart failure with mildly reduced EF and minor improvement was noted (Heart failure with mildly reduced EF-Unchanged). Around 4 patients with new onset HFmrEF features were due to ACS (Heart failure with mildly reduced EF- no prior EF determination). The contribution of mitral regurgitation and RV dysfunction was less in this study than in the ESC-HF-LT registry [11].

4.3 Treatment Aspects

Around 90% of patients were adequately treated with antiplatelets, statins, and beta blockers. Only 40% of patients were on ACEi, mineralocorticoid receptor antagonists & diuretics for symptomatic relief. Nearly 40%, 16% & 30% of female patients were treated with diuretics, ARNI, and SGLT2i, respectively, for the acute HF episode suggesting the milder symptomatic status of the hospitalized female patients. This data is similar to the data presented by Savarese et al. [12] and in the ESC-HF-LT registry [11].

4.4 Prognosis

Among the study population of 35 female patients after 12 months of follow-up, the mortality rate was (2.8%) in patients with HFmrEF. The death in that 1 case was due to long-standing heart failure with multiple comorbidities. The prognosis of Heart failure has slightly improved, but mortality is high ranging from 15–30% at 1 year to 75% at 5years [13]. Prognosis was better in patients who had positive left ventricular ejection fraction trajectories which was in accordance with previous studies [14].

4.5 Clinical Predictors of Incident HFmrEF

In this study, we found that old age, hypertension and its treatment, overweight BMI subset, CAD, and revascularization predicted incident HF similar to previous studies in heart failure with mildly reduced EF [12,14]. It also helped to identify the risk factors such as elderly patients, male sex, CKD, overweight BMI subset, NYHA class, mean EF, elevated NT-proBNP, prior myocardial infarction, and revascularization for CAD which contribute in worsening of heart failure with mildly reduced ejection fraction ($P<0.05$ for all).

4.6 All-cause Mortality Rates for HFmrEF

After HF onset, there was one death per 35 female patients compared to 2 deaths among 105 male patients with HFmrEF. The all-cause mortality rate was 497 events per 10,000 person-years among participants with heart failure with mildly reduced ejection fraction as per previous meta-analysis [6]. Hence this study needs a further long-term follow-up for the foreseeable mortality as expressed in other larger studies.

Patients with HF had readmission rates of 28% within 12 months, suggesting that HFmrEF has the highest chance of being readmitted. According to Cheng et al. HFmrEF has a higher rate of cardiac readmissions, followed by the HFpEF subset and HFrEF [15]. According to Laursen et al. meta-analysis, HFmrEF readmission rates were significantly lower than HFrEF readmission rates, whereas HFpEF readmission rates were higher [16]. Our study group showed a readmission rate of about 28% vs 17% in males, which is identical to the global studies highlighting similarities between HFrEF.

Our study demonstrates that age, sex, blood pressure, diabetes mellitus, and previous myocardial infarction anticipate incident HFmrEF. As suggested by Bhambhani et al., incident HFmrEF has identical poor survival to those with incident HFrEF but a mildly improved better survival than with incident HFpEF [6]. The study's Strengths, Recommendations and limitations are illustrated in Table 3.

5. CONCLUSION

HFmrEF is a transitioning stage in the natural course of heart failure that differs from other phenotypes of HF subsets. Male sex, elderly, overweight BMI subset, NYHA class at presentation, presence of CAD & CKD predicted incident and worsening HFmrEF. Morbidity and mortality were higher in hospitalized patients with HFmrEF than ambulatory patients. Among the individual subset of HFmrEF, there exists a gender difference in baseline characteristics, disease presentation for early identification of specific triggers and targets of HFmrEF, expedited medical management for avoiding readmission rates, and mortality aiming to improve LV ejection fraction.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Institutional Ethical Committee approval was obtained.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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