

Research Article

Demographics, Clinical and Therapeutic Characteristics of Hospitalized Heart Failure Patients with Mildly-Reduced Ejection Fraction in Yemen: Data from the Gulf Acute Heart Failure Registry (Gulf CARE)

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Received: July 12, 2024

Accepted: August 02, 2024

Published: August 09, 2024

Abstract

Background: Heart Failure (HF) with mildly reduced ejection fraction (HFmrEF) was recently recognised as a distinct clinical entity with different epidemiological, clinical and echocardiographic characteristics from HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). However, most of the available data about HFmrEF is limited to western countries. Other world regions, including Yemen, lack real-world HFmrEF data, which could help guide diagnosis and prognosis, and treatment.

Objectives: This study describes the demographic, clinical, echocardiographic, and therapeutic characteristics of Acute Heart Failure (AHF) patients in Yemen who satisfied the current clinical definition of HFmrEF.

Methods: We retrospectively analysed Yemeni patients with AHF enrolled in the Gulf aCute heArt failuRe rEgistry (CARE). We stratified patients into three EF groups based on the 2016 European HF guidelines: reduced EF (HFrEF < 40%), mid-range EF, now redefined as mildly reduced HF (HFmrEF, EF 40%-49%), and preserved EF (HFpEF, EF ≥ 50%), then compared admission characteristics, in-hospital treatment and on-discharge medications. **Results:** The study included 1,408 (91.7%) AHF Yemeni patients with echocardiographic data from the Gulf CARE Registry. HFmrEF patients accounted for a quarter (n = 361; 25.6%) of the cohort. The majority had HFrEF (n = 748, 53.1%), and HFpEF had the least proportion (n = 299, 21.2%). Compared to HFrEF and HFpEF, HFmrEF patients were older, had male preponderance and more risk factors. They also had a higher prevalence of Coronary Artery Disease (CAD), Diabetes Mellitus (DM), and Hypertension (HTN) but lower cases of Valvular Heart Disease (VHD) and Atrial Fibrillation (AF). They had a distinctive clinical profile, de novo HF, lower symptomatic burden and more clinically stable, but higher Left Ventricular Hypertrophy [LVH] and lower prevalence of Pulmonary Hypertension (PHTN).

Conclusion: Hospitalized Yemeni AHF patients stratified by ejection fraction represent heterogeneous groups in terms of demography, clinical presentation, and medications. HFmrEF patients accounted for a large proportion representing a demographically and clinically diverse group with many intermediate features compared to HFrEF and HFpEF patients.

Keywords: Heart Failure; HFmrEF; Yemen

Introduction

Background

Heart Failure (HF) affects more than 64 million people globally, and the prevalence is expected to continue to increase due to improved post-diagnosis survival and longer life expectancy in the general population. Yet despite significant advancements in treatment, HF morbidity and mortality remain unacceptably high. The heavy burden on health expenditures is also concerning [1-4]. However, current efforts to classify HF subtypes into distinct disease entities recognize differences in pathophysiology and therapeutic approaches that have improved the safety and efficacy of clinical management [1]. Left Ventricular (LV) Ejection Fraction (LVEF) has been the mainstay of HF classification. Up to 2013, the two HF subtypes were preserved EF (HFpEF), described as LVEF \geq 50%, and HF with reduced EF (HFrEF), defined as LVEF $<$ 40% [3]. The classification omitted patients with LVEF 40-49%, which the American College of Cardiology and American Heart Association (ACC/AHA) HF guidelines were recognized in 2013 [5]. However, changes in terminology for patients with LVEF 40-49% and LVEF definition have undermined comparative studies. Initially, the ACC/AHA labelled them as HF with borderline LVEF and, in 2014, renamed them to HF with Mid-Range EF [6]. Later, the European Society of Cardiology (ESC) HF guidelines in May 2016 recognized mid-range HF as a distinct clinical entity. [7] Recently in 2021, the writing committee of the 2021 ESC/HFA HF guidelines renamed mid-range to mildly-reduced EF (HFmrEF) and revised the LVEF definition from 40-49% to 41-49% [8,9]. Despite concerted efforts to recognize HFmrEF as a distinct clinical entity and inspire epidemiological and review studies, consensus on its clinical characteristics still needs to be reached [10-17]. Specifically, gaps exist in the safety and efficacy of the current evidence-based therapy for HFrEF and HFpEF to HFmrEF patients [18-20]. Since most evidence-based research on the epidemiology of HFmrEF are from western countries with differences in genetics, environment, lifestyles and healthcare delivery to the Middle East and the Arabian Gulf [21-23]. Thus, this study aims to fill the gap by analysing and describing demographics, clinical, echocardiographic, and therapeutic characteristics of HFmrEF patients in Yemen.

Rationale and Aim of the Study

Classification of HF subtypes into distinct clinical entities based on LVEF cut-off points with different morbidity, mortality, pathophysiology and therapeutic outcomes has substantially contributed to improvement in clinical management. However, a firm understanding of the distinguishing demographic and clinical features is necessary to improve the diagnosis, prognosis and treatment of HFmrEF. Yet, in Yemen, such population-based data is lacking. Two studies examined hospitalized Acute Heart Failure (AHF) patients and provided a general description without delineating them into HF subtypes [24,25]. Hence, the present study seeks to describe the demographic, clinical echocardiography and treatment of HFmrEF patients. The findings hope to improve the diagnosis accuracy of HFmrEF patients and determine whether current HF therapies are effective for this recently described HF subtype.

Ethics Approval

This study re-used existing data from the Gulf CARE registry. The Institutional Review Board (IRB) recognises that a study analysing de-identified publicly available data does not constitute human research subjects as defined at 45 CFR 46.102. Thus, the

present study did not require IRB review or approval.

Materials and Methods

Study Design

This retrospective cohort study analysed AHF Yemeni patients from the Gulf CARE registry, whose design, methodology and characteristics have been described in detail elsewhere [26,27]. In brief, the Gulf CARE registry is the first prospective, a multinational, multicentre observational survey of patients \geq 8 years admitted with a diagnosis of AHF to 47 hospitals in seven Middle Eastern countries: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen. The inclusion criteria were all AHF patients $>$ 18 years of age admitted to participating hospitals between 14 February 2012 and 14 November 2012, irrespective of aetiology. However, we excluded patients whose final diagnosis was not HF. The Gulf CARE study adopted the 2008 ESC guidelines definition of AHF as a rapid onset or change in the signs and symptoms of HF, resulting in the need for urgent therapy. HF is a clinical syndrome presenting with a combination of symptoms, signs and objective evidence of structural or functional abnormality. The symptoms are dyspnoea at rest or on exercise, fatigue, tiredness, and ankle swelling. The signs are tachycardia, tachypnoea, elevated jugular venous pressure, pulmonary rales, pleural effusion, hepatomegaly, and peripheral oedema. Objective evidence of structural or functional cardiac abnormalities is a third heart sound, murmurs, cardiomegaly, abnormal echocardiogram, and raised natriuretic peptide concentration. AHF was further classified as Acute Decompensated Chronic HF (ADCHF), defined as the worsening of HF in patients with a previous diagnosis or hospitalisation for HF or de novo AHF. Definitions of data variables in the CRF were based on the 2008 ESC guidelines and the 2005 ACC clinical data standards [29]. Exposure to khat is chewing khat plants or leaves within one month after index admission [30].

Data Variables

In the definition of comorbidities, CAD diagnosis was the presence of any of the following conditions. At least one major epicardial coronary artery determined by coronary angiography to have $>$ 70% obstruction, history of Myocardial Infarction (MI) associated with wall motion abnormality on echocardiography or gated blood pool imaging, and/or stress testing (with or without imaging). Hypertension was defined as a history of hypertension diagnosed and treated with a hypertensive medication or BP $>$ 140 mm Hg systolic or 90 mm Hg diastolic on at least two occasions or BP $>$ 130 mm Hg systolic or 80 mm Hg diastolic on at least two occasions for patients with diabetes or Chronic Kidney Disease (CKD). Baseline and admission-based variables captured demographics, comorbidities, risk factors, clinical presentation, laboratory data including troponin and BNP, medication regimens, in-hospital outcome, aetiology, and precipitating factors for AHF. The Gulf CARE registry collected echocardiography and coronary angiogram data along with cardiac procedures such as PCI, coronary artery bypass surgery (CABG), device therapy, or any cardiac surgery data during admission and on follow-up. Follow-up of patients at three months and one year was performed. Follow-up was done by telephone at three months, via phone, or a clinic visit at one year. Data was entered online using a custom-designed electronic Case Record Form (CRF) at the Gulf CARE website (www.gulfcare.org). Institutional or national ethical committee or review board approval was obtained in the seven participating countries. The study is registered at clinicaltrials.gov (NCT01467973).

Study Population and Data Analysis (Categorization of LVEF)

The present study included Yemeni patients enrolled in the Gulf CARE Registry with a clinical diagnosis of HF with LVEF information. Yemen data came from eight major hospitals across the country. The Gulf CARE study obtained institutional ethical approval in each participating hospital, and all patients provided informed consent. In total, 1,536 Yemeni patients enrolled Gulf CARE registry from February 14, 2012, to November 13, 2012. However, this study included only 1,408 (91.7%) AHF Yemeni patients with echocardiographic data. We adopted the 2016 European HF guidelines definition of HFmrEF (LVEF: 40-49%), HFrEF (LVEF<40%), and HFpEF (LVEF ≥50%). We stratified HF patients into the three LVEF groups and compared them based on admission characteristics, in-hospital treatment, and on-discharge medications.

Statistical Analysis

We employed descriptive statistics to summarise the data into HFrEF, HFmrEF and HFpEF subtypes. We reported frequencies and percentages for categorical variables, and differences between the three HF subtypes were analysed using Pearson's 2 test or Fisher's exact test. For continuous variables, we used measures of central tendency (mean and standard deviation) to summarise the data and analysed using a t-test to compare the difference in means. The level of significance was set at *p-value* < 0.05. Statistical analysis was conducted using IBM SPSS Statistics version 26.

Results

Initially we analysed the distribution of the three HF subtypes from the 1,408 AHF Yemeni patients included in the study. Most patients had HFrEF (n = 748; 53.1%), followed by HFmrEF (n = 361; 25.6%) and HFpEF (n =299; 21.2%). The findings suggest that in Yemen, about a quarter of patients diagnosed with AHF fall within the HFmrEF LVEF clinical cut-off.

Demographic Characteristics

Demographic characteristics stratified by the three HF subtypes are summarized in Table 1. Overall, the 1,408 AHF patients were old (mean age = 53.5±15.4 years), more males (64.1%),

smoked tobacco (34%) and chewed Katt (58%). The mean age of HFmrEF patients was older than HFrEF and HFpEF (57±12.9 vs. 53±14.6 vs. 50±18.9), more males (71.7% vs 70.6% vs 43.1%) and higher rate of smoking (39% vs. 36% vs. 24%) and chewing Katt (68% vs. 61% vs 38%). However, the mean BMI among entire cohort 25.8±4.4 kg/m² with no significant difference between groups (p= 0.077).

Clinical Characteristics

Overall, most of the patients had underlying heart diseases. The most prevalent were CAD (50%), HTN (36.5%), VHD (14%) and AF (8.5%). The most frequently encountered comorbidity was DM (21.4%). However, heart diseases significantly varied across the three HF subtypes. Compared to HFrEF and HFpEF, HFmrEF had higher cases of CAD (52% vs 39% vs 13%), DM (29.6% vs 18% vs 21%), and HTN (46.5% vs 34.0% vs 30.8%) but lower cases of VHD (6.4% vs 8.8% vs 34.1%) and AF (2.2% vs 5.5% vs 10.0%). In addition, HFmrEF shared a similar prevalence of hyperlipidaemia with HFrEF and an intermediate prevalence of asthma/COPD, lower than HFpEF but higher than HFrEF. However, HFpEF Patients compared to HFrEF and HFmrEF were younger (51±18.9 vs 53±14.6 vs 57±12.9) with a higher prevalence of comorbidity – VHD (34% vs 8.8% vs 6.4%, AF (10% vs 5.5% vs 2.2%) Asthma/COPD, (17% vs 0.4% vs 2.2%). Three rare conditions with no significant heterogeneity among the three HF subtypes were Chronic Kidney Disease (CKD)/dialysis, peripheral vascular disease (PVD) and Stroke/Transient Ischaemic Attack (TIA). Table 1 summarises the underlying heart disease and comorbidities of the 1,408 AHF patients.

Clinical Presentation and Physical Examination

The most frequently presenting HF symptoms were dyspnoea in almost all cases, with 75% in NYHA Class III/IV, orthopnoea (82.5%), Paroxysmal nocturnal dyspnoea PND: (77%) and easy fatigability (76%), as summarized in Table 2. A striking difference in the clinical presentation of patients was observed among the different HF types. Compared to others, HFmrEF was the least presented in NYHA Class IV (21% vs 49% vs 26%), orthopnoea (69% vs 88% vs 85%), PND (65% vs 84% vs 73%), lower limb oedema (34%, 73%, 62%) and weight gain (18% vs 55% vs 39%). HFmrEF patients were the most frequent group

Table 1: Demographic and Baseline Characteristics of AHF patients.

Characteristics	EF (< 40%) (N = 748)	EF (40–49%) (N = 361)	EF (≥ 50%) (N = 299)	All (N = 1408)	p-value
Age, mean± SD	53.3 ± 14.6	57.0 ±12.9	51.1 ±18.9	53.5 ± 15.4	
Male	528 (70.6%)	259 (71.7%)	129 (43.1%)	916 (65.1%)	0
Smoking	266 (35.6%)	140(38.8%)	72 (24.1%)	478 (33.9%)	0.001
Chowing Katt	454 (60.7%)	245 (67.9%)	114 (38.1%)	813 (57.7%)	0
Admission for Heart Failure	369 (49.3%)	94 (26.0%)	121 (40.5%)	584 (41.5%)	0
Known Systolic LV dysfunction	348 (46.5%)	77 (21.3%)	16 (5.4%)	441 (31.3%)	
Cardiologist	551 (73.7%)	226(62.6%)	238 (79.6%)	1015 (72.1%)	0
Underlying Heart Disease & Co-Morbidities					
Known CAD	288 (38.5%)	189 (52.4%)	40 (13.4%)	517 (36.7%)	0
HTN	254 (34.0%)	168(46.5%)	92 (30.8%)	514 (36.5%)	0
VHD	66 (8.8%)	23 (6.4%)	102 (34.1%)	191 (13.6%)	0
Atrial Fibrillation	41 (5.5%)	8 (2.2%)	30 (10.0%)	79 (5.6%)	0
Diabetes mellitus	132 (17.7)	107(29.6%)	63 (21.0%)	302 (21.4%)	
Hyperlipidaemia	93(12.4%)	49 (13.6%)	6 (2.0%)	148 (10.5%)	0
Asthma/ COPD,	3 (0.4%)	8 (2.2%)	50 (16.7%)	61 (4.3%)	0
CKD / Dialysis	10 (1.3%)	6 (1.7%)	5 (1.7%)	21 (1.5%)	0.878
PVD	11 (1.5%)	11 (3.0%)	7 (2.3%)	29 (2.1%)	0.207
Stroke/ TIA	38 (5.1%)	13 (3.6%)	10 (3.3%)	61 (4.3%)	0.336

Table 2: Clinical Presentation, Physical examination & Laboratory Data of AHF Patients N (%).

Characteristics	EF (< 40%) (N = 748)	EF (40–49%) (N = 361)	EF (≥ 50%) (N = 299)	All (N = 1408)	p-value
ADHF	432 (57.8%)	121 (33.5%)	166 (55.5%)	719 (51.1%)	
New-Onset HF	316 (42.2%)	240 (66.5%)	133 (44.5%)	689 (48.9%)	
Clinical Presentation					
NYHA III-IV	616 (82.3%)	228 (63%)	211 (70.5%)	1059 (75.3)	
Orthopnea	659 (88.1%)	248 (68.7%)	255 (85.3%)	1162 (82.5%)	0
PND	629 (84.1%)	236 (65.4%)	218 (72.9%)	1083 (76.9%)	
LL Swelling	545 (72.90%)	125 (34.60%)	184 (61.50%)	854 (60.70%)	0
Weight gain	414 (55.3%)	65 (18.0%)	86 (28.8%)	565 (40.1%)	
Chest pain	396 (52.9%)	260 (72.0%)	114 (38.1%)	770 (54.7%)	
Palpitation	373 (49.9%)	168 (46.5%)	134 (44.8%)	675 (47.9%)	
Easy Fatigability	641 (85.7%)	226 (62.6%)	199 (66.6%)	1066 (75.7%)	
Syncope	68 (9.1%)	28 (7.8%)	32 (10.7%)	128 (9.1%)	
Physical examination					
HR, Mean, ±SD	104.2 ± 18.2	93.5 ± 22.4	98.3 ± 24.6	100.2 ± 21.3	
SBP (mmHg) -	131.7 ± 32.2	136.3 ± 27.1	125.1 ± 29.6	131.5 ± 30.6	
DBP (mmHg) -	83.3 ± 19.5	84.7 ± 16.3	76.6 ± 17.0	82.3 ± 18.4	
RR (/min)	27.2 ± 4.7	24.6 ± 5.7	25.7 ± 6.1	26.2 ± 5.4	
BMI (kg/m ²)	25.7 ± 4.0	26.2 ± 4.4	25.5 ± 5.2	25.8 ± 4.4	0.077
mean ± SD					
Raised JVP	530 (70.90%)	161 (44.60%)	189 (63.20%)	880 (62.50%)	0
LL Oedema	565 (75.5%)	144 (39.9%)	200 (66.9%)	909 (64.6%)	
Enlarged Tender Liver	522 (69.8%)	132 (36.6%)	186 (62.2%)	840 (59.7%)	
Gallop	518 (69.30%)	150 (41.60%)	122 (40.80%)	790 (56.10%)	0
Basal Crepitations	722 (96.50%)	343 (95.00%)	269 (90.00%)	1334 (94.70%)	
Signs of PE	280 (37.40%)	73 (20.20%)	84 (28.10%)	437 (31.00%)	0

Raised (> 6 cm) JVP, Syncope in last one-year, Acute decompensated Chronic HF, Acute New-Onset HF, PE Pleural Effusion FH Family history, CMP Cardiomyopathy, Haemoglobin

that reported chest pain (72% vs 53% vs 38%). HFmrEF was also associated with the lowest mean heart rate (93±22 vs 98±24 vs 104 ±18) and highest admission mean Systolic BP (136(±27 vs. 125± 29 vs. 131± 30) (p. < 0.05). HFpEF is associated with the lowest mean systolic BP. Overall basal lung crepitations were the most typical clinical sign reported (95%), with no significant differences among HF types. Other relatively common signs of HF were peripheral oedema (65%), raised (> 6 cm) JVP

Table 3: Workup Data of AHF patients.

Characteristics	EF (< 40%) (N = 748)	EF (40–49%) (N = 361)	EF (≥ 50%) (N = 299)	All (N = 1408)	p-value
High Troponin-I/T	73 ± 9.8%	112 ± 31.0%	63 ± 21.1%	248 ± 17.6%	
Hg (g/dL) M±SD	12.7 ± 2.4	14.0 ± 2.6	13.3 ± 2.7	13.1 ± 2.6	0
Creatinine mg/dL	1.305 ± .9090	1.124 ± .9178	1.123 ± 1.1752	1.220 ± .9772	
ECG					
AF/Flutter,	59 (7.9%)	16 (4.4%)	44 (14.7%)	119 (8.5%)	
LV hypertrophy	224 (29.9%)	155 (42.9%)	96 (32.1%)	475 (33.7%)	
ST-Depression/T-	344 (46.0%)	209 (57.9%)	86 (28.8%)	639 (45.4%)	
Inversion					
STEMI	57 (7.6%)	92 (25.5%)	29 (9.7%)	178 (12.6%)	
Pathological Q	215 (28.7%)	126 (34.9%)	23 (7.7%)	364 (25.9%)	
LB BB	176 (23.5%)	29 (8.0%)	4 (1.3%)	209 (14.8%)	
Echo					
Large LA	645 (86.2%)	231 (64.0%)	159 (53.2%)	1035 (73.5%)	
Conc. LVH	139 (18.6%)	164 (45.4%)	101 (33.8%)	404 (28.7%)	
MR,	304 (40.6%)	74 (20.5%)	28 (9.4%)	406 (28.8%)	
TR,	17 (2.3%)	9 (2.5%)	42 (14.0%)	68 ((4.8%))	
PASP (mmHg),	55.0 ± 15.4	53.1 ± 17.5	71.2 ± 25.5	58.8 ± 20.4	0
Significant CAD*	63 (8.4%)	52 (14.4%)	-6.70%	135 (11.6%)	

Significant CAD on CAG Pulmonary Artery Systolic Pressure (PASP) (mmHg), mean ± SD, QRS Duration = > 0.12 msec. Coronary Angiogram within one year of AHF patients, Normal coronaries/non-significant CAD, Normal /non-significant CAD

(62.5%), enlarged tender liver (60%), gallop rhythm (56%) and signs of pleural effusion (31%), with significant heterogeneity among the different HF types. All these signs were generally seen significantly more frequently among HFpEF patients than the other two types, except for the S3 gallop rhythm. HFmrEF was associated with the lowest prevalence compared to other types (p<0.05). Gallop rhythm was observed significantly more frequently with HFpEF patients (69%), with no significant difference between HFpEF and HFmrEF patients (41.6% vs 40.8%).

Workup Data

Compared to other HF types, HFmrEF patients were associated with higher mean haemoglobin and total cholesterol levels and higher frequency of elevated Troponin-I/T levels. No significant differences among HF types regarding mean creatinine level. HFpEF, compared to other HF types, were associated with a higher prevalence of AF/Flutter (p<0.05), higher mean pulmonary artery systolic pressure (PASP) (p = 0.015), and lower prevalence of Left Bundle Branch Block (LBBB). HFpEF, compared to others, was associated with a higher prevalence of prolonged QRS duration, LBBB, and significant valve disease. HFmrEF, compared to other HF types, was associated higher prevalence of left ventricular hypertrophy, ECG evidence of ischemia (as pathological Q) or documented ischemia on coronary angiogram than others. On the other hand, the prevalence of AF/Flutter and moderate-Severe VHD was lowest among HFmrEF. Table 3 summarizes the work-up data on AHF patients.

Table 4: Baseline, In-hospital medications and Use of GDMT stratified by the different HF groups.

Pharmacological Class	EF (< 40%) (N = 748)	EF (40–49%) (N = 361)	EF (≥ 50%) (N = 299)	All (N = 1408)	p-value
Digoxin					
- Before	211 (28.2%)	23 (6.4%)	58 (19.4%)	292 (20.7%)	0
- On Discharge	344 (46.0%)	54 (15.0%)	48 (16.1%)	446 (31.7%)	0
Calcium blockers					
- Before	10 (1.3%)	13 (3.6%)	39 (13.0%)	62 (4.4%)	0
- On Discharge	7 (0.9%)	18 (5.0%)	49 (16.4%)	74 (5.3%)	0
Aspirin					
- Before	429 (57.4%)	236 (65.4%)	86 (28.8%)	751 (53.3%)	0
- On Discharge	565 (75.5%)	324 (89.8%)	180 (60.2%)	1069 (75.9%)	0
Clopidogrel					
- Before	69 (9.2%)	92 (25.5%)	10 (3.3%)	171 (12.1%)	0
- On Discharge	181 (24.2%)	220 (60.9%)	71 (23.7%)	472 (33.5%)	0
Statin					
- Before	195 (26.1%)	138 (38.2%)	27 (9.0%)	360 (25.6%)	0
- On Discharge	359 (48.0%)	267 (74.0%)	94 (31.4%)	720 (51.1%)	0
Diuretics					
- Before	369 (49.3%)	123 (34.1%)	150 (50.2%)	642 (45.6%)	0
- On Discharge	691 (92.4%)	324 (89.8%)	233 (77.9%)	1248 (88.6%)	0
Oral Nitrates					
- Before	125 (16.7%)	58 (16.1%)	6 (2.0%)	189 (13.4%)	0
- On Discharge	211 (28.2%)	95 (26.3%)	22 (7.4%)	328 (23.3%)	0
Oral Anticoagulants					
- Before	86 (11.5%)	13 (3.6%)	37 (12.4%)	136 (9.7%)	0
- On Discharge	152 (20.3%)	38 (10.5%)	60 (20.1%)	250 (17.8%)	0
beta blockers (BBs)					
Before Admission	216 (28.9%)	146 (40.4%)	38 (12.7%)	400 (28.4%)	0
On Discharge	569 (76.1%)	286 (79.2%)	123 (41.1%)	978 (69.5%)	0
ACEi)					
Before Admission	412 (55.1%)	188 (52.1%)	71 (23.7%)	671 (47.7%)	0
On Discharge	551 (73.7%)	275 (76.2%)	151 (50.5%)	977 (69.4%)	0
ARBs)					
Before Admission	25 (3.3%)	16 (4.4%)	4 (1.3%)	45 (3.2%)	0.075
On Discharge	122 (16.3%)	38 (10.5%)	20 (6.7%)	180 (12.8%)	0
MRAs					
Before Admission	118 (15.8%)	13 (3.6%)	12 (4.0%)	143 (10.2%)	0
On Discharge	592 (79.1%)	132 (36.6%)	107 (35.8%)	831 (59.0%)	0

ACE-I: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Antagonists); MRAs: Aldosterone Receptor Antagonists; BBs: Beta Blockers

Pharmacological Management

Table 4 summarizes the results of in-hospital medications and Guideline-Directed Medical Therapy (GDMT) stratified by three HF subtypes. The most prescribed HF medications on ad-

mission were aspirin, diuretics, statin, and digoxin. Specifically, 400 patients (28%) were on Beta-Blockers (BB), 671 (48%) on Angiotensin-Converting Enzyme Inhibitor (ACE-I), 45 (3.2%) on Angiotensin Receptor Antagonist (ARB), and 143 (10.2%) on aldosterone receptor antagonist (MRAs). Compared to HFrEF and HFpEF, fewer HFmrEF patients were on digoxin, diuretics, and oral anticoagulants ($p < 0.001$) but more on clopidogrel and Statin ($p < 0.005$). A similar proportion of HFrEF and HFpEF was on diuretics and oral anticoagulants. Fewer HFpEF patients were prescribed oral nitrates ACE-I and ARBs and more on Calcium Channel Blockers (CCB). More HFrEF received Mineralocorticoid Receptor Antagonists (MRAs). On discharge diuretics, BBs and ACE-I were prescribed equally to HFmrEF and HFpEF ($p < 0.001$), but HFrEF was more frequent on MRAs. Digoxin prescription is similar to HFpEF but less than HFrEF ($p < 0.001$). Aspirin, clopidogrel, and statin were prescribed more to HFmrEF than others ($p < 0.001$ except for clopidogrel that was non-significant for HFrEF versus HFpEF).

Comparison with National and International Data

Table 5 summarizes a comparison of this study's findings of demographic and clinical results from national and international registries and study findings. Data from western countries suggest variable geographical distribution and prevalence of HFmrEF [12]. North American registries indicate HFmrEF prevalence ranges between 13% in the Get with The Guidelines – HF (GWTG-HF) study [31] and 7.5% in the PINNACLE study, the largest descriptive analysis of HFmrEF patients to date [32]. European registries report a relatively higher HFmrEF prevalence, between 21% in the Swedish registry [33] and 24% in the ESC-HF-LT registry [34]. However, clinical trials report a lower prevalence, 17% in CHARM [35], 15% in TOPCAT [36] and DIG [37], and 11% in PARADIGM-PARAGON [38], and in clinical settings, 13-26% among in-patients and 9-21% among outpatients [1]. Most existing HFmrEF studies enrolled patients with chronic HF, with fewer studies on HFmrEF patients with AHF [39-42, 52]. The relatively higher prevalence of HFmrEF (25.6%) in this Yemeni AHF cohort compared to 21-22.8% reported in the Middle East by sub-analysis of the Gulf CARE Registry [43-45] and 22% of the Gulf DYSYPNEA registry [46-49] remains unknown. However, a higher prevalence of HFmrEF (36.4%) than our study has been reported among 633 rural HF patients [42].

Discussion

Main Findings

Clinical data on HF subtypes based on LVEF cut-offs in Yemen is lacking. Previous population-based studies examined the entire HF cohort without differentiating them into HF subtypes. To the best of our knowledge, this is the first study in Yemen to describe clinic-epidemiological profiles of HFrEF, HFmrEF and HFpEF subtypes. The study describes the epidemiologic, patient and clinical characteristics of AHF patients in Yemen who had enrolled in the Gulf CARE study. The significant findings of this study are, firstly, HFrEF accounts for the majority of AHF cases, with HFmrEF accounting for a quarter of the total cases. Secondly, the three most common comorbidities are CAD, HTN and DM, whereas VHD secondary to rheumatic disease did not contribute to AHF prevalence in Yemen. Thirdly, the three HF subtypes stratified by LVEF in Yemen represent distinctive and heterogeneous groups regarding demographic, clinical presentation and medication. Finally, HFmrEF patients present with features distinct from HFrEF and HFpEF, sharing some characteristics with the two or taking an intermediate position.

Table 5: Comparison of Demographic and Clinical Data with National and International Data.

Editor/Year	Current 2022	(1) Al-Jarallah 2020	(2) Kaplon-Cie'slicka et al. 2022	(3) Farmakis, D 2017	(4) Shah KS et al. 2017	(5) Rickenbacher 2017
Total & HFmrEF %	1408 (25.6%)	4577 (21%)	5951 (18%)	3257 (25%)	39,982 (8.2%)	622 (17%)
Demographic & Comorbidities						
Age	57.0 ±12.9	61 (53-70)	71 [62–79]	-	81	70
Male	-71.70%	-60	60%	-36.20%	52	53.7
Smoking	-38.80%	-23	15%	-26.70%	8	60.2
CAD	-52.40%	-74	52%	28.7%	55	79.6
HTN	-46.50%	-67	68%	76.5%	75	82.4
AF	-2.20%	-9.6	56%	-24.60%	37	39.6
DM	-29.60%	-54	38%	-45.70%	42	39.8
COPD	-2.20%	-	19%	-22.40%	26.9	21.3
VHD	-6.40%	-	14%	-15.50%	11	
Clinical Manifestations						
De-Novo	66.50%	-	27%	37.20%		
Orthopnea	68.70%	72		56.90%		63.6
NYHA III- IV	63%	69	78%	(47.0%)/(34.8%)		71.3
LL swelling	34.60%	35	58%	40.20%		45.8
HR, beats/min	93.5	80-107	86	106.6	80	76 (15)
SBP, mean	136.3	143	130	139.8	141	127 (19)
Gallop	41.60%	34		-		13.2
Rales	95%	93	72%	64.40%		45.8
Raised JVP	44.60%	43		3.90%		63.8
Medication						
Diuretic	-34.10%	-52	80	-97.40%	60	-89.8
Digitalis	-6.40%		25	-27.90%	15	-13.9
Oral nitrate	-16.10%	-30	26		19	-32.4
Statin	-38.20%	-57			43	
Beta-blocker	-40.40%	-47	77	-51.70%	37	-73.1
ACE inhibitor	-52.10%	-45	79	-68.70%	50+ARB	(90.7) +
ARB	-4.40%	-12		-12.00%		
MRA	-3.60%	-8.5		-26.90%	7	-33.3

[1] Al-Jarallah 2020, Gulf-Care [42], (2) Kaplon-Cie'slicka et al. 2022, European HF Registry [65], [3] Farmakis, D 2017, ALARM-HF [9] Europe countries [39], [4] Shah KS et al. 2017 Get with The Guidelines-HF USA, [54], [5] Rickenbacher TIME-CHF Total No 622 & HFmrEF [40].

Baseline Clinical Characteristics of AHF Subtypes

Consensus on clinical and epidemiological characteristics of HFmrEF patients remains to be elusive. Existing studies report conflicting findings and inconsistent conclusions [10,11,17,19,50,51]. Earlier studies suggest the clinical features of the HFmrEF subtype were closer to that of HFpEF [52-54]. In contrast, recent studies indicate the HFmrEF subtype has a closer relationship with HFrfEF due to similar CAD comorbidity and response to medical therapy [35-42, 54-57], which contributed to the most recent ESC guidelines changing the terminology from mid-range to mildly-reduced EF [3]. In our study, the three HF subtypes expressed distinct and heterogeneous demographic characteristics regarding age, gender and risk factors. HFmrEF patients were older, more males, smokers and chewed kat. These findings are consistent with Gulf-CARE and Omani registries [44,45]. Whereas many studies suggest, HFmrEF has a male preponderance, a large American cohort (GWG-HF) study reported equal gender representation [31]. Similarly, consistent with previous studies [44,45], our data show a higher female proportion among HFpEF patients but not of a younger age. Nevertheless, a recent study [42] reported the same findings as ours; young females are more likely to have HFmrEF.

Our study reports that in all the HF patients, CAD, HTN and DM were comorbidities with the highest prevalence. The findings were consistent with the Gulf CARE registry but with a low-

er comorbidity burden than the Gulf Area [43,44]. However, the Gulf Area had a lower case of AF and HTN and was more likely younger. Comorbidities distribution varied across the three HF subtypes. HFmrEF patients were more likely to have Ischemic Heart Disease (IHD), HTN and DM. In contrast, HFpEF patients had higher cases of AF, VHD and asthma/COPD/ HFmrEF patients had a higher history of CAD documented on invasive coronary angiography or ECG evidence of ischemia than HFrfEF and HFpEF. Several other registries and studies TIME-CHF [40], GWG-HF [31, ESC-HF-LT [34]., PINNACLE [32] and SwedeHF registry [33] also reported a higher prevalence of IHD. Additionally, the Swede HF registry indicated HFmrEF had significantly higher cases of IHD [33]. The findings suggest HFmrEF has a closer relationship with HFrfEF than HFpEF subtypes based on comorbidity burden. The higher cases of IHD may warrant the application of HFrfEF-evidence-based IHD treatment to HFmrEF patients.

Our data also indicates a significantly higher prevalence of HTN among HFmrEF patients than in HFrfEF and HFpEF. Several other studies reported similar findings of higher prevalence of HTN among HFmrEF than HFrfEF and HFpEF, the ALARM-HF registry (77% vs 66% vs 72% among 4,953 patients, $p < 0.001$) [38], Turkish AHF registries (1,606 patients) [58], Japan (1,245 patients) [59], and China (4880 patients) [60] observed similar findings. In addition, higher mean admission SBP in HFmrEF was found in 449 Indian patients [61]. The Turkish and Chinese reg-

istries [58,60] also reported a lower prevalence of AF and VHD in HFmrEF patients. A higher prevalence of HTN and admission SBP suggest HFmrEF patients may benefit from HTN treatment.

In our study, HFmrEF patients had a distinctive clinical profile. They had a significantly higher frequency of de novo HF, dyspnoea, lower symptomatic heart burden (NYHA IV, orthopnoea and PND), more clinically stable (higher SBP and lower heart rate), lower frequency of HF signs, higher prevalence of LVH, haemoglobin and cholesterol levels. In contrast, HFpEF patients exhibit an intermediate clinical profile, less symptomatic than HFrEF but more than HFmrEF. Thus, compared to HFmrEF, HFpEF patients' clinical profile suggests a greater HF disease severity is more likely to have signs and symptoms of congestive HF, higher heart rate and lower mean SBP despite preserved LVEF. HFpEF patients also exhibit a higher mean Pulmonary Artery Pressure (PAP). Consistent with the present findings, Korean and Turkey registries [58,62] report a high proportion of de novo AHF in HFmrEF patients, while Gulf CARE [45], TIME registry [40] and retrospective analysis of DIG trial [37]. A recent meta-analysis of 19 studies [63] considered HFmrEF a distinct HF subtype confirming our findings of lower cases of NYHA III-IV and the least use of digoxin. Finally, HFmrEF patients were more likely to exhibit concentric LVH by echo, which is consistent with data from Gulf CARE among 4,577 patients [43] and the ESC-HFA HF Long-Term Registry where HFmrEF (48%) and HFpEF (50%) had higher LVH than HFrEF (33%) [65].

Pharmacological Management

We found HFmrEF patients had higher prescriptions of antiplatelets and statins on-admission and GDMT of ACE-I/ARB/MRA's and beta-blockers on discharge. The higher prescriptions are consistent with the findings that HFmrEF patients are more likely to develop IHD and atherothrombotic risk factors due to high prevalence of DM and likelier to use tobacco use than HFrEF and HFmrEF patients. Despite a lack of clinical trials targeting HFmrEF patients, observational studies and post-hoc analyses of clinical trials support the potential benefits of neurohormonal therapies prescribed for HFrEF patients. Furthermore, the 2021 ESC HF guidelines [3] reported patients with LVEF 40-50% could benefit from therapies used by HFrEF patients. Recent studies also support early initiation of neurohormonal therapy for HFmrEF patients admitted to hospital is safe and with potentially favourable outcomes [64,65].

Limitations

The findings of this study should be considered alongside the limitations encountered. Firstly, the study methodology is retrospective, using data from the Gulf-CARE registry. The data was collected from 2014, which means it may not include recent changes in epidemiology, diagnosis or treatment. Secondly, another limitation is the use of LVEF as the central measure of stratifying patients into three HF subtypes, HFrEF, HFmrEF and HFpEF. Our study used the latest ESC guidelines defining mildly-reduced HF as LVEF 41-49%, yet the Gulf CARE registry defines mid-range HF as LVEF 40-49%. The 1% difference can give rise to classification bias due to significant inter- and intra-operator variability and potentially present as a confounding factor, affecting the accuracy of the findings. Thirdly, the study only includes hospitalized AHF patients, which excludes other HF cohorts, and, thus, may not represent the actual population-based clinico-epidemiological characteristics of HFmrEF patients.

Conclusion

The recent addition of HFmrEF stratified by LVEF introduced a debate as to whether it represented a genuinely distinct subtype or a transitional category between HFrEF and HFpEF clinical categories. Wide variations in its clinical and demographic characteristics undermine the ability to reach a consensus. To the best of our knowledge, this is the first study to describe the clinical and epidemiological profile of the HFmrEF entity using a large and real-world AHF cohort in Yemen and compare it with HFrEF and HFpEF. The data reveals that Yemen AHF patients categorized by LVEF represent distinctive and heterogeneous groups based on demography, clinical presentation, and medications. Hospitalized HFmrEF patients accounted for a substantial proportion of the AHF patients and represented a demographically and clinically diverse group with many intermediate features compared to HFrEF and HFpEF patients. The similarities and differences observed in our analysis are consistent with the existing registry and study findings.

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