Comparative Analysis of Short-Term Outcomes of Patients With Heart Failure With a Mid-Range Ejection Fraction After Acute Decompensation

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To determine short-term outcomes after an episode of acute heart failure in patients with mid-range ejection fraction (40%−49%; HFmrEF) compared with patients with reduced (<40%) and preserved (>49%) ejection fractions (HFrEF and HFpEF, respectively) and according to their final destination after emergency department (ED) care. This is an exploratory, secondary analysis of the Epidemiology of Acute Heart Failure in the Emergency departments Registry, which includes consecutive acute heart failure patients diagnosed in 41 Spanish EDs. Patients with echocardiography data were included and divided into HFrEF, HFmrEF, and HFpEF. The primary outcome was 30-day all-cause mortality, and secondary outcomes were in-hospital all-cause mortality, hospital length of stay >10 days, and 30-day postdischarge ED revisit due to AHF and combined end point (ED revisit and/or death). We included 6,856 patients (age 79 [10]; 52.1% women): 21.6% had HFrEF, 14.3% HFmrEF, and 64.1% HFpEF. The main destinations for the 982 HFmrEF patients after ED management were internal medicine (293, 29.8%), cardiology (194, 19.9%) and not hospitalized (241, 24.5%), whereas the remaining 254 patients were admitted to other departments, including geriatric wards, short-stay units and intensive care units. Outcomes for HFmrEF did not differ compared with either HFrEF or HFpEF. Compared with HFmrEF admitted to cardiology, internal medicine admission or direct ED discharge increased the 30-day postdischarge ED revisit (hazard ratio [HR] 1.713, 95% confidence interval [CI] 1.042 to 2.816; and HR 1.683, 95% CI 1.046 to 2.708, respectively) and the 30-day postdischarge combined end point (HR 1.732, 95% CI 1.070 to 2.803; and HR 1.727, 95% CI 1.083 to 2.756, respectively). In conclusion, patients in the newly created HFmrEF category suffering from an acute decompensation have similar short-term outcomes as those in the classical HFrEF and HFpEF categories; nonetheless, HFmrEF patients handled in cardiology wards during decompensation obtain better outcomes, and reasons for these differences have to be unmasked and corrected. **(Am J Cardiol 2019;123:84−92)**

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The recent 2016 European Society of Cardiology (ESC) Guidelines changed the classification of heart failure (HF) patients according to the left ventricular ejection fraction (LVEF). This change allocated patients with a LVEF between 40% and 49% to a new category named HF mid-range ejection fraction (HFmrEF) located between the two classical categories consisting of patients with a reduced (<40%) and preserved (>49%) LVEF (HFrEF and HFpEF, respectively).[1] Many recent reports and pooled analysis have defined the clinical profile of patients included in the HFmrEF group, which seems to be mid-point between HFrEF and HfpEF,[2−5] and the long-term prognosis of HFmrEF is also intermediate between HFrEF and HFpEF.[2−7] Interestingly, a meta-analysis of individual data from almost 40,000 patients with HF found that the adjusted risks of mortality progressively increased with every 5% to 10% decrease in LVEF below 40% but were not significantly different in the groups with a LVEF >40%.[7] Conversely, fewer studies have focused on the short-term outcomes of this new category of patients after presenting an acute decompensation.[8−11] Additionally, whereas HFrEF and HFpEF patients tend to preferably be admitted to cardiology and internal medicine departments, respectively,[12,13] there are no data on where HFmrEF patients are managed during an acute heart failure (AHF) episode, and whether there is any impact on short-term outcome according to the department in which the patient receives care during a decompensation. Remarkably, most of the studies on the short-term outcome of patients with HFmrEF with AHF only included patients hospitalized in cardiology departments,[8−11] which may impose a bias toward a particular HFmrEF patient profile. The present study analyzed the Epidemiology of Acute Heart Failure in the Emergency departments (EAHFE) Registry that includes consecutive unselected patients with AHF recruited at Spanish emergency departments (EDs), focusing on the short-term outcomes of patients with HFmrEF in order to: (1) compare these outcomes with those of patients with HFrEF and HfpEF, (2) investigate their destination after ED care, and (3) detect any significant differences in short-term outcomes according to the main final destinations.

Methods

This study is an exploratory, secondary analysis within the EAHFE Registry. The EAHFE Registry was initiated in 2007 and every 2−3 years carries out in 1- to 2-month recruitment period of all consecutive patients diagnosed with AHF in Spanish EDs participating in the project. To date, 5 recruitment phases (in 2007, 2009, 2011, 2014, and 2016) have been performed with the participation of 41 EDs from community and university hospitals across Spain (which represent about 13% of the Spanish public health care system hospitals), enrolling a total of 13,791 AHF patients. The study evaluated the 12,843 patients recruited in phases 2 to 5. Details of patient inclusion have been reported in previous studies.[12−14] The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the ED attending physician decisions. The EAHFE Registry protocol was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 49/2010, 69/2011, 166/13, and 160/15. All participating patients gave informed consent to be included in the registry and to be contacted for follow up. The study was carried out in strict compliance with the Declaration of Helsinki principles.

Patients with a final diagnosis of AHF in whom the LVEF had been determined within 6 months before the current decompensation were included in this study. The patients were divided into 3 groups according to the definition of LVEF in the 2016 ESC Guidelines: HFrEF (<40%), HFmrEF (40%−49%), and HFpEF (>49%). Thirty-four independent variables that could potentially affect clinical outcomes were recorded (see Supplemental Table 1). The department where the patients were initially hospitalized (cardiology, internal medicine, geriatrics, short-stay unit, intensive and/or coronary care unit, and others) following ED care was recorded in patients requiring hospital admission.

The primary end point was 30-day all-cause mortality, assessed by a phone call and review of primary care and hospital medical records. As secondary end points, in-hospital all-cause mortality and prolonged length of stay (LOS)—defined as a hospital admission (from the ED admission to hospital discharge) longer than 10 days −were calculated for hospitalized patients; and 30-day postdischarge ED revisit due to AHF and 30-day postdischarge combined end point (ED revisit or death) were calculated for patients discharged alive after the index AHF episode. Since this was an exploratory study, a pre-hoc sample size calculation was not made.

Quantitative variables are expressed as mean and standard deviation (SD) and qualitative variables as absolute values and percentages. Comparison in groups was carried out using one-way analysis of variance for quantitative variables and the chi square test for qualitative variables. For the primary end point, patients with HFmrEF were compared with HFrEF and HFpEF patients by calculating the hazard ratios (HR) with 95% confidence intervals (95% CI) for 30-day death using the Cox regression model. These HR were adjusted for all the independent variables showing a significantly different distribution in groups ($p < 0.05$) in the univariate analysis. A second adjustment was carried out by replacing missing values using the multiple imputation technique with previous ascertainment of random pattern in the missing variables. The same analysis was repeated in patients with HFmrEF in order to compare the primary end point achieved for patients admitted to the internal medicine department and for nonhospitalized patients with those admitted to the cardiology department (reference category), as these were the three main destinations of the HFmrEF patients after the ED care. For the secondary end points, the unadjusted and adjusted (without and with multiple imputation) odds ratio (OR) with 95% CI for the in-hospital mortality and prolonged LOS were calculated using logistic regression, as well as the HR (95% CI) for the 30-day postdischarge ED revisit and combined end point. Statistical significance was accepted if the 95% CI of the HR or OR excluded the value 1, or the p value was <0.05.

Results

Of the 12,843 patients included in the phases 2 to 5 EAHFE registries, 6,856 (53.4% of patients; with a mean age of 79 [SD = 10] and 52.1% women) had undergone LVEF measurement within the 6 months before the index AHF episode and were included in the INTERICA-2 Study. These patients were younger and more frequently males, and had higher rates of co-morbidity than those without LVEF data; additionally (Supplemental Table 2). The distribution of patients included in the INTERICA-2 study was as follows: 1,481 (21.6%) had HFrEF, 982 (14.3%) had HFmrEF, and 4,393 (64.1%) had HFpEF (Table 1).

The three most frequent destinations after ED care in patients with HFmrEF were internal medicine (293 patients, 29.8%), cardiology (194, 19.9%) and not hospitalized (241, 24.5%) (Table 2). On comparison of the characteristics of the patients admitted to these 3 main destinations significant differences were observed in 17 variables (Supplemental Table 3). Patients admitted to internal medicine were older and more frequently had co-morbidities (chronic kidney failure, cerebrovascular disease, chronic obstructive pulmonary disease, and previous episodes of AHF).

Only 7 patients were lost to follow-up (1 HFmrEF, 3 HFrEFA, 3 HFpEF), and the primary end point of 30-day mortality was observed in 613 patients (9.0%). With respect to secondary end points, the rate for in-hospital mortality was 8.4% for the prolonged LOS 30.5%, for 30-day postdischarge ED revisit 26.6%, and for 30-day postdischarge combined end point 28.8%. The raw analysis showed that, while the 30-day mortality of patients with HFmrEF did not differ from that observed in HFpEF patients, these patients had a

Table 1
Characteristics of the patients included in the study and comparison among the three ejection fraction categories

Variable	Total (n = 6,856)	Missing values	HFrEF (n = 1,481)	HFmrEF (n = 982)	HFpEF (n = 4,393)	p value
Age (years) (mean [SD])	79 (10)	13 (0.2)	76 (11)	79 (10)	80 (9)	< 0.001
Women	3,561 (52.1%)	25 (0.4%)	497 (33.6%)	406 (41.5%)	2,658 (60.8%)	< 0.001
Hypertension	5,858 (86.9%)	5 (0.1%)	1,208 (81.7%)	835 (85.2%)	3,815 (86.9%)	< 0.001
Diabetes mellitus	3,088 (45.1%)	6 (0.1%)	726 (49.1%)	464 (47.3%)	1,898 (43.2%)	< 0.001
Ischemic heart disease	2,474 (36.1%)	6 (0.1%)	777 (52.5%)	462 (47.1%)	1,235 (28.1%)	< 0.001
Chronic kidney failure	2,057 (30.0%)	4 (0.1%)	478 (32.3%)	315 (32.1%)	1,264 (28.8%)	0.011
Cerebrovascular disease	925 (13.5%)	5 (0.1%)	212 (14.3%)	138 (14.1%)	575 (13.1%)	0.413
Atrial fibrillation	3,746 (54.7%)	6 (0.1%)	640 (43.3%)	523 (53.4%)	2,583 (58.8%)	< 0.001
Peripheral arterial disease	741 (9.6%)	5 (0.1%)	197 (13.3%)	123 (12.6%)	421 (9.6%)	< 0.001
Heart valve disease	2,457 (35.9%)	6 (0.1%)	422 (28.6%)	339 (34.6%)	1,696 (38.6%)	< 0.001
Chronic obstructive pulmonary disease	1,776 (25.9%)	10 (0.1%)	373 (25.3%)	247 (25.2%)	1,156 (26.3%)	0.624
Prior episodes of acute heart failure	4,881 (71.9%)	71 (1.0%)	1,144 (78.1%)	741 (76.5%)	2,996 (68.8%)	< 0.001
Baseline status						
Barthel Index (points) (mean [SD])	81 (23)	670 (9.8)	82 (23)	82 (23)	80 (23)	0.017
NYHA class III–IV	1,738 (26.8%)	368 (5.4%)	467 (33.1%)	199 (21.3%)	1,072 (25.9%)	< 0.001
Chronic treatments at home						
Diuretics (any)	5,498 (82.9%)	222 (3.2%)	1,273 (88.2%)	801 (83.4%)	3,424 (80.9%)	< 0.001
ACE inhibitor or ARB	3,931 (59.3%)	222 (3.2%)	930 (64.4%)	573 (59.7)	2,428 (57.4%)	< 0.001
Beta-blocker	3,336 (50.3%)	222 (3.2%)	919 (63.6%)	521 (54.3)	1,896 (44.8%)	< 0.001
Mineralocorticoid-receptor antagonist	1,441 (21.7%)	222 (3.2%)	495 (34.3%)	227 (23.6)	719 (17.0%)	< 0.001
Digoxin	1,156 (17.4%)	227 (3.3%)	258 (17.9%)	163 (17.0)	735 (17.4%)	0.836
SBP (mm Hg)	140 (27)	82 (1.2)	132 (27)	140 (28)	142 (27)	< 0.001
Heart rate (bpm)	88 (23)	124 (1.8)	87 (23)	85 (22)	87 (23)	0.059
Air-room pulsioxymetry (%)	92 (6)	212 (3.1)	93 (6)	93 (6)	92 (7)	< 0.001
Glucose (mg/dl)	150 (93)	716 (10.4)	158 (121)	153 (79)	146 (85)	< 0.001
Creatinine (mg/dl)	1.39 (0.82)	77 (1.1)	1.51 (0.86)	1.41 (0.79)	1.34 (0.82)	< 0.001
Haemoglobin (g/l)	119 (20)	67 (1.0)	123 (19)	120 (21)	118 (20)	< 0.001
Potassium (mmol/L)	4.41 (0.69)	381 (5.6)	4.47 (0.72)	4.44 (0.65)	4.38 (0.69)	< 0.001
Sodium (mmol/L)	138.0 (4.9)	144 (2.1)	137.6 (4.9)	137.8 (4.6)	138.2 (4.9)	< 0.001
Management at ED						
Need for intravenous diuretics	5,873 (86.7%)	80 (1.2%)	1,290 (88.2%)	853 (88.0%)	3,730 (85.9%)	0.030
Need for intravenous morphine	371 (6.0%)	640 (9.3%)	111 (8.7%)	45 (5.3%)	215 (5.3%)	< 0.001
Need for intravenous nitrates	1,048 (15.5%)	74 (1.1%)	245 (16.7%)	171 (17.6%)	632 (14.5%)	0.017
Need for inotropics/vasopressors	150 (2.2%)	79 (1.2%)	72 (4.9%)	18 (1.9%)	60 (1.4%)	< 0.001
Need for noninvasive ventilation	459 (6.8%)	74 (1.1%)	111 (7.6%)	65 (6.7%)	283 (6.5%)	0.367
Need for mechanical ventilation	215 (3.2%)	74 (1.1%)	50 (3.4%)	24 (2.5%)	141 (3.2%)	0.388
Admission to hospital	5,216 (76.1%)	5 (0.1%)	1,151 (77.7%)	739 (75.4%)	3,326 (75.8%)	0.264

Values are mean ± standard deviation or n (%). ACE = angiotensin-converting enzyme; ARB = angiotensin-II receptor blocker; bpm = beats per minute; ED = emergency department; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; SD= standard deviation.

Table 2
Main destination of patients with acute heart failure after emergency department care according to the left ventricular ejection fraction category

Variable	Total (n = 6,856)	HFrEF (n = 1,481)	HFmrEF (n = 982)	HFpEF (n = 4,393)	p value*
Not hospitalized	1,635 (23.8%)	330 (22.3%)	241 (24.5%)	1,064 (24.2%)	0.273
Admission to internal medicine department	2,150 (31.4%)	411 (27.8%)	293 (29.8%)	1,446 (32.9%)	< 0.001
Admission to cardiology department	1,337 (19.5%)	422 (25.8%)	194 (19.9%)	721 (16.4%)	< 0.001
Admission to short stay unit	816 (11.9%)	150 (10.1%)	103 (10.5%)	563 (12.8%)	0.007
Admission to geriatric department	391 (5.7%)	63 (4.3%)	54 (5.5%)	274 (6.2%)	0.017
Admission to intensive/coronary care unit	82 (1.2%)	23 (1.6%)	22 (2.2%)	37 (0.8%)	< 0.001
Admission to other departments	415 (6.1%)	77 (5.2%)	71 (7.2%)	267 (6.1%)	0.117
Unknown	30 (0.4%)	5 (0.3%)	4 (0.4%)	21 (0.5%)	0.769

* Comparison of each destination was performed versus the remaining patients not included in this particular destination.HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

significantly better prognosis than patients with HFrEF (OR 0.757, 95% CI 0.584 to 0.981, p = 0.036). However, after adjustment for the 27 discordant independent variables, the survival curves for the three groups became closer and statistical significance disappeared (Figure 1). Similar findings were found when adjustment was made by multiple imputation for missing values. Compared with the other 2 categories, no statistically significant differences were observed in the secondary end points in patients with HFmrEF either, unadjusted or adjusted analysis (Table 3).

According to the final destination after ED care in the raw analysis, the 30-day mortality for patients admitted to internal medicine departments was significantly higher than that observed in those admitted to cardiology departments (OR 2.621, 95% CI 1.257 to 5.464, p = 0.010), but this difference disappeared after both adjustments (without and with multiple imputation). No differences were observed in 30-day mortality between patients not hospitalized and those admitted to cardiology departments in either the unadjusted or adjusted models (Figure 1). Regarding the secondary end points, no significant differences were observed in in-hospital mortality and prolonged LOS rates in either the unadjusted or adjusted analysis. Conversely, in the raw analysis 30-day postdischarge ED revisit due to AHF and the combined end point (ED revisit or death) were higher in patients with HFmrEF admitted to internal medicine departments and not hospitalized compared with those admitted to cardiology departments, and most of these differences remained statistically significant after adjustment with multiple imputation (Table 3).

Discussion

The results of this study showed 3 main findings. First, short-term primary and secondary outcomes of patients with HFmrEF did not significantly differ with respect to HFrEF and HFpEF. Second, the main destinations after ED care were internal medicine, cardiology, and direct ED discharge. And third, compared with HFmrEF patients admitted to cardiology departments for an episode of AHF, those admitted to internal medicine departments or not hospitalized had significantly worse outcomes after hospital or ED discharge, which were measured in terms of need for a 30-day postdischarge ED revisit for AHF or the combined end point (30-day postdischarge ED revisit or death).

With respect to short-term outcome considering the LVEF as a classificatory parameter, the adjusted results were very similar in the three groups according to the 2016 ESC Guidelines, with no significant differences. Few studies have been previously published in this regard. A secondary analysis of 5,687 hospitalized patients in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure clinical trial showed that the three clinical categories had similar adjusted 30-day mortality.[8] The Spanish REDINSCOR-II cohort of patients' hospitalized in cardiology wards analyzed 1,420 also failed to demonstrate significant differences in the three groups in in-hospital and 30-day mortality and 30-day rehospitalization.[10] The analysis of the 99,825 hospitalized patients included in Get With the Guidelines-Stroke registry,[11] however, reported decreased in-hospital mortality in HFmrEF (2.62% in front of 3.21% and 3.02% in HFrEF and HFpEF, respectively). Finally, Farmakis et al,[9] on analyzing 3,257 patients with echocardiographic data included in the ALARM-HF cohort, found that 30-day all-cause mortality in HFmrEF patients admitted to cardiology departments was at an intermediate position between those observed in HFpEF and HFrEF patients; however, compared with HFpEF patients there was no significant difference (HR 1.026, 95% CI 0.605 to 1.741, p = 0.923), whereas statistically significant differences were observed with respect to HFrEF (HR 0.635, 95% CI 0.419 to 0.963, p = 0.033). Remarkably, the HRs for 30-day mortality in this study were similar to those found in the ALARM-HF cohort (1.150 and 0.810, respectively), but statistical significance was not achieved in our cohort.

In this sense, since the clinical characteristics and outcomes of HFmrEF patients are usually halfway between those of HFrEF and HfpEF patients, and HFmrEF dynamically transitions to HFpEF or HFrEF (especially within 1 year), some authors have suggested that HFmrEF represents a transitional status or an overlap zone between HFpEF and HFrEF rather than an independent entity.[4,15] Our data regarding short-term outcomes also agree with this concept. Overall, the data in the present study obtained in 6,856 unselected patients recruited in the EDs confirm and further extend most of the data described in previous studies in patients admitted to cardiology departments to a more generic population of HFmrEF patients with AHF admitted to any hospital ward or who are not

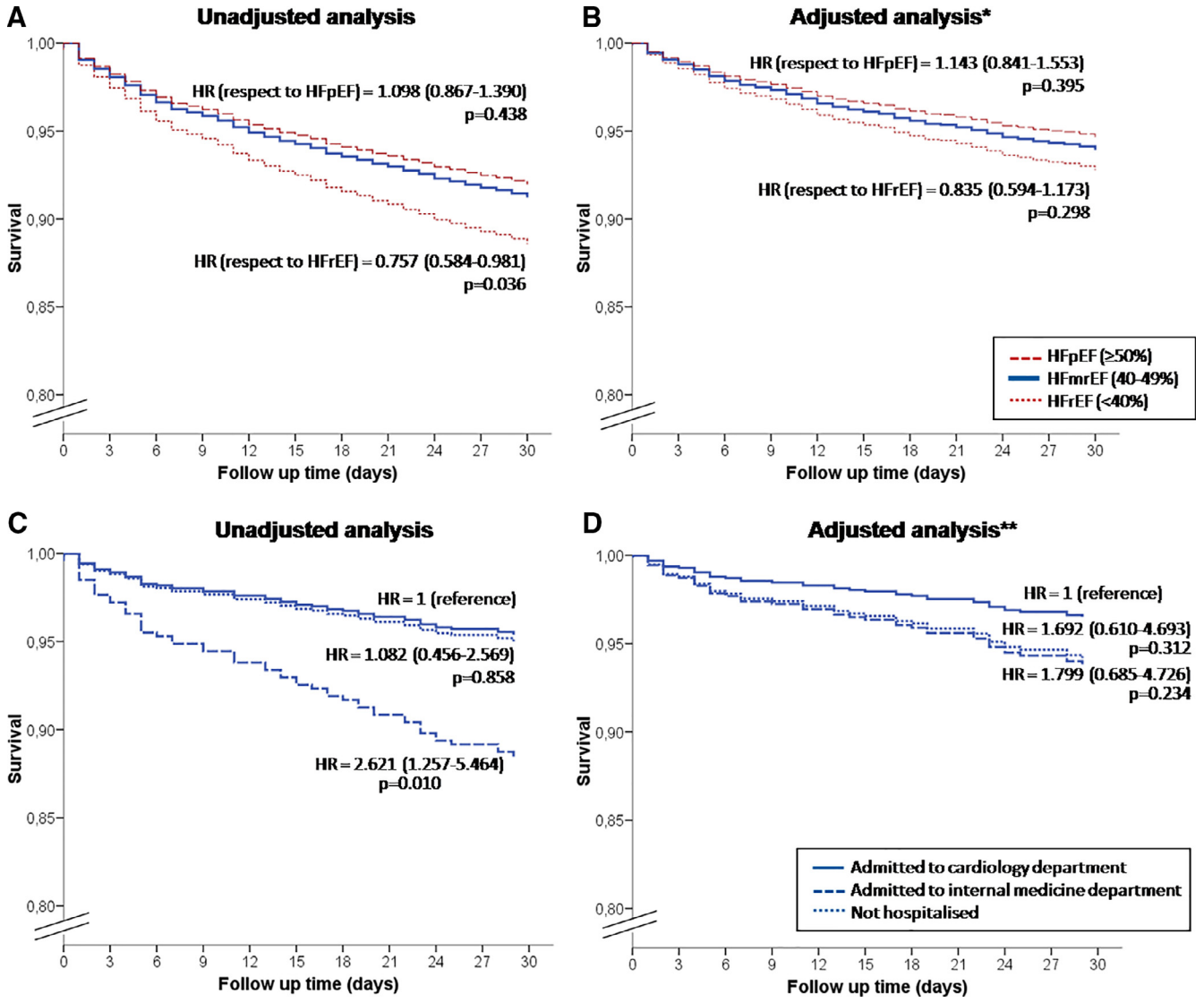

Figure 1. Unadjusted (*A-C*) and adjusted* (*B-D*) cumulative hazard ratios (HR) for 30-day survival for the patients included in the study according to the ejection fraction category (*A-B*), and for patients with heart failure with mid-range ejection fraction according to the three main destinations after emergency department care (*C-D*). *Adjustment was made for differences found in the univariate analysis: age, sex, co-morbidities (hypertension, diabetes mellitus, ischemic heart disease, chronic kidney failure, atrial fibrillation, peripheral arterial disease, heart valve disease, and previous episodes of acute heart failure), baseline status (Barthel index, NYHA class III−IV), chronic treatments at home (diuretics, angiotensin-converter enzyme inhibitor or angiotensin-receptor blocker, beta-blocker, mineralcorticoid-receptor blocker), vitals at emergency department arrival (systolic blood pressure, air-room pulsioximetry), results of blood tests at emergency department (glucose, creatinine, hemoglobin, potassium, and sodium) and management at emergency department (use of intravenous diuretics, nitrates, morphine, and inotropic/vasopressor drugs). **Adjustment was made for differences found in the univariate analysis: age (disease, chronic kidney failure, cerebrovascular disease, chronic obstructive pulmonary disease, previous episodes of acute heart failure), baseline status (Barthel index, NYHA class III−IV), chronic treatments at home (diuretics, beta-blocker), vitals at emergency department arrival (heart rate, air-room pulsioximetry), results of blood tests at emergency department (hemoglobin, potassium, and sodium) and management at emergency department (use of intravenous diuretics, nitrates, and noninvasive ventilation). HFmrEF = heart failure mid-range ejection fraction; HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction.

even hospitalized. At this point, it could be a matter of debate if HFmrEF category really defines a truly different category aside to the two classically recognized ones: HFrEF and HFpEF. Until now, no clear benefits or dedicated interventions have been drawn from studies or analysis performed in the patients with HFmrEF, although a recent report suggests they should be treated with the same therapy schemes as HFrEF patients.[16] In addition, to set the cutoff for this category in the interval of 40% to 49% was quite arbitrary, and it is not known if different cut-off point selection could have led to greater differentiation between the three proposed categories. In contrast, as this range is very narrow, and LVEF can mildly change in short time periods and also can slightly differ in estimation by different explorers, and even by the same explorer in different assessments, it can be difficult to know if a

Table 3
Primary and secondary end points for heart failure mid-range ejection fraction (HFmrEF) patients compared with patients with heart failure with reduced (HRrEF) and preserved ejection fraction (HfpEF), and according to the three main destinations after emergency department health care

				HFmrEF compared with HFrEF			HFmrEF compared with HFpEF		
	HFmrEF N events	HFrEF N events	HFpEF N events	Unadjusted odds/hazard ratio (95% CI) p value	Adjusted* odds/hazard ratio (95% CI) p value	Adjusted† odds/hazard ratio (95% CI) p value	Unadjusted odds/hazard ratio (95% CI) p value	Adjusted* odds/hazard ratio (95% CI) p value	Adjusted*, † odds/hazard ratio (95% CI) p value
30-day all-cause mortality (HR)	86 (8.8%)	170 (11.5%)	357 (8.1%)	0.757 (0.584 −0.981) 0.036	0.835 (0.594 −1.173) 0.298	0.810 (0.619 −1.060) 0.124	1.098 (0.867 −1.390) 0.438	1.143 (0.841 −1.553) 0.395	1.150 (0.902 −1.467) 0.260
In-hospital all-cause mortality (OR)	58 (7.9%)	116 (10.1%)	263 (7.9%)	0.761 (0.548 −1.059) 0.105	0.782 (0.483 −1.266) 0.318	0.837 (0.575 −1.216) 0.350	0.995 (0.740 −1.338) 0.973	0.877 (0.584 −1.317) 0.527	1.014 (0.735 −1.397) 0.935
Prolonged length of stay (> 10 days) (OR)	224 (30.8%)	362 (32.0%)	981 (29.9%)	0.883 (0.769 −1.013) 0.076	1.114 (0.869 −1.428) 0.393	1.022 (0.839 −1.245) 0.829	1.040 (0.874 −1.238) 0.657	0.936 (0.790 −1.242) 0.936	1.014 (0.844 −1.219) 0.882
30-day postdischarge ED revisit due to AHF (HR)	223 (25.3%)	336 (26.3%)	1066 (27.0%)	0.894 (0.730 −1.094) 0.276	1.085 (0.834 −1.410) 0.544	1.009 (0.818 −1.246) 0.931	0.904 (0.762 −1.074) 0.251	0.889 (0.712 −1.110) 0.299	0.872 (0.729 −1.042) 0.132
30-day postdischarge combined end point (HR)	241 (27.2%)	384 (29.8%)	1142 (28.8%)	0.909 (0.771 −1.070) 0.252	1-057 (0.856 −1.304) 0.609	0.997 (0.83 −1.180) 0.975	0.940 (0.816 −1.082) 0.387	0.970 (0.810 −1.163) 0.746	0.911 (0.788 −1.053) 0.208
				HFmrEF hospitalized in internal medicine wards compared with HFmrEF hospitalized in cardiology wards			HFmrEF discharged from ED to home without hospitalization compared with HFmrEF hospitalized in cardiology wards		
	Cardiology N events	Internal medicine N events	ED Direct discharge N events	Unadjusted odds/ hazard ratio (95% CI) p value	Adjusted** odds/ hazard ratio (95% CI) p value	Adjusted**, † odds/ hazard ratio (95% CI) p value	Unadjusted odds/ hazard ratio (95% CI) p value	Adjusted** odds/ hazard ratio (95% CI) p value	Adjusted**, † odds/ hazard ratio (95% CI) p value
30-day all-cause mortality (HR)	9 (4.6%)	34 (11.6%)	12 (5.0%)	2.621 (1.257 −5.464) 0.010	1.799 (0.685 −4.726) 0.234	1.881 (0.837 −4.227) 0.126	1.082 (0.456 −2.569) 0.858	1.692 (0.610 −2.569) 0.312	1.061 (0.425 −2.652) 0.899
In-hospital all-cause mortality (OR)	10 (5.2%)	29 (9.9%)	N.A.	2.021 (0.961 −4.249) 0.063	1.224 (0.446 −3.359) 0.695	1.410 (0.589 −3.376) 0.441	N.A.	N.A.	N.A.
Prolonged length of stay (> 10 days) (OR)	70 (36.3%)	101 (34.8%)	N.A.	0.939 (0.642 −1.373) 0.746	0.947 (0.553 −1.622) 0.844	0.869 (0.551 −1.370) 0.418	N.A.	N.A.	N.A.
30-day post-discharge ED revisit due to AHF (HR)	29 (16.1%)	68 (26.7%)	67 (29.5%)	1.777 (1.150 −2.745) 0.010	1.520 (0.847 −2.729) 0.161	1.713 (1.042 −2.816) 0.034	1.879 (1.143 −3.088) 0.013	1.697 (0.968 −2.975) 0.065	1.683 (1.046 −2.708) 0.032
30-day post-discharge combined end point (HR)	30 (16.7%)	76 (29.7%)	70 (30.7%)	1.885 (1.232 −2.884) 0.003	1.505 (0.860 −2.634) 0.152	1.732 (1.070 −2.803) 0.025	1.886 (1.229 −2.896) 0.004	1.733 (1.000 −3.001) 0.050	1.727 (1.083 −2.756) 0.022

* Adjustment was made for differences found in the univariate analysis: age, sex, co-morbidities (hypertension, diabetes mellitus, ischemic heart disease, chronic kidney failure, atrial fibrillation, peripheral arterial disease, heart valve disease, previous episodes of acute heart failure), baseline status (Barthel index, NYHA class III−IV), chronic treatments at home (diuretics, angiotensin-converter enzyme inhibitor or angiotensin-receptor blocker, beta-blocker, and mineralcorticoid-receptor blocker), vitals at emergency department arrival (systolic blood pressure, air-room pulsioximetry), results of blood tests at emergency department (glucose, creatinine, hemoglobin, potassium, sodium) and management at emergency department (use of intravenous diuretics, nitrates, morphine, and inotropic and/or vasopressor drugs).

** Adjustment was performed using multiple imputation for missing values.AHF = acute heart failure; ED = emergency department; HR = Hazards ratio; N.A = not applicable; NYHA = New York Heart Association; OR = odds ratio.

† Adjustment was made for differences found in the univariate analysis: age, co-morbidities (chronic kidney failure, cerebrovascular disease, chronic obstructive pulmonary disease, and previous episodes of acute heart failure), baseline status (Barthel index, NYHA class III−IV), chronic treatments at home (diuretics, beta-blocker), vitals at emergency department arrival (heart rate, air-room pulsioximetry), results of blood tests at emergency department (hemoglobin, potassium, and sodium) and management at emergency department (use of intravenous diuretics, nitrates, and noninvasive ventilation).

patients initially classified in the HFmrEF category really pertain to it if they have LVEF close to the borders of the category.

The probability of patient admission in the different hospital departments after the ED care significantly differed for some of them. In all but one of these cases of unequally distribution, HFmrEF was in between HFrEF and HFpEF percentages, and only admission in the ICU was more frequently seen in HFmrEF than in the HFrEF. In global, and as seen in the other 2 categories, the most frequent ED disposition for HFmrEF was internal medicine wards, followed by direct ED discharge and cardiology wards.

We do not find differences in the 30-day mortality and in-hospital mortality and in prolonged LOS of HFmrEF patients according to their three main destinations after ED care. Conversely, postdischarge outcomes were worse for patients not admitted to cardiology wards. No previous study has compared AHF outcomes in HFmrEF patients according to the department in which the patients were admitted. Previous general studies, not focused on HFmrEF, suggested better outcomes for patients with AHF attended by cardiologists in hospital,[17] and those admitted in internal medicine wards have significant higher in-hospital and 1-year mortality rates than those admitted in cardiology wards, even after adjustment for differences.[18] Hypothetically, our findings could be related to a different efficacy in patient follow-up after discharge, as many HF clinics are linked to cardiology rather than to internal medicine departments.[19] This could be even more evident for patients discharged directly from the ED, where it is sometimes more difficult to get an appointment to a general physician, specialist or specialized clinic before being discharged.[20,21] In a very recent meta-analysis, the pooled analysis of 41 randomized trials testing transitional care interventions found a significant reduction in the risk of rehospitalization and ED visits by 8% and 29%, respectively,[22] when a transition plan was implemented. In addition, another recent meta-analysis has showed the benefits of HF clinics in reducing hospitalization for HF and all-cause mortality, which was greater in patients with recent ED visit or hospitalization due to decompensation.[23] Indeed, in contrast with usual care, patients managed in HF clinics had an OR of 0.71 (0.56 to 0.91) for all-cause mortality, 0.68 (0.53 to 0.88) for hospitalization for HF, and 0.58 (0.43 to 0.78) for the combined end point. Although specialty managing decompensation of HFmrEF patients did not impact on 30-day mortality, in-hospital mortality and prolonged LOS, the results of this study suggest that all these strategies are probably more developed in cardiology departments and teams, as patients discharged from these areas had better outcomes. Internal medicine and emergency medicine departments should review their protocols and pathways for patients with AHF in order to improve their postdischarge short-term outcomes in patients with HFmrEF.

Our study has some limitations. First, this is a secondary analysis limited to hypothesis generation that will require confirmation by future trials. Second, since there was no sample size calculation due to its exploratory nature, a type-II error cannot be excluded, especially in the comparisons according to the final destination of HFmrEF patients. Third, this a real life cohort, and the selection of patients for direct discharge from ED to home or hospital admission, and the allocation in a particular hospital department, may differ from hospital to hospital. Then, external validation, especially in other countries, is needed. Fourth, the time to treatment initiation (in the prehospital phase and in the ED) was not recorded, and there is an increasing evidence that this can have influence short-term outcomes.[11,24,25] Fifth, the LVEF used to classify patients was measured within a 6-month period before the index AHF episode. Therefore, it may not accurately describe the LVEF at the event and could have ultimately led to misclassification of a small portion of patients. Sixth, some of the secondary outcomes have reached statistical significance in subgroups of patients with HFmrEF only after multiple imputation, in some cases by narrowing the 95% CI of estimations, in others by shifting the HR (and its 95% CI) away from null. Although patterns of missing were random, we cannot definitively exclude that multiple imputation imposed a systematic bias causing OR to move away from null. Seventh, we only included and analyzed patients with previously known LVEF, and this strategy may have imposed an additional bias.

In conclusion, short-term outcomes after an acute decompensation in patients classified as HFmrEF by the ESC 2016 Guidelines did not differ from the other two classical groups: HFrEF and HFpEF. Remarkably, we have found that, in HFmrEF patients managed in cardiology, postdischarge outcomes are significantly better than when patients are managed at internal medicine wards or directly discharged home. This could be driven by a better therapeutic approach during the acute phase or an improved management after discharge. Accordingly, we believe that an in-depth analysis to look for the causes for these differences, and actions to correct them if these differences in short-term outcomes are confirmed in specifically-designed studies, are urgently needed.

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.09.021.

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