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Do patients with heart failure and preserved, mid-range or reduced ejection fraction have different outcomes?

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SOUHRN

Kontext: Terminologie používaná v souvislosti se srdečním selháním (heart failure, HF) je podle doporučených postupů Evropské kardiologické společnosti z roku 2016 (2016 European Society of Cardiology Guidelines) založena na naměřených hodnotách ejekční frakce levé komory srdeční (EF LK) s následující klasifikací: ≥ 50 %, HF se zachovanou ejekční frakcí (HF with preserved EF, HFpEF), < 40 %, HF se sníženou ejekční frakcí (HF with reduced EF, HFrEF) a 40–49 %, HF s ejekční frakcí ve středním pásmu (HF with mid-range EF, HFmrEF). Prognóza pacientů s HFpEF a HFmrEF se zatím stanovuje poměrně obtížně.
Cíl: Cílem tohoto článku je popsat etiologii, rizikové faktory, klinické a echokardiografické charakteristiky a prognózu pacientů s HFpEF, HFmrEF a HFrEF v Bulharsku.
Metody: V naší observační studii byly všechny údaje pacientů získány z naší nemocniční databáze. Ve studii se hodnotily údaje 890 pacientů přijatých na kliniku kardiologie v období 2012 až 2014 pro dekompenzované chronické srdeční selhání.
Výsledky: Parametry sledovanými u hodnocených skupin pacientů s HFpEF (609; 68,4 %), HFmrEF (145; 16,3 %) a HFrEF (136; 15,3 %) byly mortalita z jakýchkoli příčin a rehospitalizace. Během sledování v délce 5,8 ± 1,5 roku dosáhla mortalita hodnot 34,6 % v případě HFpEF, 55,9 % u HFmrEF a 61,8 % u pacientů s HFrEF. Po adjustaci byla mortalita významně vyšší u HFrEF a HFmrEF oproti HFpEF (HR 3,67; 95% CI 1,74–5,56; $p < 0,01$ v případě HFrEF a HR 2,96; 95% CI 1,48–4,76; $p < 0,01$ u HFmrEF). Podle našich údajů došlo po druhém roce sledování u pacientů s HFrEF ke statisticky nevýznamnému zkrácení přežití ve srovnání s pacienty s HFmrEF (HR 1,72; 95% CI 1,49–2,48; $p = 0,12$). V období s mediánem 1,2 roku bylo znovu hospitalizováno 22,3 % pacientů s HFpEF, 33,1 % s HFmrEF a 33,7 % pacientů s HFrEF. U pacientů s HFrEF i HFmrEF bylo zjištěno významně vyšší riziko opakovaného příjmu pro dekompenzované HF než u pacientů s HFpEF (HR 1,67; 95% CI 1,20–2,35; $p < 0,01$ u HFrEF, a HR 1,58; 95% CI 1,12–2,22; $p < 0,01$ u HFmrEF). Riziko rehospitalizace bylo u pacientů s HFrEF a HFmrEF podobné (HR 1,03; 95% CI 0,93–1,08; $p = 0,65$). Analýza ROC určila jako mezní hodnotu EF 50 %, protože EF LK < 50 % byla spojena s vyšší mortalitou i vyššími počty opakovaných hospitalizací u všech hodnocených skupin jedinců s HF (AUC 0,67; senzitivita 65 %; specificita 72 %; $p < 0,01$).
Závěr: Naše údaje prokázaly příznivější prognózu pacientů s HFpEF než u pacientů s HFmrEF a HFrEF. Hodnoty úmrtí a opakovaných hospitalizací byly nicméně u pacientů s HF < 50 % podobné; to znamená, že HFmrEF může představovat časné stadium HFrEF a pro pacienty s HFmrEF mohou být přínosné stejné strategie léčby jako u pacientů s HFrEF.

ABSTRACT

Introduction: The therapeutic strategies and prognosis in heart failure with reduced ejection fraction (HFrEF) are well established. However, the prognosis of HF patients with preserved EF (HFpEF) and HF with mid-range EF (HFmrEF) remains not well understood.
Purpose: To investigate the risk factors, clinical and echocardiographic characteristics and prognosis of Bulgarian patients with HFpEF, HFmrEF, and HFrEF.
Methods: In this observational study 890 patients were included. All of them were admitted to our Cardiology department between the years 2012 and 2014 for decompensated chronic HF.
Results: The patients with HFpEF (609, 68.4%), HFmrEF (145, 16.3%), and HFrEF (136, 15.3%) were followed up for all-cause mortality and rehospitalizations. The adjusted 5.8 years mortality rate was significantly higher in HFrEF (61.8%) and HFmrEF (55.9%) versus HFpEF (34.6%). After the second year of follow-up the HFrEF patients had a non-significantly reduced survival versus HFmrEF ones. Over a period of 1.2 year the HFrEF and HFmrEF patients had significantly higher risk of readmissions due to decompensated HF (33.7%

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and 33.1%, respectively) in comparison to HFpEF patients (22.3%). The risk of rehospitalizations was similar for HFrEF and HFmrEF. The ROC-analysis showed that LVEF <50% was associated with higher mortality and rehospitalization rates among all studied HF patients.
Conclusion: Our HFpEF patients had better prognosis than those with HFmrEF and HFrEF. The mortality and rehospitalization rates were similar in HF patients with EF below 50%. HFmrEF may represent an early stage of HFrEF and HFmrEF patients may benefit from the same therapies used for HFrEF.

Background

The European Society of Cardiology (ESC) Guidelines categorize patients with heart failure (HF) by left ventricular ejection fraction (LVEF) to either preserved EF (≥50%, HFpEF), mid-range EF (40–49%, HFmrEF), or reduced EF (<40%, HFrEF) with the efficacy of evidence-based therapies varying by EF grouping.[1] As the population continues to age, a thorough understanding of clinical characteristics, risk factors, comorbidities and predictors of long-term outcomes of patients with different types HF will be a crucial step in the investigation and development of strategies to reduce the burden of HF morbidity and mortality.[2–7]

The attention on HFpEF has increased in the years, with more studies and larger trials being focused on this group of patients, but there is still no effective evidence-based therapy.[8–10]

Patients with HFpEF represent approximately 50% of all hospital admissions for HF. Although some studies have suggested that HFpEF patients have a substantially better prognosis compared to those with HFrEF, others have suggested that the mortality and hospitalization rates are similar.[11–17]

HFmrEF is defined as "grey" area because this group has been poorly characterized and the data on the prognosis of this type of patients are scarce.[18–26] The most therapeutic evidence has been accumulated in group with HFrEF only, including effective pharmacological and device therapies that have led to significant improvements in survival.[1]

Aim

Our manuscript aims to investigate the etiology, risk factors, clinical and echocardiographic characteristics and prognosis of Bulgarian patients with HFpEF, HFmrEF and HFrEF.

Materials and methods

We performed an observational study. All patients' data were obtained from our Cardiology department database. The study population included 886 patients admitted to our department between the years 2012 and 2014 for decompensated chronic HF. The HF patients were stratified by EF into one of three groups: HFrEF, HFmrEF, and HFpEF based on the 2016 ESC Guidelines for diagnosis and treatment of acute and chronic HF.[1] We compared the main characteristics of these three groups, such as demographics, etiology of HF, comorbidities, laboratory data, treatment (including medications), and echocardiographic parameters. The collected data of all subjects were analyzed from the moment of their first visit at our department, regardless of the time of HF diagnosis.

Complete echocardiographic investigation (including left ventricular dimensions and ejection fraction, left atrial dimensions, pulmonary artery systolic pressure) was obtained by experienced sonographer. The echocardiographic equipment Phillips iE33 was used for all measurements. LV images in each systolic and diastolic phase were acquired and recorded as four-chamber and two-chamber images from the transapical view. LVEF was calculated according to the modified Simpson method, with manual tracing of the LV endocardial border.

Definition of comorbidities

Arterial hypertension (HTN) was defined by systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, physician-documented history of HTN, or current use of antihypertensive medications according to the Guidelines recommendations.[27] Diabetes mellitus (DM) was defined by the presence of physician-documented history of DM or the use of oral hypoglycemic agents or insulin for the treatment of hyperglycemia. The valvular heart diseases (VHD, mitral or aortic) were assessed according to the Guidelines recommendations.[28] Coronary artery disease (CAD) was defined by the presence of physician-documented history of CAD, known coronary stenosis >50%, history of myocardial infarction (MI), percutaneous intervention or coronary artery bypass grafting. Chronic kidney disease (CKD) was divided into the stages according to National Kidney Foundation (NKF).[29]

Informed consent forms were signed by all patients prior to their enrolment and an approval of the study was obtained from the local Ethics Committee, ethical code number 244A/20.09.2017. The investigation was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Statistical analyses were performed using the SPSS version 22.0. Continuous variables were expressed as mean values ± standard deviation and the normality of their distribution was assessed by Shapiro–Wilk test. Categorical variables were presented as percentages and compared by Chi-square tests. Kaplan0ľMeier survival curves were constructed for mortality and log-rank tests were used to compare the survival curves of the three groups. Cox proportional hazard regression analysis was performed to assess the probability of re-hospitalizations in the studied HF groups. The results were considered to be statistically significant at p-value <0.05.

Table 1 – Clinical characteristics of patients with HF stratified by the ejection fraction

	HFpEF n (%)	HFmrEF n (%)	HFrEF n (%)	*p*-value
Age (years)	67.3 ± 11.3	68.2 ± 11.7	68.6 ± 10.6	0.160
Female	341 (56.0%)	57 (39.3%)	55 (40.4%)	< 0.001
Arterial hypertension (HTN)	586 (96.2%)	130 (89.7%)	121 (88.9%)	< 0.01
Diabetes mellitus (DM) type 2	141 (23.2%)	51 (35.2%)	47 (34.6%)	< 0.05
Valvular heart disease (VHD)	162 (26.6%)	58 (40.0%)	54 (39.7%)	< 0.01
Coronary artery disease (CAD)	256 (42.1%)	76 (52.4%)	81 (59.6%)	< 0.001
Carotid vascular disease	115 (18.8%)	20 (13.8%)	21 (15.4%)	0.256
Peripheral artery disease (PAD)	86 (9.19%)	17 (11.7%)	25 (18.4%)	< 0.05
Cerebrovascular disease (CVD)	111 (18.2%)	28 (19.3%)	25 (18.4%)	0.634
Atrial fibrillation (AF)	337 (55.3%)	102 (70.3%)	91 (66.9%)	< 0.001
Thyroid gland diseases	103 (16.9%)	18 (12.4%)	18 (12.4%)	0.388
Chronic obstructive pulmonary disease (COPD)	104 (17.1%)	25 (17.5%)	24 (17.6%)	0.857
Anemia	221 (36.3%)	47 (32.4%)	55 (41.2%)	< 0.001
GFR (ml/min/1.73 m^2)	75.8 ± 25.8	75.2 ± 27.9	66.2 ± 29.9	< 0.001

GFR – glomerular filtration rate.

Table 2 – Data of echocardiography in the three studied HF groups

	HFpEF mean ± SD	HFmrEF mean ± SD	HFpEF mean ± SD	*p*-value
EF (%)	62.2 ± 6.2	45.7 ± 3.2	32.4 ± 5.3	< 0.001
LA parasternal diameter (mm)	45.3 ± 4.5	48.9 ± 10.1	49.0 ± 4.8	< 0.001
LA apical diameter (mm)	47.3 ± 4.3	48.7 ± 7.7	50.0 ± 5.3	< 0.001
LA apical length (mm)	54.1 ± 6.3	59.3 ± 9.9	58.8 ± 6.9	< 0.001
Pulmonary artery systolic pressure (PASP, mmHg)	42.5 ± 10.7	45.9 ± 12.7	48.7 ± 10.9	< 0.001
End-diastolic volume (EDV, ml)	116.9 ± 36.9	146.3 ± 46.8	186.2 ± 56.4	< 0.001
End-systolic volume (ESV, ml)	44.5 ± 19.1	77.1 ± 28.7	127.7 ± 53.2	< 0.01
End-diastolic diameter (EDD, mm)	49.2 ± 5.6	54.3 ± 8.3	60.8 ± 9.9	< 0.02
End-systolic diameter (ESD, mm)	31.5 ± 4.7	39.0 ± 6.9	47.9 ± 11.9	< 0.001
Right ventricle (RV, mm)	28.4 ± 5.6	32.7 ± 5.4	32.3 ± 5.8	0.356

EF – ejection fraction; HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; LA – left atrium; SD – standard deviation.

Results

The number of patients in different subgroups was as follows: 609 patients (68.8%) had HFpEF, 145 (16.3%) HFmrEF, and 136 patients (15.3%) had HFrEF. The comparison of the clinical characteristics between these three HF groups is shown in Table 1. The mean age of patients was similar in HFpEF (67.3 ± 11.3 years), HFmrEF (68.2 ± 11.7 years) and HFrEF (68.6 ± 10.6 years). The proportion of females was higher among HFpEF population (56.0%), as compared to HFmrEF (39.3%) and HFrEF (40.4%).

Examination of the distribution of HF etiology showed that patients with HFpEF exhibited significantly higher rate of arterial hypertension (96.2%, $p < 0.01$), while HFmrEF and HFrEF patients had rather higher rate of diabetes mellitus type 2 ($p < 0.05$). Interestingly, the prevalence of atrial fibrillation (AF) was found to be significantly higher in patients with HFmrEF than in those with HFpEF or HFrEF ($p < 0.001$). In HFrEF group the rates of coronary artery disease and peripheral artery disease (PAD) were significantly higher than in HFmrEF and HFpEF groups (for CAD: 59.6% vs. 52.4% and 42.1%, $p < 0.001$; for PAD: 18.4% vs. 11.7% and 9.19%, respectively, $p < 0.05$).

Patients with HFrEF had higher frequency of anemia then those with HFpEF and HFmrEF (41.2% vs. 36.3% and 32.4%, accordingly, $p < 0.001$). HFrEF patients had also significantly worse renal function than patients with HFpEF and HFmrEF ($p < 0.001$).

The evaluated echocardiographic characteristics of our patients are presented in Table 2 and the medications at discharge in Table 3.

Table 3 – Therapy at discharge of the HFpEF, HFmrEF, and HFrEF patients

	HFpEF n (%)	HFmrEF n (%)	HFrEF n (%)	*p*-value
Diuretics	497 (81.6%)	126 (88.1%)	122 (89.7%)	< 0.001
Beta-blockers	424 (69.0%)	100 (70.4%)	110 (80.9%)	< 0.001
ACE inhibitors	217 (35.6%)	53 (37.1%)	51 (37.5%)	0.215
ARBs	210 (34.5%)	34 (23.8%)	34 (25.0%)	< 0.01
MRA	54 (8.9%)	31 (21.7%)	51 (37.5%)	< 0.05
Anticoagulant	225 (66.7%)	76 (74.5%)	61 (67.0%)	< 0.05
Antiplatelet drug	259 (42.5%)	58 (40.0%)	47 (34.6%)	< 0.05
Antiarrhythmic therapy	173 (51.3%)	27 (26.5%)	53 (58.2%)	< 0.001
Rate control therapy	167 (48.7%)	75 (73.5%)	38 (41.8%)	< 0.05

ACE – angiotensin-converting enzyme; ARBs – angiotensin II receptor blockers; HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; MRA – mineralocorticoid-receptor antagonists.

Table 4 – Mortality in HFpEF, HFmrEF, and HFrEF groups after adjustment for age, sex, CVD, NYHA class and risk factors

All-cause mortality	HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
HFpEF	1.621 (1.352–2.154)	1.591 (1.245–2.034)	1.625 (1.203–2.225)
HFmrEF	2.251 (0.092–0.686)	2.061 (1.683–2.525)	2.146 (0.091–0.666)
HFrEF	3.167 (2.132–3.522)	2.773 (1.595–2.975)	2.841 (1.660–3.218)
Age		1.178 (0.959–1.446)	1.102 (0.891–1.362)
Female gender		1.038 (1.027–1.048)	1.032 (1.021–1.044)
Arterial hypertension			1.891 (1.218–2.286)
Diabetes mellitus			1.850 (1.067–2.677)
Coronary artery disease			1.458 (0.981–1.913)
Cerebrovascular disease			1.400 (0.988–1.811)
NYHA FC			1.579 (1.303–2.106)
Atrial fibrillation			1.680 (1.112–2.122)

CI – confidence interval; HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; HR – hazard ratio; NYHA FC – New York Heart Association Functional Classification.

Over a median follow-up of 5.8 ± 1.5 years the mortality rate among HFpEF patients was found to be 34.6%, whereas in HFmrEF group 55.9% and in HFrEF 61.8%. The adjusted mortality was significantly higher in both HFrEF and HFmrEF versus HFpEF (for HFrEF: HR 3.67; 95% CI 1.74–5.56; $p< 0.01$ and for HFmrEF: HR 2.96; 95% CI 1.48–4.76; $p< 0.01$).

After the second year of follow-up the HFrEF patients had a non-significantly reduced survival as compared to those with HFmrEF (HR 1.72; 95% CI 1.49–2.48; $p = 0.12$) (Fig. 1).

In the Cox proportional hazards model, including age and gender, patients with HFpEF and HFmrEF had lower mortality than those with HFrEF (Model 1). When age, gender, history of hypertension and diabetes, ischemic etiology, NYHA class, AF and CVD were included, patients with HFpEF and HFmrEF remained at lower risk of death from any cause compared to those with HFrEF (Table 4, Model 2).

The rehospitalization rate for median period of 1.2 year was 22.3% for HFpEF, 33.1% for HFmrEF and 33.7% for HFrEF. The patients with HFrEF and HFmrEF had a significantly higher risk of readmissions for decompensated HF in comparison to HFpEF ones (for HFrEF: HR 1.67; 95% CI 1.20–2.35; $p< 0.01$ and for HFmrEF: HR 1.58; 95% CI 1.12–2.22; $p< 0.01$). The risk of rehospitalizations was similar for HFrEF and HFmrEF patients (HR 1.03; 95% CI: 0.93–1.08; $p = 0.65$) (Fig. 2).

The composite of mortality/readmission rates during the follow-up period was 46.6% for HFpEF, 57.2% for HFmrEF, and 63.2% for HFrEF patients. The risk of this composite end-point was significantly higher in HFrEF (HR 2.49; 95% CI 1.14–1.87; $p< 0.01$) and HFmrEF (HR 1.57; 95% CI 1.23–2.00; $p< 0.01$) as compared to HFpEF (Fig. 3). The patients with HFmrEF had slightly (non-significantly) lower risk of composite mortality/readmissions than those with HFrEF (HR 0.86; 95% CI 0.82–1.04; $p = 0.104$). The ROC analysis showed a cut-off point of 50% EF, i.e. LVEF < 50% was associated with higher mortality and rehospitalization rates among the entire studied HF population (sensitivity 65%, specificity 72%, AUC 0.67, $p< 0.01$).

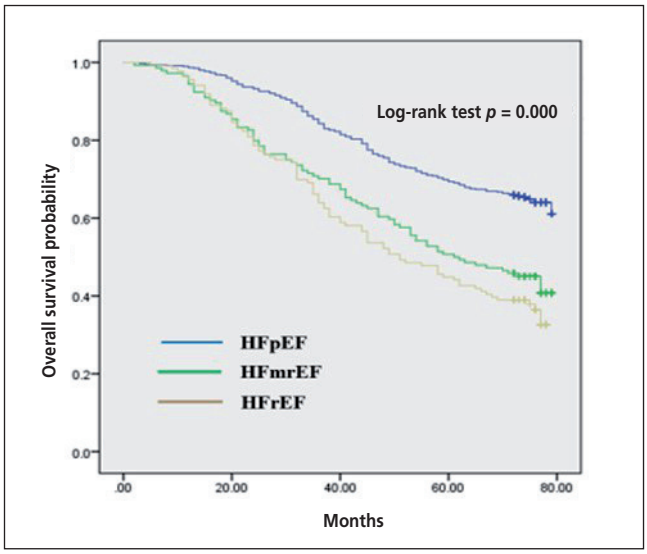

Fig. 1 – Survival of patients with HFpEF, HFmrEF, and HFrEF. HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction.

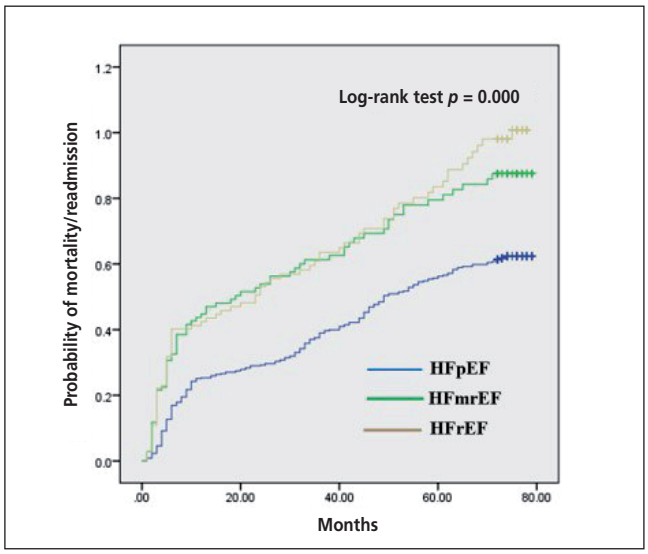

Fig. 3 – The risk of composite mortality/readmissions in patients with HFpEF, HFmrEF, and HFrEF. HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction.

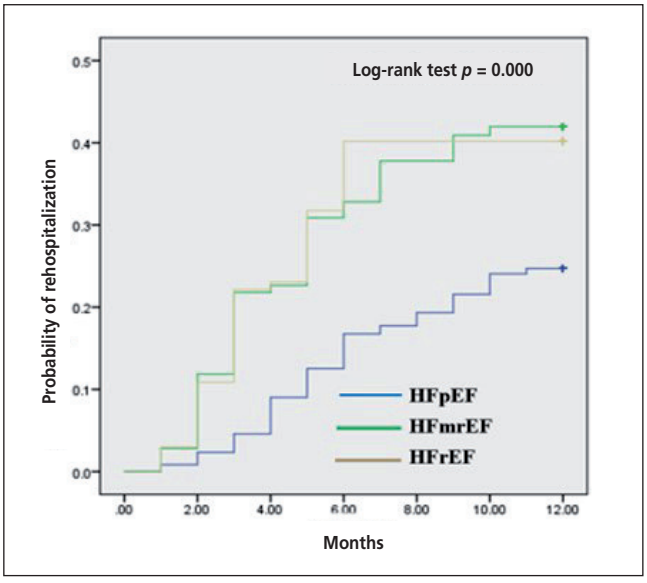

Fig. 2 – The risk of rehospitalizations in patients with HFpEF, HFmrEF, and HFrEF.
HFmrEF – heart failure with mid-range ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction.

Discussion

This is the first study in Bulgaria which investigated the etiology, risk factors, clinical and echocardiographic characteristics, and prognosis of altogether 890 patients with HFpEF, HFmrEF, and HFrEF. The obtained data showed the prognosis of HF patients was primarily linked to the differences in LVEF. This is the main reason for dramatic decrease of incidence of acute myocardial infarction during the last ten years.

The data from registries and epidemiological studies indicate that up to 50% of patients with heart failure have a preserved ejection fraction, and this proportion has increased over the time. The prompt and effective treatment of ACS patients, coupled with a lack of evidence-based effective treatments for HFpEF, is resulting in an emerging epidemic of HFpEF and lower number of patients left ventricular systolic dysfunction. The prevalence of HFpEF is increasing over the time, and a population burden of aging and comorbidities predicts even higher rates of HFpEF in the coming decades. This is the reason for higher proportion of patients with HFpEF in our center.

In our study the HFpEF patients were more often females and more frequently had arterial hypertension compared to those with HFmrEF and HFrEF, while most of the clinical characteristics of HFmrEF patients were similar to HFrEF ones. Baseline co-morbidities such as diabetes mellitus type 2 and atrial fibrillation were more frequent in HFmrEF and HFrEF groups in comparison to HFpEF. Importantly, CAD and PAD were presented more frequently in HFrEF patients and the renal function was worse in this group as well.

The all-cause mortality after approximately 5.8 years of follow-up was lowest among HFpEF patients. It should be pointed out the mortality rate in our HFrEF group began to increase as compared to HFmrEF, after the second year of follow-up, but the difference was not significant. Similarly, the readmissions rate after 1.2 year of follow-up was markedly lower in HFpEF patients and similar in those with HFmrEF and HFrEF. The rehospitalization rates of our HFpEF and HFrEF patients were close to those in ESC-HF-LT Registry,[30] but higher in our HFmrEF patients (33.1% vs. 22.0%), probably because they often remain untreated or insufficiently treated in outpatient (ambulatory) settings. The incidence of the composite end-point of rehospitalizations and mortality was significantly lower in our patients with HFpEF in comparison to those with HFmrEF and HFrEF. The same results were shown in ESC-HF-LT Registry.[30]

Actually, in the literature the data about mortality rates for HFpEF varied from 22% to 65%.[31,32] The published mortality rates in HFpEF and HFrEF patients were markedly influenced by the type of the study from which the data had been taken and by the heterogeneity of the study population. The survival rate in MAGGIC meta-analysis (adjusted for age, gender, etiology, and history of hypertension, diabetes, and atrial fibrillation)[15] was ~32% higher in HFpEF than in HFrEF, whereas epidemiological studies presented similar outcomes in both groups.[31,33] It is important to note that the mortality difference between HFpEF and HFrEF has been decreased in the very elderly. In other meta-analysis with 24 501 patients from 17 studies, Somaratne et al. demonstrated that HFpEF patients had half the odds of death compared with patients with HFrEF.[34] Gottdiener et al. found 6-year mortality for HFpEF 43% and 54% for HFrEF.[35] Probably, this relatively high mortality rate in HFpEF was due to the higher proportion of elderly patients and the advanced stage of HF.

We paid special attention on HFmrEF patients because of the insufficient data in the literature concerning their prognosis. The data in CHARM study showed that patients with LVEF over 45% had a much lower risk of adverse cardiovascular outcomes than those with reduced systolic function, with HR 1.31 for every 10% reduction of LVEF below 45%.[36] In our study the ROC-analysis revealed a cut-off point of 50% EF: values < 50% EF were associated with higher mortality and rehospitalization rates among all studied HF patients (AUC 0.67; sensitivity 65%; specificity 72%, $p< 0.01$). In OPTIMIZE-HF and ADHERE registries the mortality rates in HFpEF and HFmrEF patients were similar and lower than in HFrEF patients.[37,38] GWTG-HF registry showed in HFmrEF population a mortality percentage between these ones in HFpEF and HFrEF, but closer to HFpEF.[39]

Overall, the epidemiological findings demonstrated that the HFmrEF category occupied an intermediate position between the two established categories (HFpEF and HFrEF) concerning clinical profile and burden of comorbidities. In our study, the extent of left/right ventricular and atrial enlargement, pulmonary hypertension and valve abnormalities in HFmrEF patients were midway between HFpEF patients and those with HFrEF, which was in accordance with previous observations. However, our HFpEF patients had better prognosis during 5.8-year follow-up period than the other two HF groups. In this context, HFmrEF may represent an early stage of HFrEF and HFmrEF patients may have benefit from the same therapeutic strategies, approved and used in patients with HFrEF. This suggestion could be supported by the data of Tsutsui et al. who concluded that HFmrEF showed a transitional status between HFpEF and HFrEF rather than an independent entity.[40] Moreover; in our study the frequency of prescription of guideline-recommended medications for HFrEF patients (ACEI/ARBs, beta-blockers, and MRAs) was not as high as expected. Thus, improvement in the management of our HFrEF and HFmrEF patients is urgently needed.

Limitations

It must be acknowledged that this study has some important limitations. First, we enrolled patients from a single center in Sofia; therefore, our results may not be extended to other populations with different ethnicity and/or from other geographical areas. Second, we did not have serial data about the EF in our study, so we cannot determine if there are patients with HFmrEF and HFpEF that were previously with HFrEF, and these patients with improved EF may have different outcomes. Likewise, we do not have data on whether some patients were previously HFmrEF or HFpEF, who subsequently had reduction in EF. Third, postdischarge data were not directly tracked or recorded. In addition, because we did not investigate cardiovascular-specific mortality, we were not able to comment on potential differences between HF groups for this end-point. Cause-specific readmissions were based on diagnostic-related group codes and could be a subject to misclassification.

Conclusion

Our data showed that patients with HFpEF had better prognosis than those with HFmrEF and HFrEF. However, the mortality and rehospitalization rates were similar in HF patients with EF below 50%. This means that HFmrEF may represent an early stage of HFrEF and HFmrEF patients may have benefit from the same therapeutic strategies used for patients with HFrEF.

Conflicts of interest
The authors declare no conflict of interest.

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