Prospective Analysis of Patients with Heart Failure with Mildly Reduced Ejection Fraction: A Tertiary Care Observational Study

ABSTRACT

Background: Heart failure (HF) is growing in epidemic proportion due to a spectrum of cardiovascular diseases leading to myocardial dysfunction. HF with mildly reduced ejection fraction (HFmrEF) is a unique phenotype of HF with differences in clinical features as compared to other phenotypes of HF.
Materials and Methods: A single center tertiary care hospital-based prospective observational study comprising urban/rural based 157 patients aged 18 years. Heart failure of any etiology will be included after primarily excluding Sepsis as an inciting factor for worsening/initiation of HFmrEF. These patients will be followed up for a period of 6 months with their clinicopathological correlates.
Results: Study analysis revealed Male sex, overweight BMI subset, NYHA class at presentation, presence of CAD & CKD predicted both incident and worsening HFmrEF. Hospitalized patients with HFmrEF have more morbidity and mortality than ambulatory patients. HF with mildly reduced LVEF in their lower range (LVEF 41-45%) had a poor prognosis compared to those with upper ranges of HFmrEF (46-49%). There were patient and drug-related factors in initiating core heart failure medications as suggested by ESC HF guidelines
Conclusion: Heart failure with mildly reduced ejection fraction is a clinical spectrum of heart failure characterized as a transitioning stage in the natural course of heart failure. There are significant differences in patient profiles demanding individualized protocol for addressing specific triggers and targets of HFmrEF. Phenotyping, treatment options, early achievement in LVEF recovery, and serial follow-up of LVEF with echocardiography of this small subset of HF will help in changing the trajectory of natural history of HFmrEF patients.

Keywords: Heart failure ejection fraction; coronary artery disease; chronic kidney disease; recurrent heart failure hospitalization.

ABBREVIATIONS

HFmrEF : Heart Failure with Mildly Reduced Ejection Fraction
CAD : Coronary Artery Disease
CKD : Chronic Kidney Disease
NYHA : Newyork Heart Association
LVEF : Left ventricular Ejection Fraction
ESC : European Society of Cardiology

1. INTRODUCTION

Cardiovascular diseases have become the leading cause of death and morbidity worldwide [1]. Ischemic Heart Disease (IHD) and Stroke are two important etiology accounting for more than 80% of CV deaths [2]. Heart failure (HF) a major public health concern, particularly among older adults is a final pathway to mortality in cardiovascular disease with or without sudden cardiac death. HF is a clinical syndrome characterised by typical symptoms such 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/or functional cardiac abnormalities, resulting in a reduced cardiac

output and/or elevated intracardiac pressures at rest or during stress [3].

The incidence of HF in India is 0.5-1.8 million cases per year (0.05-0.17%) [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]. Valvular heart disease continues to be a major threat in india especially lower socioeconomic strata unlike western countries. Other important causes include diabetes mellitus, systemic hypertension, dilated cardiomyopathy, non valvular rheumatic heart disease, post myocarditis heart failure, Endomyocardial fibrosis in certain locales of India such as Kerala and west Bengal [6-9].

Heart failure (HF) is a global epidemic in health care and a leading cause of mortality and morbidity worldwide. In Asian countries, causes of mortality and morbidity have shifted or have been shifting from infectious diseases and/or nutritional deficiencies to lifestyle-related diseases, such as cardiovascular disease, cancers and diabetes, in conjunction with the transition from developing to developed countries during the past decades (so-called "the epidemiologic transition"). Because the effect of this epidemiologic transition varies among countries, the aetiology, prevalence, management and outcomes of HF also differ among the countries. Thus, we need to assemble and comprehensively analyse the available evidence to date for daily HF practice in Asia and to systematically conduct future epidemiologic approaches to establishing appropriate prevention programs against the burden of HF in Asia [6,8].

Based on the ejection fraction, HF was previously classified into HF with reduced ejection fraction and preserved ejection fraction, but there was frequent transitioning in HF groups which led to refinement of existing guidelines until 2013. As per, the ACC/AHA guidelines (2013) a newer subset of patients were identified with HF but EF that did not fall into either the reduced or preserved groups, they ere termed as HF with borderline EF (HFbEF) [10]. In 2016, the European Society of Cardiology (ESC) guidelines defined this group of patients as having heart failure with mid-range EF (HFmrEF with LVEF 40%-49%) [11] which was recently renamed as heart failure with mildly reduced ejection fraction [12].

The prevalence of HFmrEF in the entire population of patients with HF is 10–25% [13]. Extensive contemporary research supports the evidence that HFmrEF as a intermediate category between HFrEF and HFpEF shares distinct similarities & the term HF with ‘mildly reduced’ EF, was also proposed by authors over past 2 years as suggested by Lam CS et al. [4,8,14]. In this study, we aim to compare with global estimates in epidemiology, clinical profile, prognosis and deteriorating factors in disease progression of HFmrEF with mildly reduced EF [12].

These observations suggest that it could be a ‘pure’ HFmrEF which is new onset type of HFmrEF, unlike transitioning HF phenotypes mentioned in other studies influencing confounding effects over prognosis.

2. MATERIALS AND METHODS

This study aims to select the cross section of patient population falling under the Heart failure with mildly reduced ejection fraction [15]. Available clinical, etiopathological profile, laboratory, imaging parameters in patients with HFmrEF, ongoing treatment, recent modifications in drugs and health status causing worsening heart failure will be assessed. Major deteriorating factors will be used to prognosticate a subset of Heart failure patients. This study will also be used to identify and analyse certain reversible factors in HFmrEF subset which can aid in management of heart failure. Thereby correlating the study findings with the global data in order to find the ethnic variation and influence of cultural, socio economic and health infrastructure background in the natural course of heart failure with narrow LV ejection fraction range that is, HFmrEF

This is a hospital based prospective observational study comprising Urban/rural male & female patients >18 years. This involves patient population of 157 patients seeking treatment in tertiary care hospital after obtaining scientific & ethical committee approval. In hospital and OPD records of heart failure patient, The Minnesota Living With Heart Failure Questionnaire [16], Boston criteria and ESC guidelines for heart failure diagnosis will be used to obtain data for analyses.

All patients aged > 18 years with confirmed heart failure of any etiology will be included after primarily excluding Sepsis as inciting factor for worsening/initiation of heart failure. These

patients will be followed up for a period of 6 months with clinical profile, available laboratory parameters, echocardiographic assessment of ejection fraction using modified Simpson's method, angiographic evidence for heart failure worsening.

2.1 Statistical Methods

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

For the follow-up, all patients will be given a telephone contact, and telephone contacts will be taken if available. Follow-up will be done in ward or cardiology outpatient department for a duration of 6 months following the index admission. Patients who do not come for follow-up will be traced by telephone if available.

3. OBSERVATIONS AND RESULTS

The assessment of 157 patients admitted with a diagnosis of HF with mildly reduced ejection fraction showed distinct differences in key baseline characteristics, causes and re-hospitalization among the three categories.

3.1 Baseline Characteristics

Almost less than 40 % of patients were from the 56-65 age group & nearly 25% were from 46-55 & 66-75 age groups. Minority of patients represented the 35-45 & > 75 years' subset. There was no significant variation in age among the study groups. Two thirds of the patients were from urban locality and the remainder subset were from rural/remote places Around 26% of patients were women. The mean age of female patients was 64 years.

3.2 Etiological Factors

Type 2 diabetes mellitus was present in 70% of patients & systemic hypertension was present in nearly 76 % of patients as shown in the Fig. 1.

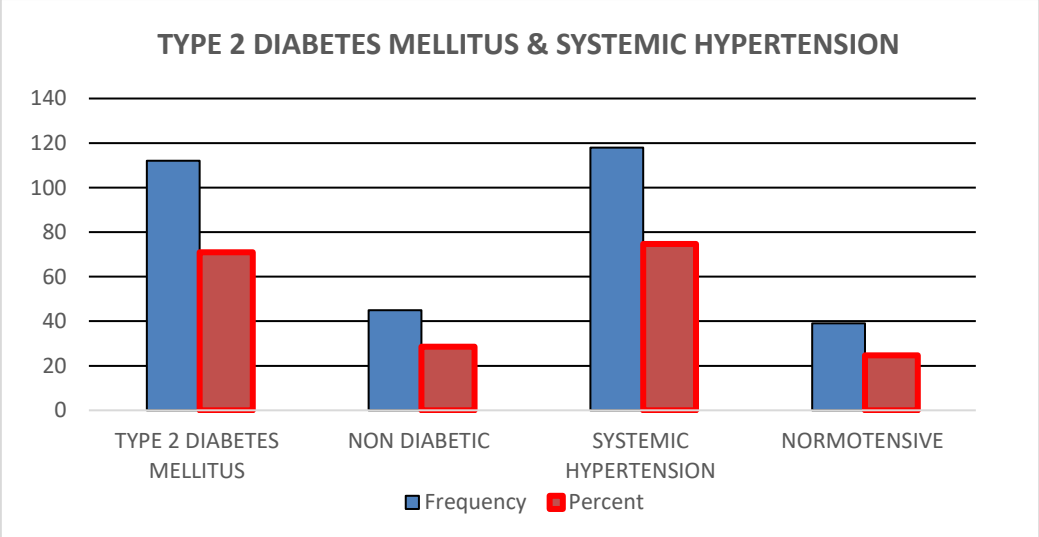

Fig. 1. Showing distribution of diabetes mellitus and hypertension in CAD

CAD was present in almost 88% of patients. Out of them, obstructive CAD was present in only in 57% patients, remaining 37% of them had only mild/insignificant CAD. There was statistical significance in comparing the CAD patients with revascularization done in past with previous HF admission suggesting patients with obstructive CAD who are revascularized had more frequent hospitalization than those with non-obstructive CAD.

Also that, more than half of the CKD patients had prior HF hospitalization history and it was statistically significant. On comparing the number of prior HF admission, CKD patients had

statistical significance revealing they had frequent hospitalization. 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. Sleep disorders was present in around 14% of patients but it was not statistically significant.

3.3 Revascularization for CAD

Less than 40% of them had undergone revascularization for CAD as shown in Fig. 2. 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.

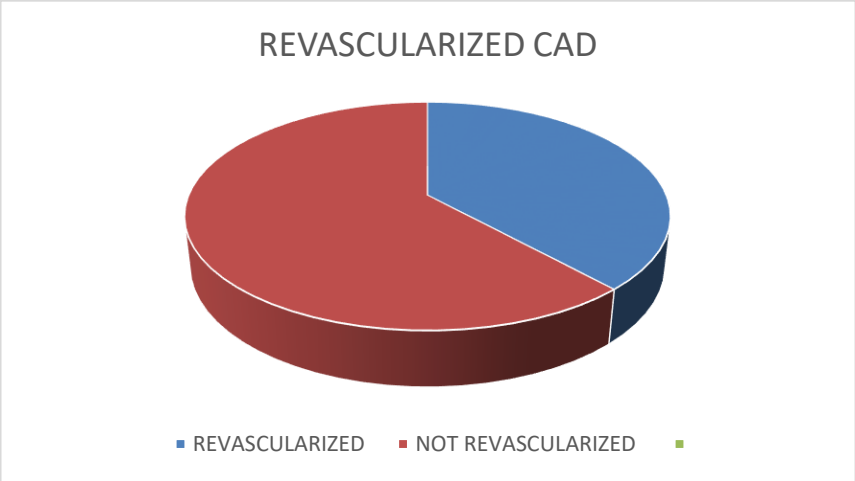

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Fig. 2. Percentage of revascularization for CAD

There was statistical significance in comparing the CAD patients with revascularization done in past with previous HF admission suggesting patients with obstructive CAD who are revascularized had more frequent hospitalization than those with non-obstructive CAD.

Around 102 patients with type 2 diabetes mellitus had CAD and 37 patients with type 2 diabetes mellitus did not have CAD. The association was more but the overall statistics were insignificant

3.4 Prior HF Hospitalization

Almost 24% of patients had prior HF admission and the remainder represented de novo subsets of the HfmrEF patients in study as depicted in Fig. 3.

3.5 Comparison Table of CKD, CAD, Anemia with Number of HF Admission in Last Year

On comparing the presence and absence of CAD, CKD and anemia with number of heart failure hospitalization in last one year, the analysis revealed that the presence of CAD, CKD and anemia had statistical significance for causal association as shown in Table 1.

Chronic kidney disease was prevalent in 20% of HF patients with 8% of patients with existing CKD. Stage II/III kidney disease was predominant among the study patients. Fifty percent of CKD population in this study had more than one HF admission episode than those without CKD suggesting the CKD being a major precipitating factor for HF admission.

On comparing the CKD patients with mean ejection fraction, the mean ejection fraction was 44.6%, with the minimum EF being 41% & maximum being 48%. There is no statistical significance in comparing non CKD patients and their mean EF._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.

3.6 Reasons for avoiding core drugs

On analysing 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'S 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 were initiated in only 14% of patients either due to worsening CKD and mild symptomatic/asymptomatic status. Around 3 patients had lost to follow up and 2 patients had suboptimal follow up leading unclear idea about their core HF drug coverage. Other insignificant reasons such as sleep disorders, contrast induced AKI, immediate post-operative period, awaiting a surgical/ intervention, aortic valve pathology have played a minor role.

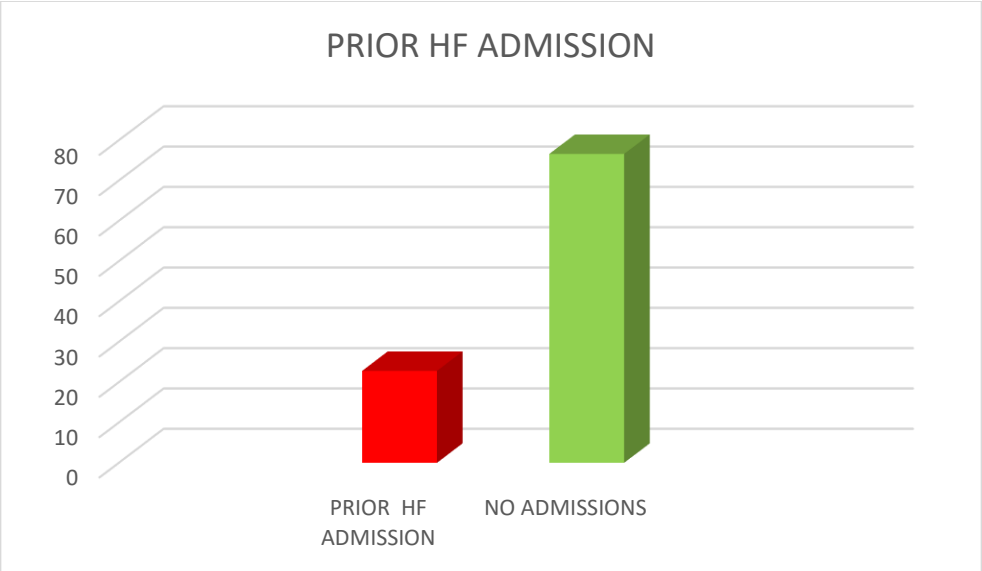

Fig. 3. Percentage of Prior HF hospitalization

Table 1. Showing ananlysis of CAD, CKD, & anemia with HF hospitalization

	Number of HF admissions in last year		Statistical significance (p- value)
	1 admission	> 1 admission	
Chronic kidney disease (n-157 patients)			
Present	13	7	0.001
Absent	13	1	
Coronary artery disease(n-157 patients)			
Present	13	6	0.02
Absent	13	2	
Anemia			
Present	19	8	0.002
Absent	43	2	

3.7 Mortality at 6 months

After 6 months of follow up and 5 patients (3.9 %) were lost for follow up due to different reasons, it was observed that, the mortality rate was (1.9%) in 3 patients with HFmrEF. The reason for death in 2 cases (3.2%) were acute complication of ACS-STEMI- arrhythmia related and in-hospital cardiac arrest due to ACS. Other death in a female was due to long standing heart failure with multiple comorbidities such as CKD on CPPD, anaemia, post COVID status, junctional bradycardia related death.

3.8 Improvement in LVEF

Among the study population of 157 patients after 6 months of follow up, it was noted that around 124 patients (79%) had no change in the ejection fraction (HFMREF UNCHANGED), 15% had deteriorated ejection fraction (HFREF/ HFMREF - DETERIORATED) and 12% patients had improved ejection fraction (HFPEF/HF WITH IMPROVED EF CATEGORY)

4. DISCUSSION

Prospective analysis of 157 patients for 6 months follow up revealed important differences in heart failure outcomes. Males were more prone for

recurrent HF hospitalization compared for females highlighting the gender difference HF. Around 32 diabetic patients had previous heart failure hospitalization. There was statistical significance in the comparing diabetic patients with prior HF hospitalization.

Almost 24% of patients had prior HF admission and the remainder represented de novo subsets of the HfmrEF patients in study. The analysis suggests that the HF was more common with males compared to females and also that the females had more frequent hospitalization even though they are less in number. Around 32 diabetic patients had previous heart failure hospitalization. There was statistical significance in the comparing diabetic patients with prior HF hospitalization.

Majority of the population were in overweight category as per the asian ethinicity consideration of BMI ranges followed by normal BMI peoples. Overweight class of patients had more than mild and moderate PAH. Mean NYHA class as per ESC HF-LT registry [17] was class II/III compared for HFrEF with higher NYHA class. Our study also had lower NYHA class suggesting milder symptoms scale. We observed that NYHA and increasing BMI scale had more statistical siginficance. The mean EF comparison with BMI ranges suggested that extremes of BMI ranges had very low ejection fraction (EF 42-43%) compared to patients with intermediate BMI ranges had EF of 44-45% implying the role of cachexia / obesity related worsening in HF. The mean EF of population with RWMA had no major difference but the patients with anterior RWMA had more frequent HF admissions.

4.1 Investigations

Biochemical analysis revealed that around mostly all patients had euthyroid status, mean haemoglobin in their lower normal range, mean creatinine of 1.6mg %. NTproBNP was available in 40% of patients whose mean value was 7970pg/mL. Higher mean values of NTproBNP when compared with HF burden, deterioration in LVEF, there was statistical significance. The mean values of laboratory parameters of the patients are given in the Table 2 below:

Table 2. Showing the mean, median & Interquartile range of various biochemical and echocardiographic parameters

Lab parameters	Mean +/- SD	Median	Interquartile range
Hemoglobin (n-157) (gm/dL)	12.24 +/- 2.7	12.150	5.5 - 16.9
Urea (n-157) (mg/dL)	48.66 +/- 41.4	35.00	6- 303
Creatinine (n-157) (mg/dL)	1.659 +/- 1.73	1.100	0.4 - 11.4
Sodium (n-157) (mEq/L)	135.6 +/- 5.86	137.0	115 -154
Potassium (n-157) (mEq/L)	4.31 +/- 0.6	4.2	3.0 -6.5
HbA1c (n-157) (%)	3.86 +/- 3.8	5.4	5.5-12.0
Echo ejection fraction (%) (n-157)	70%	45%	41-49%
Ferritin (n-29)	167 +/- 421	31	10-1805
TSAT (n-21)	33.129 +/- 24	28.000	4.4-100
TSH (mIU/L) (n-125)	2.77 +/- 6.72	2.38	0.01- 16.00
Troponin I (ng/mL) (n-34)	5.36 +/- 6.6	2.35	0.00-32.00
NT-PROBNP (pg/mL) (n-68)	7970	2957	181-35000

4.2 Echocardiographic Aspects

Among the study population of 157 patients after 6 months of follow up, 124 patients had no improvement in LVEF. Of which 101 patients remained in their pre-existent HFmrEF ranges, whereas 23 patients had reduction in LVEF with transition to HFrEF/ HFmrEF - Detoriated. Around 14 patients were still in HFmrEF range LVEF with minor improvement (HFmrEF-Unchanged). Nineteen patients had improvement in their LVEF with transition into HFpEF/HF with improved EF category. Around 13 patients who had features of new onset HFmrEF were due to ACS and its mechanical complication related (HFmrEF- no prior EF determination). Contribution of mitral regurgitation and RV dysfunction was less in this study as comparable to the ESC-HF-LT registry [17].

4.3 Treatment Aspects

Almost around 90% of patients were adequately treated with antiplatelets, statin and beta blockers as depicted in Fig. 4. Around 40% patients were on ACEi, mineralocorticoid receptor antagonist & diuretics for symptomatic relief. Only 40% patients were treated with diuretics for the acute HF episode suggesting the

milder symptomatic status of the patients who were hospitalized. This data is similar to data of the savarese et al and ESC-HF-LT registry [15,17,18].

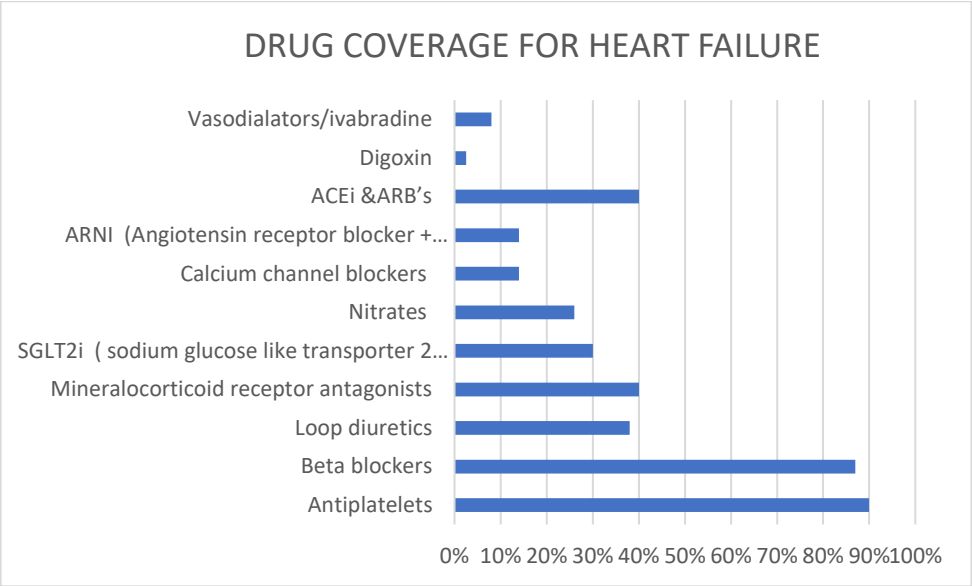

Fig. 4. Showing the drug coverage for HF in the population under study

4.4 Prognosis

Among the study population of 157 patients after 6 months of follow up, 23 patients had reduction in LVEF with transition to HFrEF/ HFmrEF with Detoriated EF subset. Around 14 patients were still in HFmrEF range LVEF with minor improvement (HFmrEF-Unchanged). 19 patients had improvement in their LVEF with transition into HFpEF/HF with improved EF category. Around 13 patients who had features of new onset HFmrEF were due to ACS and its mechanical complication related (HFmrEF- no prior EF determination). This analysis revealed that, the mortality rate was (1.9%) in 3 patients with HFmrEF. The reason for death in 2 cases were acute complication of ACS-STEMI-arrhythmia related and in-hospital cardiac arrest due to ACS. Other death in a female was due to long standing heart failure with multiple comorbidities

On comparing females versus males it was noted that males had more improving ejection fraction and less drug compliance and quality of life indicators compared to females.

There was 3 in-hospital mortality and 6-month mortality was noted in 1.9% patients of HFmrEF suggesting the similar mortality rates as in MAHFER registry in Uganda [19]. Farre et al in his multicentric prospective observational study in spain observed that there was equal all-cause mortality among HFmrEF and HFrEF (43.8% vs 45.8%) but was lower in HFpEF group (52.6%) inferring the poorer natural course of HFmrEF [20]. There was even higher mortality rates in HFmrEF than HFpEF groups especially in ambulatory patients but not in hospitalized patients [21]. This finding differs from our study in that the mortality rate was seen predominantly in hospitalized patients than ambulatory patients.

4.5 Clinical Predictors of Incident HFmrEF

In this study we found that the old age, hypertension and its treatment, overweight BMI subset, CAD and revascularization predicted incident HF as per savarese et al. [18]. It also helped to analyse the older age patients, male sex, CKD, overweight BMI subset, NYHA class, mean EF, elevated NTproBNP, prior myocardial infarction and revascularization which are the key determinants predicting worsening of HFmrEF ($P<0.05$ for all). Influence of male gender over HFmrEF was higher in this study as compared to savarese et al where gender indifferences in HF was prominent (HR 1.63, 95% CI 1.18–2.24) [18]. There association of BMI with HFmrEF is stronger as compared to savarese et al (HR 1.30, 95% CI 1.23) [13,18]. Increase in biomarker such as NTproBNP is associated with a 1.5-fold increased hazard of HFmrEF (HR 1.51, 95% CI 1.20–1.90) as per savarese et al. [18.

Likewise, our study group was associated with higher risk of HFmrEF

4.6 All-cause Mortality Rates for HFmrEF

After HF onset, there was 3 deaths per 157 patients as compared to 32 deaths among 200 participants with HFmrEF in a meta-analysis study [18]. The all-cause mortality rate was 497 events per 10,000 person years among participants with HFmrEF, hence this study needs a further long term follow up for the foreseeable mortality as expressed in other larger studies.

When compared to other larger trials across the world in heart failure with mid-range ejection fraction [11], the prevalence of type 2 diabetes mellitus was found to be less than 50% of patients. Our study also records this number as high as 70% thereby confirming the finding of high prevalence of type 2 diabetes mellitus in Asian population.

Patients with HF had readmission rates of 32.2% within 6 months suggesting that HFmrEF has the highest chance of being readmitted. According to Cheng et al, HFmrEF category has a higher rate of cardiac readmissions which is followed by HFpEF subset and HFrEF [22]. According to Lauristen et al meta-analysis, HFmrEF readmission rates were significantly lower than HFrEF readmission rates, whereas HFpEF readmission rates were higher [23]. Our study group showed a readmission rate of about 23% which is close to the global studies which shows similarity between HFrEF.

Our study demonstrates that age, sex, blood pressure, diabetes mellitus, and previous myocardial infarction anticipates incident HFmrEF. Amongst the spectrum of HF, HFmrEF had higher male population with overweight BMI, CAD history was present in higher prevalence which is similar to HFpEF patient's clinical profile but having an increased moratlity comparable to HFrEF profile as suggested in bhambhani et al. [24].
There are discrete data equating lower LVEF with worse outcomes available, especially the TOPCAT trial depicting a lower survival (LVEF 44–50%) than patients with LVEF > 50% [25-28]. Adding to contradiction there are few other studies which gave no difference in mortality between HF spectrum categorizing by LVEF [29-31]. Therefore considering the existing data of population based cohorts with no evidence of HF and a mildly reduced LVEF carries a poor prognosis comparing those with normal LV ejection and LVEF 50 to 55% [32-34]. As suggested by bhambhani et al, incident HFmrEF have identical poor survival to those with incident HFrEF, but a mildly improved better survival than with incident HFpEF [13].

5. STRENGTH OF THE STUDY

1. This is one of the studies done in heart failure with mildly reduced ejection fraction comparing asian population and their outcomes with the prevailing scientific data being scarce.
2. There is a high annual mortality of heart failure patients as reported in scientific evidences. We demonstrated certain reversible risk factors such as BMI, anemia which can prevent deterioration in HFmrEF.
3. We demonstrated results with near similarity of prevailing scientific papers which studied the outcomes of heart failure with mildly reduced ejection fraction.
4. It is a follow up prospective observational study without further investigation of patients who are under optimal medical therapy. Hence observation of outcomes helped in identifying the reversible risk factors thereby aiming to reduce financial constraints.
5. We demonstrated the deteriorating risk factors for HFmrEF, reasons for avoiding guideline directed optimal medical treatment, reversible risk factors that would be implicated as a risk factor for disease worsening.

6. CONCLUSION

Heart failure with mildly reduced ejection fraction (15) is a clinical spectrum of heart failure characterized as a transitioning stage in natural course of heart failure. There are significant differences in patient profiles demanding individualized protocol for addressing specific triggers and targets of HFmrEF. Male sex, overweight BMI subset, NYHA class at presentation, presence of CAD & CKD predicts both incident and worsening HFmrEF. Hospitalized patients with HFmrEF have more morbidity and mortality than ambulatory patients. Even among patients with evidence of mildly symptomatic/ asymptomatic HF and a mildly reduced LVEF in the lower range (LVEF 41-45%), there was a poor prognosis comparing those with upper ranges of HFmrEF (46-49%).

Even after categorization of HF spectrum, individualizing the diagnostic and treatment protocol for initiating the classic four pillar drugs of heart failure, there exists a clinical inertia to omit guidelines recommended HF drugs due to underlying patient and drug related factors. Greater depth in understanding the pathophysiology of this very narrow HF spectrum, prioritizing treatment, early achievement in LVEF recovery, serial follow up of LVEF with echocardiography is mandatory to make a valuable change in course of natural history.

7. LIMITATIONS OF THE STUDY

1. Recruitment bias while selecting a certain subset of HFmrEF might have led to selection of HFrEF with recovered EF/HFpEF with deteriorated EF/ transient causes of HF such as tachycardiomyopathy.
2. Echocardiographic imaging with modified simpson's method was employed for including a narrow range of LVEF for labelling as HFmrEF. But with unstandardized operator variability, lack of core lab and single operator might result in misclassification.
3. Clinical history after HF onset was restricted because non cardiac illness, HF device therapy, arrhythmia treatment, cross referrals might hinder the mortality assessment after HF onset.
4. Our study could not use biochemical markers like B-natriuretic peptide (pro BNP) routinely for diagnosing HF as no additional costs were panned to incur in this study. But whenever it was available, it was well used to correlate the disease severity and improvement over time with optimal medical treatment.
5. The patients could only be followed up for 6 months due to logistic and administrative reasons. A prolonged follow up period might have improved the power of statistics and also in prognosis of heart failure with mildly reduced ejection fraction.
6. The population in our study has ethnic variability and could not represent the core population of India solely because of the specific ethnicity of people being treated in our institute.

8. RECOMMENDATION

1. A multicentre study is vital in India for addressing the important aspects in diagnosis, identifying reversible risk factors and in treatment HF with mildly reduced ejection fraction so as to reduce the mortality of heart failure which is already a major healthcare concern than cancer mortality
2. Further studies targeting at long term follow up of patients to identify the prevailing deteriorating factors in disease progression of heart failure may reduce the burden over the treating physicians for easy incorporation as in structured protocol for heart failure management across major centres in India.
3. Above all, adding strength to existing unicentric heart failure registry, nationwide heart failure registry can help categorize the heart failure for aiming at well-structured protocols for management so as to reduce heart failure as being the national burden.
4. Serial echocardiographic follow up with CPET (cardiopulmonary exercise testing) can be suggested to include in clinical practice to identify the subset of patients with improved ejection fraction.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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