Austin Journal of Endocrinology and Diabetes

Open Access

Austin Publishing Group

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)

Adnan AL-Radhy[1]; Nora Al Sagheer[1]; Abdulkafy Shujaa[1]; Ali Al-Zaazaai[2]; Aref Al Bakri[3]; Khaled Al Khamesy[4]; Saleh Bahaj[5]

[1]Department of Cardiology, Faculty of Medicine and Health Sciences, Sana'a University-Yemen

[2]St-Marien hospital Bonn Venusberg, department of internal medicine, Bonn, Germany

[3]Department of physiology, Faculty of Medicine and Health Sciences, Sana'a University-Yemen

[4]MS.C Clinical Pharmacy, Faculty of Medicine and Health Sciences, Wenzhou Medical University-China

[5]Department of microbiology, Faculty of Medicine and Health Sciences, Sana'a University-Yemen

***Corresponding author:** **Nora Alsagheer**
Faculty of Medicine & Health Sciences, Sana'a University, Yemen.
Email: nalsageer@gmail.com

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 HRmrEF 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 CoronaryArtery 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

Citation: AL-Radhy A, Al Sagheer N, Shujaa A, Al-Zaazaai A, Al Bakri A, et al. 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). Austin J Endocrinol Diabetes. 2024; 11(1): 1106.

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 ≥ 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 ≥ 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 fFrm (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/m^2 with no significant difference between groups (p= 0.077).

Table 1: Demographic and Baseline Characteristics of AHF patients.

Characteristics	EF (< 40%)	EF (40–49%)	EF (≥ 50%)	All	p-
	(N = 748)	(N = 361)	(N = 299)	(N = 1408)	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

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

Characteristics	EF (< 40%)	EF (40–49%)	EF (≥ 50%)	All	p-
	(N = 748)	(N = 361)	(N = 299)	(N = 1408)	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/m2)	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 (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 HFrEF 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 HFrEF patients (69%), with no significant difference between HFpEF and HFmrEF patients (41.6% vs 40.8%).

Table 3: Workup Data of AHF patients.

Characteristics	EF (< 40%)	EF (40–49%)	EF (≥ 50%)	All	p-
	(N = 748)	(N = 361)	(N = 299)	(N = 1408)	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%)	
LBBB	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

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). HFrEF, 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%)	EF (40–49%)	EF (≥ 50%)	All	p-value
	(N = 748)	(N = 361)	(N = 299)	(N = 1408)	
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 BB	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 admission 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 HFrEF ($p < 0.001$), 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 DYSPNEA 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) Kapłon-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) Kapłon-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 HFrEF 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 heterogenous 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 lower 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 HFrEF and HFpEF. Several other registries and studies TIME-CHF [40], GWTG-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 HFrEF than HFpEF subtypes based on comorbidity burden. The higher cases of IHD may warrant the application of HFrEF-evidence-based IHD treatment to HFmrEF patients.

Our data also indicates a significantly higher prevalence of HTN among HFmrEF patients than in HFrEF and HFpEF. Several other studies reported similar findings of higher prevalence of HTN among HFmrEF than HFrEF 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 benefits 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 heterogenous 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.

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJ. Global burden of heart failure: a comprehensive and updated review of epidemiology, Cardiovascular Research. 2022; 118: 3272-3287.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. heart disease and stroke statistics — 2021 update: a report from the American Heart Association. Circulation. 2021; 143: e254–e743.
3. Chen X, Xin Y, Hu W, Zhao Y, Zhang Z, Zhou Y. Quality of life and outcomes in heart failure patients with ejection fractions in different ranges. PLoS ONE. 2019; 14: e0218983.
4. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014; 171: 368–376.
5. Yancy, CW, Jessup, M, Bozkurt, B, Butler J, Casey DE, Drazner MH, et al. ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation (New York, NY). 2013; 128: e240-327.
6. Lam, CS, Solomon, SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail. 2014; 16: 1049-1055.
7. Ponikowski, P, Voors, AA, Anker, SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (ESC). developed with the special contribution of the heart failure association (HFA) of the ESC. Eur J Heart Fail. 2016; 18: 891–975.
8. Bozkurt B, Coats A, Tsutsui H. Universal definition and classification of heart failure [published online ahead of print, 2021 Feb 7]. J Card Fail. 2021; S1071-9164: 00050-6.
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726.
10. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol. 2022; 19: 100-116.
11. Branca L, Sbolli M, Metra M, Fudim M. Heart failure with mid-range ejection fraction: pro and cons of the new classification of Heart Failure by European Society of Cardiology guidelines. ESC Heart Fail. 2020; 7: 381–99.

12. Mesquita ET, Barbetta L, Correia ETO. Heart Failure with Mid-Range Ejection Fraction - State of the Art. Arq Bras Cardiol. 2019; 112: 784–90.

13. Shang Z, Wang X, Gao W. Heart failure with mildly reduced ejection fraction: emerging frontiers in clinical characteristics, prognosis, and treatment. Rev Cardiovasc Med. 2022; 23: 30.

14. Boulet J, Massie E, Rouleau JL. Heart Failure with Midrange Ejection Fraction-What Is It, If Anything? Can J Cardiol. 2021; 37: 585-594.

15. Palazzuoli A, Beltrami M. Are HFpEF and HFmrEF So Different? The Need to Understand Distinct Phenotypes. Front Cardiovasc Med. 2021; 8: 676658.

16. Martone R, Marchionni N, Cappelli F. Heart failure with mid-range ejection fraction: Current evidence and uncertainties. Monaldi Arch Chest Dis. 2019; 89.

17. Srivastava PK, Hsu JJ, Ziaeian B, et al. Heart failure with mid-range ejection fraction. Curr Heart Fail Rep. 2020; 17: 1–8.

18. Cvijic M, Rib Y, Danojevic S, Radulescu CI, Nazghaidze N, Vardas P. Heart failure with mildly reduced ejection fraction: from diagnosis to treatment. Gaps and dilemmas in current clinical practice. Heart Fail Rev. 2022: 28.

19. Stolfo D, Fabris E, Lund LH, Savarese G, Sinagra G. From mid-range to mildly reduced ejection fraction heart failure: A call to treat. Eur J Intern Med. 2022; 103: S0953-6205(22)00209-6.

20. Talha KM, Butler J. Breakthroughs in the treatment of heart failure with mildly reduced and preserved ejection fraction. Clin Cardiol. 2022; 45: S31-S39.

21. Elasfar A, Alhabeeb W, and Elasfar S. Heart failure in the Middle East Arab countries: current and future perspectives. J Saudi Heart Assoc. 2020; 32: 236–41.

22. Bennis A, Ogola EN, Klug E, Skouri HN, Saffaret al. Strategic Recommendations to Bridge the Gaps in Awareness, Diagnosis and Prevention of Heart Failure in the Middle East Region and Africa. Journal of the Saudi Heart Association. 2022; 34: 53-65.

23. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, et al. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Global Health. 2017; 5: e665–72.

24. Al-Zendani A, Al-Emad A, Al-Motarreb A, Amen M, Al-Sagheer N, Hadi HA, et al. Acute heart failure in Yemen. J Cardiovasc Med (Hagerstown) 2019; 20: 156-8.

25. Munibari AN, Al-Motarreb A, Al-Sagheer N, Hadi HA, Othman A, Al-Wather N, et al. Clinical characteristics and outcomes of Yemeni patients with acute heart failure aged 50 years or younger: Data from Gulf Acute Heart Failure Registry (Gulf CARE). Int J Cardiol. 2017; 229: 91-5.

26. Sulaiman KJ, Panduranga P, Al-Zakwani I, Alsheikh-Ali A, Al-Habib K, Al-Suwaidi J, et al. Rationale, design, methodology and hospital characteristics of the first gulf acute heart failure registry (Gulf CARE). Heart Views. 2014; 15: 6-12.

27. Sulaiman K, Panduranga P, Al-Zakwani I, Alsheikh-Ali AA, Al Habib KF, Al-Suwaidi J, et al. Clinical characteristics, management, and outcomes of acute heart failure patients: observations from the Gulf acute heart failure registry (Gulf CARE). Eur J Heart Fail. 2015; 17: 374–84.

28. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008; 10: 933–89.

29. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005; 112: e154–235.

30. Ali WM, Al Habib KF, Al-Motarreb A, Singh R, Hersi A, Al Faleh H, et al. Acute coronary syndrome and khat herbal amphetamine use: an observational report. Circulation. 2011; 124: 2681–2689.

31. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail. 2016; 4: 464–472.

32. Ibrahim NE, Song Y, Cannon CP, Doros G, Russo P, Ponirakis A, et al. Heart failure with mid-range ejection fraction: characterization of patients from the PINNACLE Registry? ESC Heart Fail. 2019; 6: 784–92.

33. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom, et al. A comprehensive population- based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail. 2017; 19: 1624–34.

34. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017; 19: 1574–85.

35. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018; 20: 1230–9.

36. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J. 2016; 37: 455–62.

37. Abdul-Rahim AH, Shen L, Rush CJ, Jhund PS, Lees KR, McMurray JJV, et al. Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. Eur J Heart Fail. 2018; 20: 1139–45.

38. Solomon SD, Vaduganathan ML, Claggett B, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020; 141: 352–61.

39. Farmakis D, Simitsis P, Bistola V, Triposkiadis F, Ikonomidis I, Karsanos S, et al. Acute heart failure with mid-range left ventricular ejection fraction: clinical profile, in-hospital management, and short-term outcome. Clin Res Cardiol. 2017; 106: 359–368.

40. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail. 2017; 19: 1586–96.

41. Guisado-Espartero ME, Salamanca-Bautista P, Aramburu-Bodas Ó, Conde-Martel A, Arias-Jimenezet al. Heart failure with mid-range ejection fraction in patients admitted to internal medicine departments: findings from the RICA registry. Int J Cardiol. 2018;255:124–128.

42. G Murtaza, T Paul, ZU Rahman, Kelvas D, Lavine SJ. Clinical characteristics, comorbidities and prognosis in patients with heart failure with mid-range ejection fraction; Am J Med Sci. 2020; 359: 325-333.

43. Al-Jarallah M, Rajan R, Heshmat H, Al-Zakwani I, Dashti R, Bulbanat B, et al. Comparison of demographics and outcomes of acute heart failure patients with reduced, mid-range and preserved ejection fraction. Ann Clin Cardiol. 2020; 2: 86-94.

44. Al-Jarallah M, Rajan R, Al-Zakwani I, Dashti R, Bulbanat B, Ridha M, et al. Mortality and morbidity in HFrEF, HFmrEF, and HFpEF patients with diabetes in the middle east. Oman Med J. 2020; 35: e99.

45. Jan RK, Alsheikh-Ali A, Mulla AA, Sulaiman K, Panduranga P, Wael AM, et al. Outcomes of guideline-based medical therapy in patients with acute heart failure and reduced left ventricular ejection fraction: observations from the Gulf acute heart failure registry (Gulf CARE). Medicine. 2022; 101: e29452.

46. Zubaid M, Rashed W, Ridha M, Bazargani N, Hamad A, Al Banna R, et al. Implementation of guideline- recommended therapies for patients with heart failure and reduced ejection fraction: a regional Arab middle east experience. Angiology. 2020; 71: 431–7.

47. Hanbali DA, Hashmi KA, Za'abi MA, Al Zakwani I. Evaluation of guideline-based cardiovascular medications and their respective doses in heart failure patients in Oman. Int J Clin Pharm. 2021; 43: 878–883.

48. Manal M Alem. Clinical, Echocardiographic, and Therapeutic Characteristics of Heart Failure in Patients with Preserved, Mid-Range, and Reduced Ejection Fraction: Future Directions, Int J Gen Med. 2021; 14: 459–467.

49. Subki AH, Almalki MA, Butt NS, Alsallum MS, Almutairi HM, Khatib HA, et al. Echocardiographic and clinical correlates of ejection fraction among 2000 patients with heart failure in Western Saudi Arabia. Int J Gen Med. 2020; 13: 281–288.

50. Straw S, Cole CA, McGinlay M, Drozd M, Slater T, Lowry JE, et al. Guideline-directed medical therapy is similarly effective in heart failure with mildly reduced ejection fraction. Clin Res Cardiol. 2022: 112.

51. Zhou Q, Li P, Zhao H, Xu X, Li S, Zhao J, et al. Heart Failure With Mid-range Ejection Fraction: A Distinctive Subtype or a Transitional Stage?. Front Cardiovasc Med. 2021; 8: 678121.

52. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J Am Coll Cardiol. 2007; 50: 768–777.

53. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol. 2008; 101: 1151–1156.

54. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol. 2017; 70: 2476–2486.

55. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid- range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018; 39: 26–35.

56. Baker C, Perkins SL, Schoenborn E, Biondi NL, Bowers RD. Pharmacotherapy Considerations in Heart Failure with Mildly-Reduced Ejection Fraction. J Pharm Pract. 2021: 8971900211027315.

57. Koufou EE, Arfaras-Melainis A, Rawal S, Kalogeropoulos AP. Treatment of Heart Failure with Mid-Range Ejection Fraction: What Is the Evidence. J Clin Med. 2021; 10: 203.

58. Sinan UY, Gurbuz DC, Celik O, Cakmak HA, Kilic S, Inci S, et al. The clinical characteristics of acute heart failure patients with mid-range ejection fraction in Turkey: A subgroup analysis from journey HF-TR study. Int J Cardiovasc Acad. 2020; 6: 5-11.

59. Shiga T, Suzuki A, Haruta S, Mori F, Ota Y, Yagi M, et al. Clinical characteristics of hospitalized heart failure patients with preserved, mid-range, and reduced ejection fractions in Japan. ESC Heart Fail. 2019; 6: 475–486.

60. Chen S, Huang Z, Liang Y, Zhao X, Aobuliksimu X, Wang B, et al. Five-year mortality of heart failure with preserved, mildly reduced, and reduced ejection fraction in a 4880 Chinese cohort. ESC Heart Fail. 2022; 9: 2336-2347.

61. Shukkoor AA, George NE, Radhakrishnan S, Velusamy S, Gopalan R, Kaliappan T, et al Clinical characteristics and outcomes of patients admitted with acute heart failure: insights from a single-center heart failure registry in South India. Egypt Heart J. 2021; 73: 38.

62. Cho JH, Choe WS, Cho HJ, Lee HY, Jang J, Lee SE, et al. Comparison of characteristics and 3-year outcomes in patients with acute heart failure with preserved, mid-range, and reduced ejection fraction. Circ J. 2019; 83: 347–356.

63. Guo P, Dai JF, Feng C, Chen ST, Feng JP. Special prognostic phenomenon for patients with mid-range ejection fraction heart failure: a systematic review and meta-analysis. Chin Med J. 2020; 133: 452–461.

64. Yaku H, Ozasa N, Morimoto T, Inuzuka Y, Tamaki Y, Yamamoto E, et al. Demographics, management, and in-hospital outcome of hospitalized acute heart failure syndrome patients in contemporary real clinical practice in Japan- observations from the prospective, multicenter Kyoto Congestive Heart Failure (KCHF) registry. Circ J. 2018; 82: 2811–2819.

65. Kapłon-Cie´slicka A, Benson L, Chioncel O, Crespo-Leiro MG, Coats AJS, Anker SD, et al. A comprehensive characterization of acute heart failure with preserved versus mildly reduced versus reduced ejection fraction– insights from the ESC-HFA EORP Heart Failure Long-Term Registry, European Journal of Heart Failure. 2022; 24: 335-350.