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Original Article

Patients with HFpEF and HFmrEF have different clinical characteristics in Turkey: A multicenter observational study

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ABSTRACT

Background: To determine and compare the demographic characteristics, clinical profile and management of patients with heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) in a Turkish cohort.

Methods: The APOLLON trial (A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejection fractiON) is an observational and multicenter study conducted in Turkey. Consecutive patients admitted to the cardiology clinics who were at least 18 years of age and had HFmrEF or HFpEF were included (NCT03026114).

Results: The study population included 1065 (mean age of 67.1 ± 10.6 years, 54% women) patients from 12 sites in Turkey. Among participants, 246 (23.1%) had HFmrEF and 819 (76.9%) had HFpEF. Compared to patients with HFpEF, those with HFmrEF were more likely to be male (57.7 vs 42.2%; $p < 0.001$), had higher N-terminal pro-B-type natriuretic peptide levels (853 vs 528 pg/ml, $p < 0.001$), were more likely to have ECG abnormalities (72.4 vs 53.5%, $p < 0.001$) and hospitalization history for heart failure (28 vs 18.6%; $p = 0.002$). HFmrEF patients were more likely to use β-blockers (69.9 vs 55.2%, $p < 0.001$), aldosterone receptor antagonists (24 vs 14.7%, $p = 0.001$), statins (37 vs 23%, $p < .001$), and loop diuretics (39.8 vs 30.5%, $p = 0.006$) compared to patients with HFpEF.

Conclusions: The results of APOLLON study support that the basic characteristics and etiology of HFmrEF are significantly different from HFpEF. This registry also showed that the patients with HFmrEF and HFpEF were younger but undertreated in Turkey compared to patients in western countries.

1. Introduction

The clinical syndrome of heart failure (HF) is associated with a wide spectrum of left ventricular structural and functional abnormalities ranging from preserved left ventricular ejection fraction (LVEF) and normal left ventricular size to severely reduced LVEF and marked dilation of the left ventricle [1]. Although HF was considered to be synonymous with reduced LVEF < 40% (HFrEF) until early 2000s, recent studies performed in the last two decades have shown that HF with preserved ejection fraction (HFpEF), the term used to define patients

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with signs and symptoms of HF with LVEF > 50%, is emerging as the most common form of HF [2]. Previous European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF had a grey area identifying patients with a LVEF ranging between 40 and 49% [3], and the recent 2016 guidelines included a new mid-range group in the classification of HF in order to stimulate research in this subpopulation of patients [4]. This guideline defined HF with mid-range ejection fraction (HFmrEF) as the presence of symptoms/signs of HF, a LVEF between 40 and 49%, elevated levels of natriuretic peptides and evidence of other cardiac functional or structural alterations such as left atrial enlargement, left ventricle hypertrophy or diastolic dysfunction [4].

Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older and at least.

half of these patients have HFmrEF or HFpEF [4]. Clinical profile, presentation, and pathophysiology of HFmrEF and HFpEF are heterogeneous [5] and most of the HFpEF and HFmrEF studies have been conducted in western countries and limited information is available in other regions of the world.

Previous studies have shown that patients with HFmrEF have a baseline profile in-between of HFrEF and HFpEF, with some characteristics closer to HFrEF and others to HFpEF. Given the differences in demography, clinical presentation, etiology and prognosis in the three groups, some authors suggest that HFmrEF has a phenotype closer to HFpEF whereas other authors consider it closer to HFrEF [6]. However, there are no data regarding the epidemiology, clinical features and causes of HFmrEF or HFpEF in our country. As Turkey is a wide country with different ethnicities, multicenter studies that emphasize epidemiologic and clinical features of HFmrEF and HFpEF are needed to elucidate their pattern in Turkey. Therefore, we performed a comprehensive study to determine the epidemiologic profile and clinical features of HFmrEF and HFpEF in a Turkish cohort.

2. Methods

2.1. Study design

The APOLLON (A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejection fractiON) study is a cross-sectional, multicenter, and observational study conducted in HFmrEF and HFpEF patients in Turkey (ClinicalTrials.gov identifier NCT03026114). Design and rationale of APOLLON trial have been described in detail elsewhere [7]. In brief, the APOLLON registry population comprised consecutive outpatients with HFmrEF and HFpEF, presenting to cardiologists in participating Turkish cities, and all data were collected in a single visit. To ensure inclusion of adequate geographic diversity, number of patients proportionate to the total population of every region were enrolled. State, university, education and research hospitals were included in order to represent all patients treated within different health care settings. The study was initiated in March 31, 2018 and the last patient was enrolled in May 20, 2018. A total of 1065 patients who presented to the outpatient cardiology clinics with New York Heart Association class I, II, III, or IV HF sign and/or symptoms were enrolled in the study at 11 sites across the country.

Inclusion criteria were; patients aged ≥18 years at the time of enrollment who were willing to participate and provide written informed consent; patients with a LVEF ≥40% and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level > 125 pg/ml; patients with signs and symptoms of HF. One symptom must be present at the time of screening and one sign must be present in the last 12 months.

Exclusion criteria were; patients with a LVEF < 40%; patients with significant chronic pulmonary disease; patients with primary hemodynamically significant uncorrected valvular.

heart disease; patients with any history of surgically corrected heart valve diseases (e.g., mechanical or bioprosthetic heart valves); patients with myocardial infarction, stroke, or coronary artery bypass graft surgery in the past 90 days; percutaneous coronary intervention or pacemaker implantation in the past 30 days; heart transplant recipients; known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction; patients with congenital heart diseases or cor pulmonale; and pregnants.

2.2. Clinical and laboratory assessment

Participants underwent a detailed medical history, physical examination, fasting blood draw with subsequent laboratory assessment, electrocardiography, and transthoracic echocardiography. Patient characteristics were obtained by a survey recording demographic data, including age, sex, body mass index, level of education, place of residence (rural or urban), status of smoking and alcohol use, comorbidities, current and previous therapies or interventions to treat HF and all medications.

Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or the use of hypoglycaemic medications. Anemia was defined as haemoglobin < 13 g/dl in men, and < 12 g/dl in women. Blood pressure was taken as the average of two seated measurements. Body mass index was calculated as weight divided by height^2 and expressed as kg/m^2. Blood samples were obtained at admission to measure laboratory variables, including NT-proBNP. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (MDRD-4) [8]. Renal failure was defined as eGFR < 60 ml/min/1.73 m^2. Prior history of coronary heart disease was ascertained systematically using a combination of self-report, electrocardiogram, review of all available prior medical records, and physician contact. Other comorbidities was defined according to review of all available prior medical records, and physician contact.

All patients were screened by transthoracic echocardiography during their first admission to the outpatient clinics, and LVEF was assessed using the conventional apical two- and four-chamber views and the modified Simpson's method. Patients were grouped based on their LVEF record into two groups: patients with HFpEF (LVEF ≥50%) and patients with HFmrEF (LVEF 40–49%). For the determination of HFpEF and HFmrEF, at least one additional echocardiographic criterion including relevant structural heart disease or diastolic dysfunction was required. Key structural alterations were accepted as a left atrial volume index (LAVI) > 34 ml/m^2 or a left ventricular mass index (LVMI) ≥115 g/m^2 for males and ≥ 95 g/m^2 for females. Key diastolic dysfunction criteria were accepted an E/e' ≥ 13 and a mean e' septal and lateral wall < 9 cm/s.

The etiology of HF was determined based on the following algorithm: *Ischemic*, when the patient was diagnosed with ischemic heart disease; *Valvular*, when there was moderate valvulopathy with no ischemic heart disease; *Hypertensive*, when there was previous history of hypertension but no evidence of additional cardiovascular disease; *Atrial fibrillation,* when there was any type of atrial fibrillation but no evidence of additional cardiovascular disease.

The study was approved by the Local Ethics Committee of Muğla Sıtkı Koçman University. Written informed consent was obtained from all patients.

2.3. Statistical analyses

Statistics are provided as percentages (%) or as mean with standard deviations (SD). Baseline continuous variables are presented as mean ± SD or median and interquartile range, depending on the distribution of the data; categorical data are presented as counts and percentages. Categorical variables ar compared using the $\chi 2$ test and the continuous variables using the *t*-test or the Mann–Whitney *U* test, as appropriate. Univariate and multiple regression analyses are used to

Table 1
Patient demographics and characteristics.

	Overall (n = 1065)	HFmrEF (n = 246)	HFpEF (n = 819)	*p* value
Female sex	577 (54.2)	104 (42.3)	473 (57.8)	< 0.001
Age, years	67.09 ± 10.59	67.99 ± 10.18	66.83 ± 10.71	0.132
Smoking	188 (17.7)	59 (24.0)	129 (15.8)	0.004
Alcohol use	46 (4.3)	17 (6.9)	29 (3.5)	0.031
Educational status				
Illiterate	302 (28.4)	66 (26.8)	236 (28.8)	
Primary	484 (45.4)	112 (45.4)	372 (45.4)	
Secondary	124 (11.6)	28 (11.4)	96 (11.7)	0.921
High	109 (10.2)	28 (11.4)	81 (9.9)	
University	46 (4.3)	12 (4.9)	34 (4.2)	
Place of residence				
Rural	323 (30.3)	71 (28.9)	252 (30.8)	0.581
Urban	742 (69.7)	175 (71.1)	567 (69.2)	
NYHA				
I	229 (21.5)	56 (22.8)	173 (21.1)	
II	579 (54.4)	124 (50.4)	455 (55.6)	0.518
III	220 (20.7)	59 (24.0)	161 (19.7)	
IV	32 (3)	6 (2.4)	26 (3.2)	
Orthopnea	326 (30.6)	87 (35.4)	239 (29.2)	0.070
Paroxysmal nocturnal dyspnea	367 (34.5)	90 (36.6)	277 (33.8)	0.445
Bendopnea	241 (22.6)	64 (26.0)	177 (21.6)	0.164
Palpitation	502 (47.1)	94 (38.2)	408 (49.8)	0.002
Reduced exercise tolerance	879 (82.5)	202 (82.1)	677 (82.7)	0.848
Fatigue, tiredness	678 (63.7)	158 (64.2)	520 (63.5)	0.880
Ankle swelling	352 (33.1)	88 (35.8)	264 (32.2)	0.315
Chest pain	274 (25.7)	73 (29.7)	201 (24.5)	0.114
Syncope	45 (4.2)	9 (3.7)	36 (4.4)	0.720
Dizziness	210 (19.7)	48 (19.5)	162 (19.8)	1.000
Body mass index, kg/m^2	29.04 ± 5.53	28.77 ± 4.77	29.12 ± 5.74	0.332
Systolic blood pressure, mmHg	133.5 ± 20.32	134.29 ± 21.00	133.35 ± 20.12	0.524
Diastolic blood pressure, mmHg	79.01 ± 11.81	80.17 ± 12.37	78.65 ± 11.62	0.077
Heart rate, bpm	82.73 ± 18.11	82.19 ± 18.15	82.89 ± 18.16	0.593
Jugular vein distention	217 (20.4)	50 (20.3)	167 (20.4)	1.000
Cardiac murmur	498 (46.8)	118 (48.0)	380 (46.4)	0.716
Third heart sound	126 (11.8)	38 (15.4)	88 (10.7)	0.055
Peripheral edema	356 (33.4)	91 (37.0)	265 (32.4)	0.190
Pulmonary crepitations	235 (22.1)	51 (20.7)	184 (22.5)	0.600
Tachypnea	144 (13.5)	31 (12.6)	113 (13.8)	0.672
ECG abnormality	616 (57.8)	178 (72.4)	438 (53.5)	< 0.001
Ascites	79 (7.4)	23 (9.3)	56 (6.8)	0.221
Cachexia	35 (3.3)	7 (2.8)	28 (3.4)	0.839
History of hospitalization for HF in the last year	221 (20.8)	69 (28.0)	152 (18.6)	0.002

Data are presented as mean ± standard deviation, or number (%). Categorical variables are compared using the $\chi 2$ test. Continuous variables are compared using the t-test.
Abbreviations: HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association.

calculate odds ratio and 95% confidence interval. The inclusion criteria for variable selection is $p < .10$ in multivariable logistic regression model. Multivariable analysis is performed to find HFpEF and HFmrEF associated factors. Analyses are performed with SPSS system software (version 24.0 or higher).

3. Results

A total of 1065 patients (mean age of 67.1 ± 10.6 years, 54% women) were included. Among participants with HF, 819 (76.9%) had HFpEF and 246 (23.1%) had HFmrEF.

4. Demographic characteristics and comorbidities

Baseline characteristics of the total cohort according to LVEF groups are presented in Table 1. There were no significant differences in age, educational status, place of residence, New York Heart Association functional capacity, heart rate or blood pressure between the two groups. Prevalence of the signs and symptoms at presentation such as ortopnea, paroxysmal nocturnal dyspnea, chest pain, syncope, jugular vein distention, and peripheral edema were also similar between the two groups. However, compared to patients with HFpEF, those with HFmrEF were more likely to be male (57.7 vs 42.2%; p < 0.001), were more frequent smokers (24 vs 15.8%; p = 0.004), and alcohol users (6.9 vs 3.5%; p = 0.031).

HFmrEF patients were more likely to have ECG abnormalities (72.4 vs 53.5%, p < 0.001) and history of hospitalization for HF in the last year (28 vs 18.6%; p = 0.002), but had lower frequency of palpitations (38.2 vs 49.8%; p = 0.002) compared to patients with HFpEF.

Comparison of comorbid diseases are given in Table 2. Atrial fibrillation (38.2 vs 27.6%, p = 0.002) and obstructive sleep apnea (6.7 vs 2.4%, p = 0.011) were more frequent in HFpEF patients compared to HFmrEF patients. However, compared to patients with HFpEF, those with HFmrEF were more likely to have chronic kidney disease (17.9 vs 10.7%, p = 0.003), previous myocardial infarction (48 vs 9.6%, p < 0.001), *coronary artery disease (67.9 vs 33.1%, p < 0.001), coronary artery by-pass grafting (30.5 vs 9.8%, p < 0.001), and percutaneous coronary intervention (34.6 vs 16.2%, p < 0.001)*. There were no significant differences in hypertension, diabetes mellitus, anemia, hyperlipidaemia, *peripheral artery disease, cerebrovascular accident or*

Table 2
Comorbidities.

	Overall (n = 1065)	HFmrEF (n = 246)	HFpEF (n = 819)	p value
Atrial fibrillation	381 (35.8)	68 (27.6)	313 (38.2)	0.002
Hypertension	811 (76.2)	188 (76.4)	623 (76.1)	0.909
Diabetes mellitus	319 (30.0)	75 (30.5)	244 (29.8)	0.835
Anemia	372 (34.9)	87 (35.4)	285 (34.8)	0.870
Chronic kidney disease	132 (12.4)	44 (17.9)	88 (10.7)	0.003
Dialysis	5 (0.5)	3 (1.2)	2 (0.2)	0.084
Obstructive sleep apnea	61 (5.7)	6 (2.4)	55 (6.7)	0.011
Hyperlipidemia	264 (24.8)	71 (28.9)	193 (23.6)	0.092
Previous myocardial infarction	197 (18.5)	118 (48.0)	79 (9.6)	< 0.001
Coronary artery disease	438 (41.1)	167 (67.9)	271 (33.1)	< 0.001
Coronary artery by-pass grafting	155 (14.6)	75 (30.5)	80 (9.8)	< 0.001
Percutaneous coronary intervention	218 (20.5)	85 (34.6)	133 (16.2)	< 0.001
Pacemaker	15 (1.4)	3 (1.2)	12 (1.5)	1.00
Implantable cardioverter defibrillator	2 (0.2)	2 (0.8)	0 (0)	0.053
Cardiac resynchronization therapy	4 (0.4)	1 (0.4)	3 (0.4)	1.00
Peripheral artery disease	28 (2.6)	7 (2.8)	21 (2.6)	0.809
CVA/TIA	70 (6.6)	20 (8.1)	50 (6.1)	0.261
COPD	143 (13.4)	35 (14.2)	108 (13.2)	0.675
Hepatic failure	18 (1.7)	4 (1.6)	14 (1.7)	1.00
Depression	58 (5.7)	14 (5.7)	44 (5.4)	0.847
Malignancy	19 (1.8)	6 (2.4)	13 (1.6)	0.376

Data are presented as number (%). The $\chi 2$ test is used to compare variables.
Abbreviations: *COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident;* HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; *TIA, transient ischaemic attack.*

transient ischaemic attack, chronic obstructive pulmonary disease, hepatic failure, depression, and malignancy between the two groups.

5. Laboratory parameters

There were some differences according to the laboratory parameters in patients with HFmrEF and HFpEF (Table 3). Higher NT-proBNP (853 vs 528 pg/ml, p < 0.001), blood urea nitrogen (18 vs 17 mg/dl, p = 0.002), creatinine (0.9 vs 0.8 mg/dl, p = 0.001), potassium (4.6 vs 4.4 mmol/l, p = 0.004), uric acid (5.8 vs 5.5 mg/dl, p = 0.012) and ferritin (62.7 vs 52 ng/ml, p = 0.029) levels were measured in patients with HFmrEF than HFpEF.

6. Echocardiography

Comparison of echocardiographic parameters are presented in Table 4. Compared to patients with HFpEF, those with HFmrEF had larger LV end-diastolic (51 vs 47 mm, p < 0.001) and LV end-systolic (37.5 vs 32 mm, p < 0.001) dimensions, higher left atrial volume index (35 vs 34 ml/m^2, p = 0.008) and LV mass index (121.7 vs 105.3 g/m^2, p < 0.001), but lower LVEF (45 vs 60%, p < 0.001). There were more patients without mitral regurgitation in the HFpEF group (33 vs 14.2%, p < 0.001), and HFmrEF patients were more likely to have mild (57.3 vs 49.5%, p < 0.001), moderate (27.6 vs 17.2%, p < 0.001) or severe (0.8 vs 0.4%, p < 0.001) mitral regurgitation compared to patients with HFpEF. There were no significant differences in other valvular pathologies and diastolic dysfunction parameters between the two groups.

7. Medication

Comparison of drugs used by HFmrEF and HFpEF patients are given in Table 5. HFmrEF patients were more likely to use β-blockers (69.9 vs 55.2%, p < 0.001), aldosterone receptor antagonists (24 vs 14.7%, p = 0.001), ivabradine (4.1 vs 0%, p < 0.001), statins (37 vs 23%, p < 0.001), loop diuretics (39.8 vs 30.5%, p = 0.006), nitrates (6.9 vs 3.8%, p = 0.038), and antiaggregant drugs (60.6 vs 40.3%, p < 0.001) compared to patients with HFpEF. However, the use of *non-dihydropyridine calcium channel blockers (12.5 vs 6.5%, p = 0.009), dihydropyridine calcium channel blockers (21.9 vs 13.8%, p = 0.006), and anticoagulant drugs (29.3 vs 22.4%, p = 0.033) were higher in patients with HFpEF.* There were no significant differences in other medications between the two groups.

8. Etiology of heart failure

Table 6 shows the etiology of heart failure in two groups. Although *ischemia* was the most common cause of HF in patients with HFmrEF (63.4%), *atrial fibrillation* was the most frequent cause in patients with HFpEF (31.3%). Ischemia (63.4 vs 21.2%, p < 0.001) was more frequent in patients with HFmrEF compared to patients with HFpEF. However, there were more frequent atrial fibrillation (31.3 vs 15.9%, p < 0.001), hypertension (30.0 vs 8.9%, p < .001), and valve diseases (12.8 vs 6.1%, p < 0.001) in etiology of HF in patients with HFpEF compared to patients with HFmrEF.

9. Associated factors with HFmrEF and HFpEF

The univariate analysis of the associated factors with HFmrEF and

Table 3
Laboratory parameters.

	Overall (n = 1065)	HFmrEF (n = 246)	HFpEF (n = 819)	p value
NT-proBNP, pg/ml	620 (270–1172)	853 (420–1612)	528 (248–974)	< 0.001
Fasting blood glucose, mg/dl	105 (94–128)	104 (93–132)	106 (94–127)	0.554
BUN, mg/dl	17 (13.6–22.7)	18 (14.7–25)	17 (13 − 22)	0.002
Serum Creatinine, mg/dl	0.88 (0.70–1.07)	0.9 (0.8–1.1)	0.8 (0.7–1.0)	0.001
Serum Sodium, mmol/l	140 (138–142)	141 (139–142)	140 (138–142)	0.247
Serum Potassium, mmol/l	4.5 (4.2–4.8)	4.6 (4.2–4.9)	4.4 (4.1–4.8)	0.004
Serum Calcium, mg/dl	9.2 (8.9–9.6)	9.2 (8.9–9.5)	9.2 (8.9–9.6)	0.814
Uric acid, mg/dl	5.6 (4.7–6.8)	5.8 (5.0–7.0)	5.5 (4.6–6.7)	0.012
Haemoglobin, g/dl	13.0 (11.8–14.3)	13.2 (11.8–14.5)	13.0 (11.8–14.2)	0.159
Leukocyte, x10^3/μl	7.8 (6.6–9.3)	7.8 (6.8–9.4)	7.8 (6.6–9.2)	0.354
C-reactive protein, mg/dl	3.4 (1.8–7.0)	3.0 (1.8–6.9)	3.5 (1.8–7.0)	0.518
Ferritin, ng/ml	55.0 (26.8–94.8)	62.7 (31.0–101.1)	52.0 (26.1–93.0)	0.029
TSH, μIU/ml	1.4 (0.9–2.3)	1.4 (0.9–2.6)	1.4 (0.9–2.3)	0.675

Data are presented as median and interquartile range. Mann–Whitney U test is used to compare variables.
Abbreviations: BUN, blood urea nitrogen; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; TSH, thyrotropin stimulating hormone.

Table 4
Two-dimensional transthoracic echocardiographic and doppler data.

	Overall (n = 1065)	HFmrEF (n = 246)	HFpEF (n = 819)	p value
LVEF, %	57 (50–60)	45 (40–45)	60 (55–63)	< 0.001
e′, cm/sn	7 (6–8)	7 (6–8.1)	7 (6–8)	0.663
E/e′	9.3 (7.8–12.0)	9.4 (7.7–12.0)	9.2 (7.8–12.0)	0.833
LV diastolic dysfunction				
None	141 (13.2)	37 (15.0)	104 (12.7)	0.658
Grade 1	285 (26.8)	60 (24.4)	225 (27.5)	
Grade 2	408 (38.3)	97 (39.4)	311 (38.0)	
Grade 3	231 (21.7)	52 (21.1)	179 (21.9)	
LVED dimension, mm	48 (45–52)	51 (47–55.2)	47 (44.0–51.0)	< 0.001
LVES dimension, mm	32 (29–37)	37.5 (32.0–43.0)	32 (28.0–35.0)	< 0.001
IVS dimension, mm	11 (10 − 13)	11 (10.0–12.2)	11 (10.0–13.0)	0.522
LVPW dimension, mm	11 (10 − 12)	11 (10.0–11.0)	11 (10.0–12.0)	0.874
LAVI, ml/m^2	34 (29–41)	35 (30.0–43.0)	34 (29.0–40.0)	0.008
LA enlargement	524 (49.2)	132 (53.7)	392 (47.9)	0.111
LVMI, g/m^2	109.5 (90.3–129.5)	121.7 (103.6–138.2)	105.3 (89.1–125.4)	< 0.001
LV concentric hypertrophy	611 (57.4)	169 (68.7)	442 (54.0)	< 0.001
PAPs, mmHg	29 (15–35)	30 (15.0–36.0)	28.1 (15.0–35.0)	0.330
Mitral regurgitation				
None	305 (28.6)	35 (14.2)	270 (33.0)	< 0.001
Mild	546 (51.3)	141 (57.3)	405 (49.5)	
Moderate	209 (19.6)	68 (27.6)	141 (17.2)	
Severe	5 (0.5)	2 (0.8)	3 (0.4)	
Mitral stenosis				
None	1028 (96.5)	240 (97.6)	788 (96.2)	0.440
Mild	25 (2.3)	5 (2.0)	20 (2.4)	
Moderate	12 (1.1)	1 (0.4)	11 (1.3)	
Aortic stenosis				
None	1030 (96.7)	234 (95.1)	796 (97.2)	0.278
Mild	23 (2.2)	8 (3.3)	15 (1.8)	
Moderate	12 (1.1)	4 (1.6)	8 (1.0)	
Aortic regurgitation				
None	807 (75.8)	181 (73.6)	626 (76.4)	0.468
Mild	227 (21.3)	59 (24.0)	168 (20.5)	
Moderate	31 (2.9)	6 (2.4)	25 (3.1)	
Tricuspid regurgitation				
None	386 (36.2)	86 (35.0)	300 (36.6)	0.336
Mild	446 (41.9)	111 (45.1)	335 (40.9)	
Moderate	196 (18.4)	38 (15.4)	158 (19.3)	
Severe	37 (3.5)	11 (4.5)	26 (3.2)	

Data are presented as median and interquartile range or number (%). Categorical variables are compared using the $\chi 2$ test. Continuous variables are compared using the Mann–Whitney U test.
Abbreviations: IVS, interventricular septum; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVED, left ventricular end-diastolic; LVEF, Left ventricle ejection fraction; LVES, left ventricular end-systolic; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; PAPs, pulmonary artery systolic pressure.

HFpEF are shown in Fig. 1. Multivariable logistic regression analysis for the likelihood of having HFmrEF and HFpEF are shown in Table 7**.** After multivariable adjustment; presence of coronary artery disease (adjusted odds ratio [OR] 3.222, 95% confidence interval [CI] 2.136–4.861, p < 0.001), mitral regurgitation (OR 3.188, 95% CI 2.021–5.029, p < 0.001), chronic kidney disease (OR 1.345, 95% CI 1.124–2.313, p = 0.021), absence of atrial fibrillation (OR 2.045, 95% CI 1.180–3.545, p = 0.011), alcohol use (OR 2.287, 95% CI 1.080–4.843, p = 0.031), having higher NT-proBNP levels (OR 2.681, 95% CI 1.730–4.157, p < 0.001) and having abnormalities on ECG (OR 2.451, 95% CI 1.659–3.621, p < 0.001) were associated with HFmrEF. The use of aldosterone receptor antagonists (OR 1.744, 95% CI 1.131–2.690, p = 0.012) was also associated with HFmrEF. However, female sex (OR 1.555, 95% CI 1.124–2.150, p = 0.008), presence of atrial fibrillation (OR 1.468, 95% CI 1.051–2.051, p = 0.024), obstructive sleep apnea (OR 3.237, 95% CI 1.357–7.723, p = 0.008) and use of calcium channel blockers (OR 1.843, 95% CI 1.282–2.649, p = 0.001) were associated with HFpEF.

Among all clinical and laboratory parameters; coronary artery disease had the highest odds ratio for HFmrEF and obstructive sleep apnea had the highest odds ratio for HFpEF **(**Fig. 2**).**

Table 5
Medications.

	Overall (n = 1065)	HFmrEF (n = 246)	HFpEF (n = 819)	p value
Angiotensin-converting enzyme inhibitor	354 (33.2)	89 (36.2)	265 (32.4)	0.264
Angiotensin receptor blocker	292 (27.4)	64 (26.0)	228 (27.8)	0.574
Beta-blocker	624 (58.6)	172 (69.9)	452 (55.2)	< 0.001
Aldosterone antagonists	179 (16.8)	59 (24.0)	120 (14.7)	0.001
Ivabradine	10 (0.9)	10 (4.1)	0 (0)	< 0.001
Amiodarone	20 (1.9)	6 (2.4)	14 (1.7)	0.430
Propafenone	3 (0.3)	1 (0.4)	2 (0.2)	0.546
Nondihydropyridine calcium blockers	118 (11.1)	16 (6.5)	102 (12.5)	0.009
Dihydropyridine calcium blockers	213 (20.0)	34 (13.8)	179 (21.9)	0.006
Digoxin	68 (6.4)	18 (7.3)	50 (6.1)	0.495
Statin	279 (26.2)	91 (37.0)	188 (23.0)	< 0.001
Loop diuretic	348 (32.7)	98 (39.8)	250 (30.5)	0.006
Thiazide	318 (29.9)	78 (31.7)	240 (29.3)	0.470
Isosorbide	48 (4.5)	17 (6.9)	31 (3.8)	0.038
Antiaggregant	479 (45.0)	149 (60.6)	330 (40.3)	< 0.001
Anticoagulant	295 (27.7)	55 (22.4)	240 (29.3)	0.033
Nonsteroidal anti-inflammatory drug	78 (7.3)	23 (9.3)	55 (6.7)	0.164
Oral antihyperglysemic	246 (23.1)	57 (23.2)	189 (23.1)	0.976
Insulin	87 (8.2)	26 (10.6)	61 (7.4)	0.117

Data are presented as number (%). The $\chi 2$ test is used to compare variables.
Abbreviations: HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Table 6
Etiology of heart failure.

	Overall (n = 1065)	HFmrEF (n = 246)	HFpEF (n = 819)	p value
Ischemic	330 (31.0)	156 (63.4)	174 (21.2)	< 0.001
Atrial fibrillation	295 (27.7)	39 (15.9)	256 (31.3)	
Hypertension	268 (25.2)	22 (8.9)	246 (30.0)	
Valve disease	120 (11.3)	15 (6.1)	105 (12.8)	
Other	52 (4.9)	14 (5.7)	38 (4.6)	

Data are presented as number (%). The $\chi 2$ test is used to compare variables.
Abbreviations: HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

10. Discussion

APOLLON is a multicenter study first to provide data on the demographic and clinical characteristics and medication profile of patients with HFmrEF and HFpEF in our country. Our study have shown that nearly one-fourth of the patients with signs and symptoms of HF, LVEF ≥40% and increased natriuretic peptide levels had HFmrEF. APOLLON study also revealed that the patients with HFmrEF and HFpEF are younger than the patients in western countries.

HFpEF, which currently represents approximately 50% of HF cases, is common and associated with high morbidity and mortality [9].

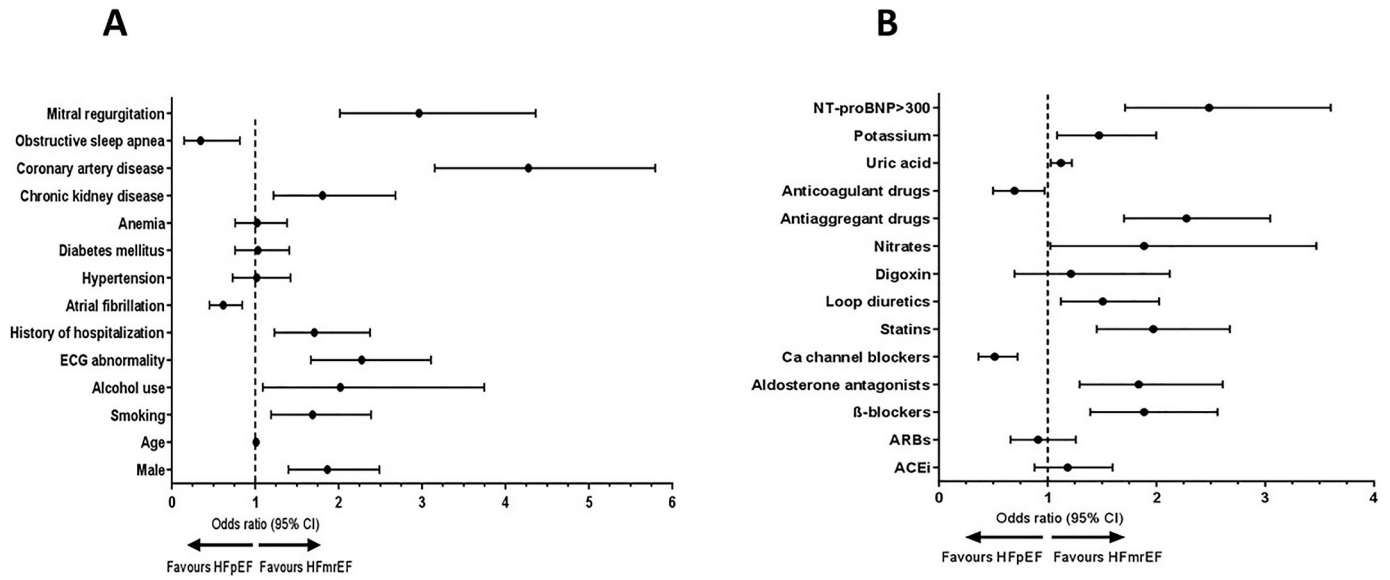

Fig. 1. Forest plots of unadjusted odds ratios for heart failure with preserved ejection fraction vs. heart failure with mid-range ejection fraction. Baseline characteristics and comorbid features (A), medications and laboratory data (B). ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 7
Associated factors for heart failure with mid-range ejection fraction and preserved ejection fraction.

For HFmrEF			
	Odds Ratio	95% CI	p value
Alcohol use	2.287	1.080–4.843	0.031
ECG abnormality	2.451	1.659–3.621	< 0.001
Coronary artery disease	3.222	2.136–4.861	< 0.001
Mitral regurgitation	3.188	2.021–5.029	< 0.001
Absence of atrial fibrillation	2.045	1.180–3.545	0.011
Chronic kidney disease	1.345	1.124–2.313	0.021
NT-proBNP, > 300 pg/ml	2.681	1.730–4.157	< 0.001
Aldosterone antagonists	1.744	1.131–2.690	0.012

For HFpEF			
	Odds Ratio	95% CI	p value
Female sex	1.555	1.124–2.150	0.008
Atrial fibrillation	1.468	1.051–2.051	0.024
Obstructive sleep apnea	3.237	1.357–7.723	0.008
Lower serum ferritin	1.000	0.998–1.002	0.840
Calcium channel blockers	1.843	1.282–2.649	0.001

Multivariable logistic regression analysis is used to obtain the odds ratios.
Abbreviations: CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction, NT-proBNP, N-terminal pro B-type natriuretic peptide.

Previous studies have shown that patients with HFpEF are predominantly elderly, more likely to be female, and have a high prevalence of comorbidities such as hypertension, coronary artery disease, diabetes mellitus, atrial.

fibrillation, obesity, anemia, and chronic kidney disease [10–12]. Although the morbidity and mortality associated with HFpEF is similar to HFrEF [13] and survival in HFrEF has significantly improved over the past decades, prognosis of patients with HFpEF has not shown any significant change within the same time period despite the use of similar drugs [14].

A new category of HF, heart failure with borderline ejection fraction was defined in 2016 ESC guidelines as the presence of the typical symptoms of HF and a LVEF of 40% to 49% [4]. Although HFmrEF is less well studied compared with HFpEF and HFrEF, its prevalence is thought to be between from 13 to 24% of the HF population [15,16]. The HFmrEF patient profile is similar in certain features typically seen in HFrEF with other features found in HFpEF [17,18]. The ESC HF Long-Term (ESC-HF-LT) Registry have revealed that HFmrEF group resembled the HFrEF group in some features, including age, gender and ischemic etiology, but had less left ventricular and atrial dilation [19]. Ischemic heart diseases appears to be a common etiology in HFmrEF, occurring in > 40% of the population in several other cohorts [15,20] which resembles to HFrEF and higher than the HFpEF. However, prevalence of atrial fibrillation was estimated to be 60%, intermediate between HFpEF (65%) and HFrEF (53%) [21]. Prevalence of atrial fibrillation was 27.6% in HFmrEF and 38.2% in HFpEF patients in our study. We also showed that patients with HFmrEF were more likely to have *coronary artery disease (67.9* vs *33.1%)* compared to patients with HFpEF. Results of our study revealed that that clinical manifestations of HFpEF are the same as those for HFmrEF. Subjects with HFpEF had a similar symptomatic profile compared with subjects with HFmrEF in respect to edema, paroxysmal nocturnal dyspnea, third heart sound, jugular venous distention, pulmonary rales, heart rate, and prevalence of New York Heart Association class III or IV symptoms, fatigue, elevated jugular venous pressure, and pulmonary rales. However, HFpEF patients were more likely to have palpitations compared to patients with HFmrEF, which may be explained by the higher prevalence atrial fibrillation in HFpEF patients.

Participant physcians were asked an open-ended question about the etiology of HF in our study. Ischemic heart diseases were the most common cause of HF in patients with HFmrEF (63.4%) followed by the atrial fibrillation (15.9%). Atrial fibrillation was the most frequent cause of HF in patients with HFpEF (31.3%) followed by hypertension (30%). There is much overlap between comorbidities, and a direct causal relationship between one and the other and HFpEF or HFmrEF has not been established. Although hypertension is a comorbidity in most of the HFpEF patients, the reason of HF may be ischemic heart diseases or valvular diseases. For example; Abebe and colleagues retrospectively assessed medical transcript of 311 patients who had been admitted with a diagnosis of HF [22]. From the study group, 164 patients had HFpEF and the remaining participants had HFrEF. Of the HFpEF patients 34% had hypertension but hypertension had been reported as the cause of HF only in %20 of the HFpEF patients. In our

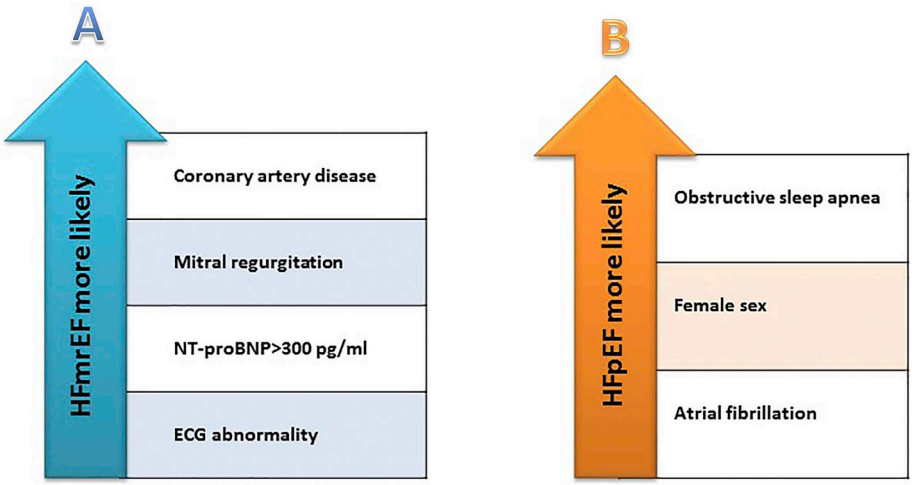

Fig. 2. Associated factors with heart failure with mid-range ejection fraction (A) and heart failure with preserved ejection fraction (B). HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

study population, nearly 76% of the HFpEF and HFmrEF patients had hypertension but the attending physicians had reported hypertension as the cause of HF in 30% of the HFpEF patients and 8.9% of the HFmrEF patients.

Another interesting finding of our study was the prevalence of valvular heart disease as a comorbidity and cause of HF. As shown in Table 4, the only significantly different form of valve disease was mitral regurgitation in HFmrEF and HFpEF patients. HFmrEF patients had more likely to have mitral regurgitation and they also had increased severity of mitral regurgitation compared to patients with HFpEF. However, there were more frequent valve diseases (12.8 vs 6.1%, $p < 0.001$) in etiology of HF in patients with HFpEF compared to patients with HFmrEF. This discrepancy may be explained by higher prevalence of the ischemic mitral regurgitaion in patients with HFmrEF; they had more and severe mitral regurgitation but the valvular disease was not the reason of HF in most of the patients.

Role of biomarkers in HFmrEF is not well established but recent studies suggest that their prognostic impact may be weakened in HFmrEF compared with HFrEF [23]. Tromp et al. recently analysed a biomarker profile for patients with acute decompensated.

HF. They found that the biomarker profile in patients with acute HFrEF was mainly related to cardiac stretch, that acute HFpEF was related to inflammation, and that patients with acute HFmrEF showed an intermediate biomarker profile between those of HFrEF and HFpEF [24].

In our study; higher NT-proBNP, blood urea nitrogen, creatinine, potassium, and uric acid levels may be explained with lower LVEF and increased prevalance of chronic renal diseases in HFmrEF patients compared to patients with HFpEF. Serum levels of the C-reactive protein is a sensitive indicator of inflammation and strongly associated with future risk of coronary heart disease [25]. However, our study did not reveal any differences in C-reactive protein levels between the two groups, although coronary artery disease was more prominent in HFmrEF.

One of the most important results of our study is younger age of both HFmrEF and HFpEF patients compared with developed countries. In our study, the mean age of the patients was 67 years (range 31–95) whereas in the Swedish Heart Failure Registry the mean age of the patients was 75 years (range 17–103 years) [26]. OPTIMIZE-HF registry was enrolled patients with ≥18 years of age and found that the mean age of the patients was 74.3 years in HFmrEF and 75.6 years in with HFpEF [27].

Mortality and morbidity in HFmrEF appear to be in between HFrEF and HFpEF. In OPTIMIZE-HF study, the mortality rates were 3.9% for patients with HFrEF, 3.0% for HFmrEF, and 2.9% for HFpEF [28]. Data from GWTG-HF trial also found that patients with HFmrEF had 30-day mortality rates (8.2%) that were intermediate between those in the HFpEF (8.5%) and HFrEF (9.5%) groups [17]. However, whether patients with HFmrEF may benefit from targeted therapies known to be beneficial in patients with HFrEF, is unknown [27]. The central feature of therapy in patients with HFpEF and HFmrEF is managing comorbidities and risk factors. The medical management of these patients include neurohormonal blockade with beta-adrenergic receptor blockers and inhibitors of the renin-angiotensin-aldosterone system. Diuretic therapy is also recommended to help alleviate symptoms in patients with congestion [29,30]. However, APOLLON study revealed angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, aldosterone antagonists, diuretics and statins are underused by clinicians to treat HF in real-world practice compared to developed world. For example, 84% of the HFmrEF patients and 72% of the HFpEF patients were treated with angiotensin receptor blockers or angiotensin-converting enzyme inhibitors in the Swedish Heart Failure Registry [26]. Whereas, 62.2% of the HFmrEF patients and 60.2% of the HFpEF patients were treated with these drugs in our study, respectively.

11. Limitations

The main limitations of the study are its observational nature and lack of follow-up data. We assessed the associations between baseline characteristics and baseline LVEF group, but we cannot demonstrate causality. The limitation of the “clinician-judged HF” diagnosis in the.

APOLLON Registry is also acknowledged. Our study results can not answer whether HFmrEF is a different disease than the HFpEF or it is a different stage of the same disease, as we did not include patients with HFrEF in APOLLON study.

12. Conclusions

Although APOLLON study is an observational study without information on prognosis, the results of this study provide a real-world analysis of a large unselected population of HF patients with mid-range and preserved left ventricular function. The main etiology of HFmrEF was coronary artery disease, whereas the main etiology of HFpEF was atrial fibrillation and hypertension in Turkey. Our study revealed that HFmrEF and HFpEF is now occurring increasingly in younger age groups but treated less aggressively in Turkey when compared with western countries. The current study data underscore the necessity of

large prospective studies evaluating HFmrEF and HFpEF in Turkey.

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Declaration of conflict of interest

All the authors declare no conflict of interest.

Acknowledgments

None

References

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr. DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013 Oct 15;128(16):1810–52.
[2] Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011 May 10;123(18):2006–13. [discussion 2014].
[3] JJ McMurray, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart failure Association (HFA) of the ESC. Eur Heart J 2012;33(14):1787–847.
[4] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 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 FailureAssociation (HFA) of the ESC. Eur Heart J 2016;37(27):2129–200.
[5] Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008 Feb;29(3):339–47.
[6] Farré N, Lupon J, Roig E, Gonzalez-Costello J, Vila J, Perez S, et al. Clinical characteristics, one-year change in ejection fraction and long-term outcomes in patients with heart failure with mid-range ejection fraction: a multicentre prospective observational study in Catalonia (Spain). BMJ Open 2017 Dec 21;7(12):e018719.
[7] Özlek B, Özlek E, Çelik O, Çil C, Doğan V, Tekinalp M, et al. Rationale, Design, and Methodology of the APOLLON trial: a comPrehensive, ObservationaL registry of heart faiLure with midrange and preserved ejectiON fraction. Anatol J Cardiol 2018 May;19(5):311–8.
[8] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999 Mar 16;130(6):461–70.
[9] Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep 2013 Dec;10(4):401–10.
[10] Georgiopoulou VV, Velayati A, Burkman G, Li S, Farooq K, Samman-Tahhan A, et al. Comorbidities, sociodemographic factors, and hospitalizations in outpatients with heart failure and preserved ejection fraction. Am J Cardiol 2018 May 15;121(10):1207–13.
[11] Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the national heart, lung, and blood institute. Circulation 2009 Jun 23;119(24):3070–7.
[12] Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B, et al. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circ Heart Fail 2013 Mar;6(2):184–92.
[13] Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008 Feb;29(3):339–47.
[14] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006 Jul 20;355(3):251–9.
[15] 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 Jun;4(6):464–72.
[16] Lauritsen J, Gustafsson F, Abdulla J. Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Fail 2018 Apr 16. https://doi.org/10.1002/ehf2.12283.
[17] Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. Am Heart J 2014 Nov;168(5):721–30.
[18] Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Ponikowski P, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail 2017 Dec;19(12):1569–73.
[19] Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. Heart failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016 Jun;18(6):613–25.
[20] 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 Dec;19(12):1586–96.
[21] Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. JACC Heart Fail 2017 Aug;5(8):565–74.
[22] Abebe TB, Gebreyohannes EA, Tefera YG, Abegaz TM. Patients with HFpEF and HFrEF have different clinical characteristics but similar prognosis: a retrospective cohort study. BMC Cardiovasc Disord 2016 Nov 21;16(1):232.
[23] Hamatani Y, Nagai T, Shiraishi Y, Kohsaka S, Nakai M, Nishimura K, et al. Investigators for the WET-NaDEF Collaboration Project. Long-Term Prognostic significance of Plasma B-Type Natriuretic Peptide Level in patients with Acute Heart failure with Reduced, Mid-Range, and Preserved Ejection Fractions. Am J Cardiol 2018 Mar 15;121(6):731–8.
[24] Tromp J, Khan MA, Klip IT1, Meyer S, de Boer RA, Jaarsma T, et al. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. J Am Heart Assoc 2017 Mar 30;6(4):e003989. https://doi.org/10.1161/JAHA.116.003989.
[25] Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999 Jan 19;99(2):237–42.
[26] Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017 Dec;19(12):1624–34.
[27] Hsu JJ, Ziaeian B, Fonarow GC. Heart failure with Mid-Range (Borderline) Ejection Fraction. Clin Impl Future Direct JACC Heart Fail 2017 Nov;5(11):763–71.
[28] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. OPTIMIZE-HF investigators and hospitals. 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 Aug 21;50(8):768–77.
[29] Nativi-Nicolau J, Ryan JJ, Fang JC. Current therapeutic approach in heart failure with preserved ejection fraction. Heart Fail Clin 2014 Jul;10(3):525–38.
[30] Komajda M, Lam CS. Heart failure with preserved ejection fraction: a clinical dilemma. Eur Heart J 2014 Apr;35(16):1022–32.