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ORIGINAL ARTICLE

The midrange left ventricular ejection fraction (LVEF) is associated with higher all-cause mortality during the 1-year follow-up compared to preserved LVEF among real-world patients with acute heart failure: a single-center propensity score-matched analysis

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Abstract
The objectives of the study were to characterize and compare different acute heart failure (AHF) subgroups according to left-ventricular ejection fraction (LVEF) in terms of all-cause mortality and HF-related readmissions during the 1-year follow-up (FU). Three hundred and fifty-six AHF patients admitted to Cardiology ward and/or CCU were retrospectively included in the study and analyzed during the 1-year FU. Patients were stratified according to LVEF as those with preserved (HFpEF), midrange (HFmrEF) and reduced LVEF (HFrEF). During the FU period, 148 (43.3%) patients died, and 116 HF-related readmission events were recorded. HFmrEF group had significantly higher standardized all-cause mortality rate, unadjusted for age, compared to HFpEF group and significantly lower than HFrEF group (41 vs. 18 and 41 vs. 62.5 events per 100 patient-years; $\chi^2 = 41.08$, $p < 0.001$ and $\chi^2 = 16.62$, $p < 0.001$, respectively). A propensity score-matched analysis in which all HF groups were matched for age and other covariates confirmed that HFmrEF group had significantly higher all-cause mortality rate than HFpEF group ($\chi^2 = 15.66$, $p < 0.001$) while no significant differences in readmission rates were observed across all groups (p = NS). The hazard risk for a composite endpoint of death and readmission was highest in HFrEF group (HR 6.53, 95% CI 3.53–12.08, $p < 0.001$), followed by HFmrEF group (HR 3.30, 95% CI 1.86–5.87, $p < 0.001$) when compared to HFpEF group set as a reference. Among AHF patients, the HFmrEF phenotype was associated with significantly higher all-cause mortality compared to HFpEF, during the 1-year FU. This finding might implicate more stringent clinical approach towards this patient group.

Keywords Heart decompensation · Heart failure · Mortality · Patient readmission · HFmrEF

Introduction

An acute heart failure (AHF) is defined as the rapid onset of symptoms and/or signs of heart failure (HF) [1]. This event can occur for the first time (de novo) or can present in the form of decompensation of preexisting cardiomyopathy (acutely decompensated heart failure, ADHF) and the latter is arguably the most common cause of hospitalization among patients older than 65 years of age [2]. This decompensatory event is usually provoked by factors such as infection, uncontrolled hypertension, acute coronary syndrome (ACS), rhythm disturbances or nonadherence with prescribed medications or diet/lifestyle modifications [3, 4]. Furthermore, heart failure has been historically defined according to the left ventricular ejection fraction (LVEF) as HF with reduced EF (HFrEF, with LVEF < 40%) and with preserved

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EF (HFpEF, with LVEF ≥ 50%) while the latest revision of European Society of Cardiology (ESC) guidelines and those published on the behalf of the American Heart Association/American College of Cardiology Foundation (AHA/ACCF) introduced the new category for patients with HF and LVEF ranging from 40 to 49%—the "*midrange*" *or* "*borderline*" HF or HFmrEF [3, 5].

From the outcomes perspective, AHF was associated with 1-year all-cause mortality rates ranging from 21 to 37% based on the data from ESC HF Long-Term registry (ESC-HF-LT) that encompassed European and Mediterranean countries [6]. Similarly, Medicare-based Get With The Guidelines-HF (GWTG-HF) registry showed that all-cause mortality within 1-year ranged from 35.1 to 37.5% depending on the left-ventricular ejection fraction (LVEF) phenotype [7]. Moreover, a 1-year mortality after hospital discharge is significantly higher among ADHF patients compared to patients with de novo AHF [8]. A study that analyzed trajectories of risk after hospitalization for HF found that readmissions to hospital and death occurred in 67.4% and 35.8% of observed hospitalization cases, during the 1-year period after hospital discharge, respectively [9].

The "*midline*" or "*borderline*" position of HFmrEF as a "*middle child*" of HF urges for definition and characterization of this group, in terms of established risk factors, therapeutic strategies, clinical outcomes, and prognosis, when compared to HF patients with reduced or preserved LVEF [10–12]. Recent data from TIME-CHF and CHART-2 studies showed that HFmrEF is a clinical entity similar to HFrEF, rather than HFpEF, in terms of disease burden and benefit from N-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided therapy [13, 14]. The analysis of ESC HF-LT registry that included 9134 HF patients demonstrated that HFmrEF group had an intermediate 1-year mortality rate (7.6%) when compared to other HF subgroups (8.8% for HFrEF and 6.3% for HFpEF) and similar findings were confirmed in the post hoc analysis of CHARM trial [15, 16]. The results from the latter also suggested that HFmrEF has the same pathophysiology as HFrEF and better outcomes than HFrEF as it most likely represented the milder form of the same syndrome. In support to this hypothesis, a study by Cleland et al. showed that beta-blockers provided similar clinical benefit in HFmrEF population compared to HFrEF and this effect was absent among HFpEF patients in sinus rhythm [17]. Finally, the large pooled-data analysis by Bhambhani et al. based on four community-based longitudinal cohorts, revealed that all-cause mortality following the onset of HFmrEF was worse than that of HFpEF and in that regard, HFmrEF was more similar to HFrEF phenotype [18].

Despite growing data on HFmrEF in the recent year, prognosis and hard endpoints for such patients need to be better defined. Therefore, the main goal of the current study was to characterize and compare clinical features and risk in terms of all-cause mortality and HF-related readmissions during the 1-year period after hospital discharge among real-world HF patients with high comorbidity burden, according to the systolic function.

Materials and methods

Participants and study setting

Data were retrieved retrospectively from HF registry of our tertiary-care medical center and included a total of 356 Caucasian/white patients with an AHF event requiring admission at the cardiology ward and/or coronary care unit (CCU) during the period from February 2008 to May 2012. Patients were entered in the registry in a consecutive fashion during the index admission and were followed for designated outcomes during the 1-year FU period after hospital discharge. Each patient case represented a unique acute hospitalization event and no patients were enrolled more than once in the respective analysis.

Inclusion criteria at admission were: (a) age of 35 years or older, and (b) a confirmed diagnosis of HF (ischemic or non-ischemic cardiomyopathy). To fulfill hospital admission criteria, patient had to be clinically symptomatic and present with one or more of the following clinical features: (a) present dyspnea as a dominant clinical symptom, (b) signs of a jugular vein distention and pulmonary crackles heard at lung bases or throughout lung fields, (c) chest X-ray findings consistent with pulmonary edema, vascular redistribution, cardiomegaly, peribronchial cuffing, etc., and (d) presence of the peripheral/pitting edema. Furthermore, patients were stratified according to their New York Heart Association (NYHA) functional HF class in the following groups: NYHA II, III and IV [19]. Exclusion criteria were: patients in NYHA I class, patients with hemorrhagic diathesis or immunocompromised, active infectious and/or autoimmune disease, patients with stroke or acute myocardial infarction (AMI) or major non-cardiac/cardiac surgery within 3 months prior to index admission, significant liver disease/cirrhosis and history of excessive alcohol or substance abuse. Upon hospital discharge, patients were assigned to follow-up visits that were performed at successive intervals: 1 month, 6 months and 12 months. Patients who did not attend their planned follow-up visits were phoned to determine their current health status.

All patients included in this study have signed informed consent and voluntarily agreed to participate in the study. Insertion of the data was blinded. All procedures followed were in accordance with the Declaration of Helsinki from 1975 and its revision in 2008. The relevant Ethics Committee of our institution reviewed the research protocol and approved the study.

Definitions

An acute heart failure (AHF) was defined as a rapid onset or worsening of symptoms and/or signs of HF leading to hospital admission. According to ESC guidelines for diagnosis and treatment of acute and chronic heart failure, AHF occurs in two main forms—as a first occurrence of HF requiring hospitalization (de novo) or as a consequence of acute decompensation superimposed on chronic HF, also known as acute decompensated heart failure (ADHF) [3]. Upon clinical evaluation, most of AHF patients in this study were admitted to cardiology in-hospital ward while high-risk patients were transferred to coronary care unit (CCU) and for this, some of following criteria had to be fulfilled: need for intubation (or already intubated at arrival), signs/symptoms of hypoperfusion, oxygen saturation (SpO_2) < 90% despite supplemental oxygenation, use of accessory respiratory muscles for breathing or respiratory rate (RR) > 25/min., heart rate (HR) < 40 or > 130 and systolic blood pressure (SBP) < 90 mmHg [3, 20]. Upon clinical stabilization and resolution of acute morbidities, these patients would then be transferred from CCU to the ward. HF-related readmission was defined according to primary discharge diagnosis of heart failure (I50) according to the 10th revision of International Statistical Classification of Diseases (ICD-10) [21].

Diagnostic and physical examinations

A full medical history has been documented and physical examination was performed for each admitted patient. The basic routine workup included chest X-ray and a standard 12-lead ECG recording. Transthoracic echocardiogram (TTE) examination was performed as soon as the patients were able to lay on their left hip, with their upper part of the body raised for about 30° and the left arm placed under the head. Echocardiographic parameters—left ventricular ejection fraction (*LVEF*, %) and left ventricular end-diastolic dimension (*LVEDd*, mm) were measured for each patient by the same cardiologist with a high expertise in echocardiography. Each patient had their LVEF measured at minimally two time points during their index hospitalization: (a) initial assessment within 2 h of admission; (b) assessment after stabilization of acute decompensation; (c) assessment within 48 h prior to hospital discharge. At each time point, multiple LVEF measurements were obtained during each session with weighted average value recorded in the database. In this current study, patients were retrospectively classified into three HF groups according to their mean LVEF value in the registry, which was the average of multiple measurements, performed during the index hospitalization. The modified biplane Simpson's rule was used for LVEF assessment in all instances [22]. For the classification of patients into three HF groups, we adhered to 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF [3].

Following variables were recorded at admission for every patient enrolled in the study: sex, age, number of previous acute decompensation events of HF that required hospitalization, functional status according to NYHA classification, diabetes mellitus (DM), anemia, chronic kidney disease (CKD), arterial hypertension, atrial fibrillation (AF) and active cancer. Variables from physical examination reported in the database included arterial blood pressure measurements and the presence of peripheral congestion. Patients were also classified according to etiology of cardiomyopathy into two groups: ischemic and non-ischemic cardiomyopathy. Biochemical laboratory analyses of peripheral blood were ordered for each patient and standard panel included measurements of creatinine, hemoglobin, urea, uric acid, sodium, and potassium. Anemia was defined by hemoglobin concentrations in plasma < 130 g/L for men and < 120 g/L for women. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation for adults [23, 24]. CKD in this study was defined as a CKD-EPI eGFR value < 60 mL/min/1.73 m^2 of body surface area.

Arterial blood pressure was average of multiple measurements during admission and index hospitalization on both arms non-invasively, supine and sitting, via digital sphygmomanometer. Hypertension was defined as 140 mmHg or higher for systolic (SBP) and/or 90 mmHg or higher for diastolic (DBP) arterial blood pressure and was graded per ESC guidelines for the management of arterial hypertension [25]. At hospital admission, a hospital nurse recorded patient's adherence and use of evidence-based therapy during the medical interview to capture real-world utilization of prescribed medications.

Statistical analysis

All data analyses were performed using IBM® SPSS Statistics for Windows, version 25.0 (IBM, Armonk, NY, USA) and p values < 0.05 were considered significant at all instances. Data were presented as frequencies along with percentages of patients or as the mean ± standard deviation (SD) within a particular category of interest. A Pearson's Chi-square test (χ^2), with Bonferroni post hoc analysis where necessary, were used for categorical variables while independent samples t test was used for determining differences between groups in respect to continuous variables. Patient' characteristics among multiple groups were compared using the one-way ANOVA analysis for continuous variables with post hoc Tukey HSD test. Kaplan–Meier survival analysis with log-rank test was used to plot and compare cumulative survival among respective HF subgroups, stratified by LVEF.

Univariate logistic regression was used to determine the association between analyzed variables set as independent predictors and all-cause death and HF-related readmission events recorded during 1-year FU that were designated as dependent outcomes of interest. After this step, independent variables with significant interaction were included in multivariate regression models. Regression model was constructed using Cox regression hazard analysis with stepwise conditional algorithm. Furthermore, this analysis was used to calculate the multivariate-adjusted hazard ratios (HR), significance levels (p value) and 95% confidence intervals (95% CI) for 1-year post-discharge all-cause mortality and HF-related readmission risk. The respective multivariate model was adjusted and included following variables: age, sex, eGFR, number of acute decompensation events requiring hospitalization prior to current admission, NYHA functional class, DM, SBP, LVEF, urea, uric acid, potassium, sodium and hemoglobin levels in plasma and medications.

Due to age differences among LVEF-stratified HF groups, a propensity score matching (PSM) analysis was undertaken to obtain matched sets of HF patients, in all three HF groups (HFpEF, HFmrEF, and HFrEF). All three groups were matched with each other and then compared directly in terms of main outcome measures in this study: all-cause mortality and HF-related readmissions during the 1-year FU. In the matching algorithm, exact matching for nearest neighbor (1:1) was set for the age while covariates in the model included sex, NYHA class, LVEDd, eGFR, urea, uric acid, sodium, potassium, hemoglobin, SBP, DBP, number of previous hospitalizations and medication use. A caliper of 0.2 of the standard deviation of the logit of the propensity score was used to minimize differences on the covariates between matched participants [26, 27]. PSM analysis was carried out by Propensity Score Matching for SPSS (version 3.0.4.) plugin developed by Thoemmes [28]. This graphical interface utilizes R packages *„MatchIt"*, *„RItools"* and *„cem."* to perform PSM analysis within SPSS [29–31]. Furthermore, survival between each HF patient group was compared with log-rank test and Kaplan–Meier analysis was used to generate survival graphs.

Results

Baseline population characteristics at admission

Three hundred and fifty-six Caucasian patients with AHF event admitted to cardiology ward and/or CCU and were eventually discharged from the hospital, were included in this retrospective registry-derived study. Out of these 356 patients, a total of 342 patients were included in the final data analysis (mean age 74.2 ± 9.9 years, 51.1% women). The loss to follow-up rate was 3.93% since 14 patients failed to complete the study due to unavailability to check post-discharge status, change in address or incomplete data. Therefore, out of 342 patients, 224 (65.5%) had acute decompensation of preexisting HF (ADHF) while 118 (34.5%) patients had de novo AHF. Baseline data of the analyzed population in respect to HF type stratified by LVEF is provided in Table 1. Moreover, patients with de novo AHF had significantly lower crude all-cause mortality reported during the 1-year FU period compared to patients with ADHF (25/118, 21.2% vs. 123/224, 54.9%; $\chi^2 = 20.24$, $p < 0.001$). Finally, de novo AHF patients were significantly younger, had lower mean NYHA class, higher LVEF and significantly differed in most of baseline clinical and laboratory parameters compared to ADHF patients (Table 2).

All-cause death and HF-related readmission outcomes among HFpEF, HFmrEF and HFrEF in age-unadjusted analysis

During the 1-year post-discharge FU period, 148 (43.3%) patients died and the total of 116 hospital readmissions due to acute HF decompensation were recorded. The HFmrEF group exhibited significantly higher mortality during FU than HFpEF group when compared head-to-head (55/133 vs. 16/86 death cases, $p < 0.001$) and significantly less than HFrEF (55/133 vs. 77/123 death cases, $p < 0.001$). The highest number of readmission events during the 1-year post-discharge period was observed for HFmrEF group (53 events per 133 patient-years) and this was similar to HFrEF (45 events per 123 patient-years, $p = 0.686$) but significantly higher compared to HFpEF group (18 events per 86 patient-years, $p = 0.043$) in the age-unadjusted analysis (Table 1).

Due to differences in respective HF subgroup sizes, standardized death and readmission rates were calculated. For HFpEF, HFmrEF and HFrEF group 1 death event occurred for every 5.37, 2.41 and 1.60 patient-years, respectively. Likewise, 1 readmission event occurred for every 4.77, 2.51 and 2.73 patient-years in HFpEF, HFmrEF and HFrEF groups, respectively. Standardized death and readmission rates calculated on the scale of 100 patient-years are provided in Fig. 1. Furthermore, all three HF subgroups significantly differed in crude survival during the 1-year FU period (log-rank $p < 0.001$) (Fig. 2).

Propensity score-matched (PSM) analysis

Due to baseline age differences among HF subgroups stratified by the LVEF, a PSM analysis was utilized to overcome this issue and enable exact age matching between respective groups. Balance diagnostics showed that in all matched pair analyses, no covariates included in the model exhibited large imbalances (defined as $|d| > 0.25$).

Table 1 Comparison of baseline parameters and medication use at admission among different acute heart failure (AHF) subgroups according to left ventricular ejection fraction

Variable	HFpEF $N=86$	HFmrEF $N=133$	HFrEF $N=123$	p*
Age, years, mean ± SD	72.1 ± 7.9	76.9 ± 8.2	72.6 ± 12.0	< 0.001
Men, %	40 (46.51)	61 (45.86)	66 (53.65)	NS
Women, %	46 (53.49)	72 (54.14)	57 (46.35)	NS
All-cause deaths, %	16 (18.60)	55 (42.30)	77 (62.60)	< 0.001
Number of HF-related readmission events	18 per 86 patient-years	53 per 133 patient-years	45 per 123 patient-years	0.185
Arterial hypertension, %	55 (63.95)	76 (57.14)	50 (40.65)	< 0.001
Atrial fibrillation, %	45 (52.32)	68 (51.13)	66 (53.66)	0.700
Chronic kidney disease, %	45 (52.32)	87 (65.41)	83 (67.47)	< 0.001
Diabetes mellitus, %	22 (25.58)	36 (27.07)	39 (31.70)	0.482
Anemia, %	27 (31.39)	68 (51.13)	61 (49.59)	0.007
Cancer, %	6 (6.98)	8 (6.02)	7 (5.69)	0.950
Peripheral congestion, %	26 (30.23)	64 (48.12)	59 (47.97)	0.007
LVEF, %, mean ± SD	54.08 ± 5.15	43.41 ± 3.07	32.25 ± 4.41	< 0.001
LVEDd, mm, mean ± SD	53.70 ± 5.54	67.73 ± 8.67	65.87 ± 6.12	0.402
SBP, mmHg, mean ± SD	146.70 ± 29.43	140.28 ± 25.01	126.32 ± 24.77	< 0.001
DBP, mmHg, mean ± SD	86.90 ± 15.82	81.18 ± 15.82	76.73 ± 15.51	< 0.001
Urea, mmol/L, mean ± SD	6.93 ± 5.1	8.32 ± 5.9	10.06 ± 6.1	< 0.001
Creatinine, µmol/L, mean ± SD	103.96 ± 39.70	144.75 ± 110.04	167.35 ± 98.14	< 0.001
Uric acid, µmol/L, mean ± SD	428.85 ± 147.95	477.09 ± 166.56	540.87 ± 181.52	< 0.001
Potassium, mmol/L, mean ± SD	4.20 ± 0.47	4.47 ± 0.72	4.61 ± 0.95	0.001
Sodium, mmol/L, mean ± SD	140.38 ± 2.69	138.75 ± 4.63	136.27 ± 4.30	< 0.001
Hemoglobin, g/L, mean ± SD	129.66 ± 21.06	123.24 ± 19.44	125.84 ± 19.73	0.059
eGFR, mL/min/1.73 m^2, mean ± SD	58.72 ± 16.31	47.55 ± 22.05	43.53 ± 25.82	< 0.001
NYHA II, %	53 (61.63)	19 (14.28)	7 (5.69)	< 0.001
NYHA III, %	28 (32.55)	90 (67.67)	46 (37.39)	< 0.001
NYHA IV, %	3 (5.82)	28 (18.05)	68 (56.92)	< 0.001
Ischemic cardiomyopathy, %	42 (48.83)	115 (86.47)	74 (60.16)	< 0.001
Non-ischemic cardiomyopathy, %	44 (51.17)	18 (13.53)	49 (39.84)	< 0.001
Patient-reported medication adherence				
Acetylsalicylic acid, %	48 (55.81)	71 (53.38)	59 (48.00)	0.753
ACE-I/ARBs, %	61 (70.93)	101 (75.94)	94 (76.42)	0.138
Beta blockers, %	38 (44.19)	40 (30.75)	45 (36.58)	0.060
Diuretics, %	58 (67.44)	129 (97.00)	121 (98.4)	< 0.001
History of previous acute HF events that required hospitalization				
None, %	58 (67.44)	37 (27.81)	23 (18.70)	< 0.001
1 event, %	18 (20.93)	40 (30.08)	19 (15.45)	< 0.001
2 events, %	7 (8.14)	32 (24.06)	40 (32.52)	< 0.001
≥ 3 events, %	3 (3.49)	24 (18.05)	41 (33.33)	< 0.001
Number of previous events per patient, mean ± SD	0.54 ± 0.87	1.40 ± 1.27	1.93 ± 1.37	< 0.001

ACE-Is angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate by CKD-EPI formula, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LVEDd* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association functional classification of heart failure, *SBP* systolic blood pressure

*Statistical significance value (2-tailed, set at 0.05 level)

In this analysis, head-to-head comparison of HFmrEF vs. HFpEF group showed that HFmrEF patients had significantly more all-cause death events than HFpEF patients (29 vs. 9 events, $\chi^2 = 15.66$, $p < 0.001$) with no significant difference between two groups in terms of HF-related readmissions during the 1-year FU period (17 vs. 12 events, $\chi^2 = 1.15$, $p = 0.284$).

Table 2 Comparison of baseline parameters between de novo AHF and ADHF patients

Variable	De novo AHF	ADHF	*p* value
Age (years)	69.7 ± 11.2	76.6 ± 8.1	< 0.001
NYHA functional class	2.6 ± 0.7	3.3 ± 0.6	< 0.001
eGFR CKD-EPI (mL/min/1.73 m^2)	64.2 ± 16.2	40.8 ± 21.8	< 0.001
LVEF (%)	46.8 ± 9.2	39.8 ± 8.6	< 0.001
LVEDd (mm)	71.2 ± 21.3	59.3 ± 17.2	0.187
Urea (mmol/L)	5.8 ± 3.4	11.2 ± 8.7	< 0.001
Uric acid (μmol/L)	403 ± 127	532 ± 177	< 0.001
Sodium (mmol/L)	140.6 ± 2.7	137 ± 4.6	< 0.001
Potassium (mmol/L)	4 ± 0.4	4.6 ± 0.8	< 0.001
Hemoglobin (g/L)	129 ± 19.5	124 ± 20	0.025
SBP (mmHg)	142 ± 24	134 ± 28	0.008
DBP (mmHg)	84 ± 14	79 ± 15	0.007

DBP diastolic blood pressure, *eGFR* estimated glomerular filtration rate by CKD-EPI formula, *LVEDd* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association functional classification of heart failure, *SBP* systolic blood pressure

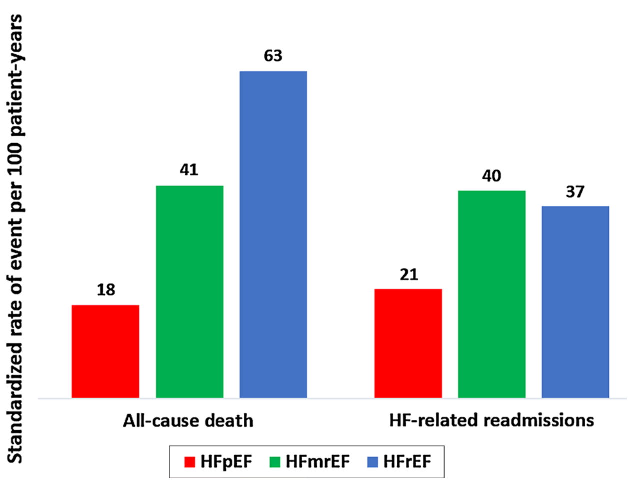

Fig. 1 Standardized outcome rates of all-cause death and HF-related readmission events expressed as the number of events per 100 patient-years among respective HF subgroups. *HFmrEF* heart failure with midrange (borderline) ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction

Results of the PSM analysis in terms of comparison of all-cause death and HF-related readmission events across all groups are provided in Table 3.

Moreover, Kaplan–Meier and log-rank analysis showed that HFmrEF group had significantly lower survival than HFpEF group ($p < 0.001$) during the 1-year FU period while the significant difference in survival was observed among all three groups in direct comparison (HFmrEF

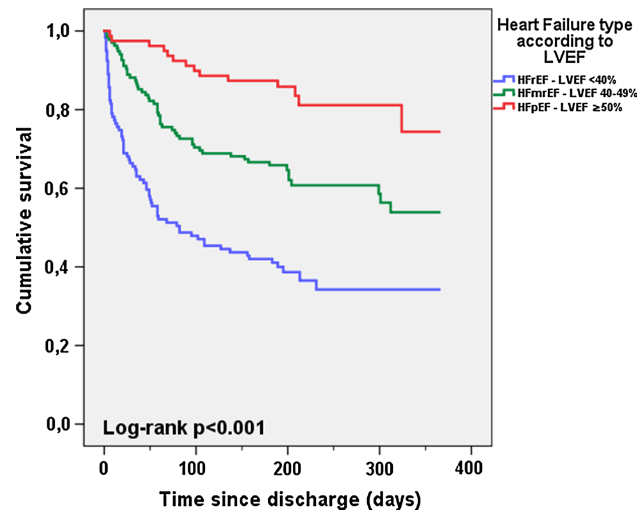

Fig. 2 Kaplan–Meier survival analysis depicting cumulative proportion of heart failure patients that were alive during the 1-year post-discharge FU period in respect to LVEF. *HFmrEF* heart failure with midrange (borderline) ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left-ventricular ejection fraction

vs. HFrEF, HFpEF vs. HFmrEF and HFpEF vs. HFrEF) (Fig. 3).

Multivariate Cox regression analysis

In respect to HFpEF group that was used as a reference, both HFmrEF and HFrEF groups showed a significant independent increase in hazard ratios (HRs) for all-cause death within a 1-year post-discharge FU period (HR 2.64, $p = 0.002$ and HR 5.70, $p < 0.001$, respectively). Similarly, both HFmrEF and HFrEF groups showed a significant increase in HRs for HF-related readmission events within a 1-year FU period, when compared to HFpEF group (HR 2.04, $p = 0.020$ and HR 3.32, $p < 0.001$, respectively). In addition, both HFmrEF and HFrEF exhibited significant hazard risks for the composite endpoint of all-cause death and rehospitalization during 1-year post-discharge with HR 3.30 ($p < 0.001$) and 6.53 ($p < 0.001$), respectively (Table 4).

Discussion

Our main results show that, in comparison to acute heart failure patients with preserved LVEF (HFpEF), patients with midrange LVEF (HFmrEF) exhibited significantly higher proportional and standardized all-cause mortality and HF-related readmission rates during the 1-year FU period after being discharged from the hospital. Additional propensity score-matched (PSM) analysis in which all HF subgroups were exactly matched for age and adjusted for other baseline

Table 3 A propensity score-matched analyses of three AHF subgroups stratified by LVEF in respect to all-cause mortality and HF-related readmission events during a 1-year follow-up

	HFrEF vs. HFmrEF (77 vs. 77 patients)	HFmrEF vs. HFpEF (58 vs. 58 patients)	HFrEF vs. HFpEF (52 vs. 52 patients)
All-cause death events, *N* (%)	51 vs. 34 (66.2% vs. 44.2%)	29 vs. 9 (50% vs. 15.5%)	34 vs. 11 (65.4% vs. 21.2%)
χ^2	7.60	15.66	20.72
*p**	0.006	< 0.001	< 0.001
HF-related readmission events, *N* (%)	27 vs. 20 (35.1% vs. 26%)	17 vs. 12 (29.3% vs. 20.7%)	12 vs. 10 (23.1% vs. 19.2%)
χ^2	1.50	1.15	0.08
*p**	0.221	0.284	0.756

*Chi-squared (χ^2) test, two-tailed significance set at $p < 0.05$ level

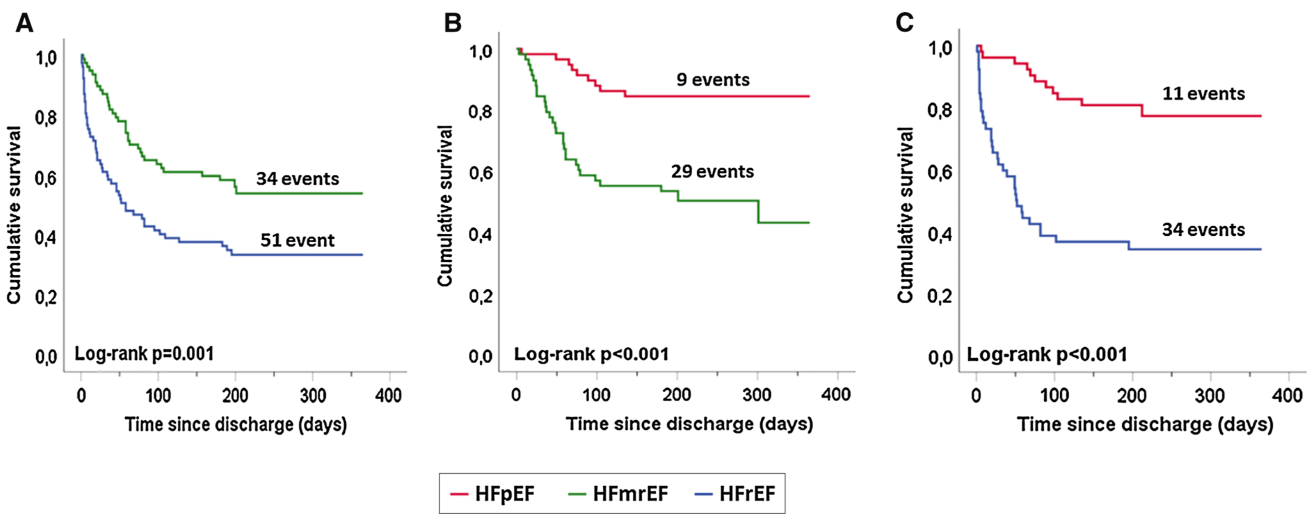

Fig. 3 Kaplan–Meier survival analysis comparing cumulative survival across all heart failure subgroups as derived from propensity score-matched (PSM) analysis. *HFmrEF* heart failure with midrange (borderline) ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction

Table 4 Multivariate-adjusted hazard ratios (HR) for all-cause death and HF-related readmission events and composite endpoint of all-cause death and HF-readmission events during the 1-year post-discharge follow-up period in respect to heart failure type (Cox-regression analysis)

Heart failure type	All-cause death event		HF-related readmissions		Composite endpoint of all-cause death and HF-related readmissions	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
HFpEF	Reference	–	Reference	–	Reference	–
HFmrEF	2.64 (1.45–4.82)	0.002	2.04 (1.12–3.74)	0.020	3.30 (1.86–5.87)	< 0.001
HFrEF	5.70 (3.17–10.23)	< 0.001	3.32 (1.79–6.15)	< 0.001	6.53 (3.53–12.08)	< 0.001

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, *95% CI* 95% confidence interval, *p* statistical significance value (2-tailed, set at 0.05 level)

covariates, confirmed that patients in HFmrEF subgroup had significantly more all-cause death events compared to HFpEF subgroup, but these subgroups did not significantly differ in terms of HF-related readmission events. Finally, PSM analysis showed that all three HF subgroups did not significantly differ regarding the number of HF-related readmission events, although they all significantly differed in terms of all-cause mortality rates, HFrEF phenotype exhibiting highest mortality rate, followed by HFmrEF, and, finally, HFpEF.

Similarly, HFmrEF phenotype was associated with a significantly increased hazard risk for all-cause death, HF-related readmissions and composite end-point of all-cause death and HF-related readmissions during the 1-year FU, compared to patients with the preserved systolic function that were set as a reference.

It is without a doubt of great practical interest to determine baseline and risk profile of HF patients that are classified as HFmrEF, especially in the acute heart failure setting [11]. An intermediate clinical profile and comparable risk for all-cause death or HF readmissions among three groups stratified by LVEF were confirmed in the analysis of data from REDINSCOR II registry [32]. Similarly, data from the CHART-2 study showed that HFmrEF group exhibited intermediate clinical profile between HFpEF and HFrEF and was described as an "*overlap*" transition zone between HFpEF and HFrEF, rather than as an independent entity [14]. Data from the Swedish Heart Failure Registry suggested that HFmrEF is an intermediate phenotype with a higher prevalence of ischemic heart disease in HFmrEF and HFrEF vs. HFpEF [33].

While our study showed that HFmrEF subgroup of AHF patients indeed had intermediate values in a majority of examined baseline parameters, our outcome data suggest that LVEF of 40–49% should indeed be regarded as a milder form of systolic function impairment and could be the "*wolf in a sheep's clothing*" among mainly elderly population of AHF patients with high comorbidity burden, such as those included in this study. Based on the post hoc analysis from CHARM trial involving HF patients treated with angiotensin II receptor antagonist candesartan, it seems that HFmrEF phenotype shares the same pathophysiology with HFrEF and most likely is the milder form of the same syndrome due to the fact that treatment with candesartan improved outcomes in HFmrEF to a similar degree as in HFrEF [16]. This notion has been recently accentuated by the study of Cleland et al. showing that among HF patients in sinus rhythm, treatment with beta-blockers conferred similar clinical benefits in patients with HFmrEF and HFrEF while this effect was not present in HFpEF group [17]. Accordingly, data from ESC HF-LT registry showed that HFmrEF phenotype had significantly better outcomes in all-cause death and HF-related hospitalizations compared to HFrEF phenotype, but this could suggest that HFmrEF is a milder form of the disease [15]. In terms of disease pathophysiology, HFpEF phenotype seems to be driven primarily by comorbidities and multiorgan remodeling secondarily leading to myocyte dysfunction whilst HFrEF and HFmrEF phenotypes have direct myocardial injury occurring first (acute coronary thrombosis, etc.) and this leads to secondary organ remodeling [34].

Finally, these findings cumulatively might suggest that ejection fraction as a direct indicator of the left ventricular systolic function should remain as the established marker for diagnosis and prognosis in HF, and finally, it has important practical repercussion as it is being used to guide therapy [35, 36].

As previously stated, data about the HFmrEF population in the context of AHF are lacking and thus far only ALARM-HF registry provided a robust analysis of this population [37]. This registry generally reported that HFmrEF phenotype showed many intermediate clinical features between HFrEF and HFpEF but had a higher prevalence of hypertension and lower prevalence of chronic renal disease. Our data show that our population had a substantial burden of renal disease with 63% of patients having CKD stage 3 or higher. Loss of GFR independently predicts mortality and accelerates HF progression and prevalence of CKD in our HF sample was notably higher than in similar studies [38]. Of note, there were some notable differences in our study compared to ALARM-HF. For example, ALARM-HF included patients in NYHA I class that were excluded from our study. Enrollment of women across the whole sample and particularly in HFmrEF group was lower in ALARM-HF analysis in comparison to ours (36.2% vs. 51.2% for the overall sample and 35.1% vs. 54.1% for HFmrEF group, respectively). Finally, clinical end-points of all-cause death and rehospitalization were measured at 1-year FU period in our study, as compared to 30 days in ALARM-HF study.

In our study, patients in HFmrEF group were significantly older, more commonly were women, belonged dominantly in NYHA III functional class and had significantly more prior decompensation events per patient when compared to HFpEF but less than HFrEF. The overall prevalence of atrial fibrillation (AF) in our sample was 52.3% and no significant differences were measured across all LVEF groups. Prevalence of AF in our sample was higher than those reported in the EuroHeart Failure Survey (43%) and in the ADHERE registry (30%) [39, 40].

Furthermore, during a 1-year FU period, 148 (43.3%) patients died to all causes and 116 HF-related readmission events were recorded. Our study also showed that patients with de novo AHF had significantly lower all-cause mortality at 1-year FU compared to patients with preexisting HF with acute decompensations (21.2% vs. 54.9%) and similar finding is generally acknowledged worldwide [8, 41, 42]. These two populations also significantly differed in most of clinical and laboratory variables and de novo AHF patients were significantly younger at presentation than ADHF patients. Regarding the 1-year mortality, in a study performed in the United States, a 1-year mortality was up to 33.1% among patients discharged after AHF hospitalization [4]. The EFFECT study conducted among community-based HF patients reported 1-year mortality rates of 30.5–32.9% [43]. One-year mortality rate could be more than 40–50% in some studies [44]. Considering our results, we need to note that rather high mortality at one year after discharge in our sample might be due to highly complex and comorbid patients that were included in the analysis that reflect "*real-world*" unselected population with advanced disease burden. Of note, a large majority of enrolled patients in our study were elderly (73.7% were > 70 years of age), most of them had an advanced degree of HF (76.8% of patients were in NYHA III or IV class), majority were previously hospitalized for an acute decompensation at least once (65.5% of them), prevalence of moderate-to-end-stage CKD was high (63%) with high prevalence of other comorbid conditions such as anemia, AF, DM, arterial hypertension, etc.

Equally important, patient-reported adherence and use of evidence-based treatments at admission in our study was generally suboptimal, and this is particularly important for HFrEF patients since most of guidelines and treatment evidence were historically established for this population. Medication adherence is an important issue since discontinuation of any component of guideline-directed medical therapy in HF is associated with greater mortality, however, this has only been established for HFrEF population [45–47]. At this moment, there are no evidence-based treatments defined and no drugs conferring mortality benefits for HF patients with preserved systolic function [48, 49]. It is likely that these patients in our sample were treated symptomatically, e.g. high prevalence of arterial hypertension in this group required prescribing of beta-blockers, ACE inhibitors, or combination of these with diuretics. In terms of HFmrEF population, it is likely that these patients were receiving treatment similar to HFrEF group due to the fact that previous clinical guidelines did not recognize this group as a separate entity, therefore, at our Center, they were treated similarly to patients with reduced LVEF.

Our study has some limitations as it was a single-center, retrospective, and registry-based study with limited sample size in terms of patient inclusion and data analysis. Furthermore, we lack data on post-discharge pharmacotherapy and disease-specific biomarkers such as NT-proBNP/BNP and data on dyslipidemia that could provide us with additional clinical and prognostic information.

In conclusion, among the highly comorbid, dominantly elderly, and unselected population with acute heart failure, the HFmrEF phenotype was associated with worse all-cause mortality outcomes during the 1-year period after hospital discharge, compared to HFpEF phenotype while HF-related readmissions rates were similar across groups stratified by LVEF. These findings suggest that more rigorous monitoring and treatment of underlying risk factors in patients with mid-range LVEF might be required in future clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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