

# Comorbidities, Fragility, and Quality of Life in Heart Failure Patients With Midrange Ejection Fraction

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## Abstract

**Objective:** To assess the effects of comorbidities, fragility, and quality of life (QOL) on long-term prognosis in ambulatory patients with heart failure (HF) with midrange left ventricular ejection fraction (HFmrEF), an unexplored area.

**Patients and Methods:** Consecutive patients prospectively evaluated at an HF clinic between August 1, 2001, and December 31, 2015, were retrospectively analyzed on the basis of left ventricular ejection fraction category. We compared patients with HFmrEF (n=185) to those with reduced (HFrEF; n=1058) and preserved (HFpEF; n=162) ejection fraction. Fragility was defined as 1 or more abnormal evaluations on 4 standardized geriatric scales (Barthel Index, Older Americans Resources and Services scale, Pfeiffer Test, and abbreviated-Geriatric Depression Scale). The QOL was assessed with the Minnesota Living with Heart Failure Questionnaire. A comorbidity score (0-7) was constructed. All-cause death, HF-related hospitalization, and the composite end point of both were assessed.

**Results:** Comorbidities and QOL scores were similar in HFmrEF ( $2.41 \pm 1.5$  and  $30.1 \pm 18.3$ , respectively) and HFrEF ( $2.30 \pm 1.4$  and  $30.8 \pm 18.5$ , respectively) and were higher in HFpEF ( $3.02 \pm 1.5$ ,  $P < .001$ , and  $36.5 \pm 20.7$ ,  $P = .003$ , respectively). No statistically significant differences in fragility between HFmrEF (48.6%) and HFrEF (41.9%) ( $P = .09$ ) nor HFpEF (54.3%) ( $P = .29$ ) were found. In univariate analysis, the association of comorbidities, QOL, and fragility with the 3 end points was higher for HFmrEF than for HFrEF and HFpEF. In multivariate analysis, comorbidities were independently associated with the 3 end points ( $P \leq .001$ ), and fragility was independently associated with all-cause death and the composite end point ( $P < .001$ ) in HFmrEF.

**Conclusion:** Comorbidities and fragility are independent predictors of outcomes in ambulatory patients with HFmrEF and should be considered in the routine clinical assessment of HFmrEF.

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Heart failure (HF) is a chronic condition associated with frequent hospital admissions and poor prognosis. In developed countries, 1% to 2% of the adult population has HF, and this prevalence rises to 10% or more in those aged 70 years and older.<sup>1</sup> The signs and symptoms of HF substantially impair patients' quality of life (QOL). Patients with HF frequently have comorbidities

that contribute to increased morbidity and mortality and further impair their QOL.<sup>2</sup> The most prevalent comorbidities are chronic kidney disease, anemia, and diabetes, which are independently associated with a higher risk of mortality and/or HF hospitalization.<sup>2</sup>

Patients with HF often have coexisting fragility. Indeed, even young patients with HF show a high degree of fragility,<sup>3-5</sup> which

also contributes to QOL impairment.<sup>5</sup> In this context, QOL is related to fragility in the full age spectrum of patients with HF.<sup>5</sup> Notably, there is still no universal definition of fragility; thus, there are no fully standardized methods for measuring it, although several tools are increasingly used in recent times.<sup>6</sup> We started to assess fragility almost 2 decades ago in ambulatory patients with HF using a set of validated geriatric scales as surrogates of fragility,<sup>3,5</sup> and with these scales we have shown that fragility is a key determinant for the prognosis of patients with HF of all ages.<sup>7</sup>

The 2016 HF European Society of Cardiology Guidelines suggest that more investigation is needed to characterize the newly defined subgroup of patients with heart failure and mildly reduced left ventricular ejection fraction (HFmrEF).<sup>8</sup> These patients, in whom the left ventricular ejection fraction (LVEF) ranges from 40% to 49%, comprise a gray area between patients with HF with reduced ejection fraction (HFrEF) and patients with HF with preserved ejection fraction (HFpEF). Accordingly, the present study aimed to assess the association of fragility, comorbidities, and QOL on the long-term prognosis of ambulatory patients with HFmrEF and to compare the characteristics of patients with HFmrEF with those of patients with HFrEF and patients with HFpEF.

## PATIENTS AND METHODS

### Study Population

The study included consecutive ambulatory patients who were referred to a structured HF clinic at a university hospital between August 1, 2001, and December 31, 2015. The clinical practice criteria for referral to the HF clinic have been reported elsewhere<sup>5,9-11</sup> and were irrespective of etiology (at least 1 HF hospitalization and/or reduced LVEF <40%). The patients, their clinical characteristics, and the events during follow-up were prospectively acquired, but the current analysis was retrospectively performed on the basis of new classification of the European Society of Cardiology.

All patients provide written informed consent at their first (baseline) visit for the collection of samples for analysis and for the use of their clinical data for research purposes. The

study was approved by the local ethics committee and undertaken in compliance with the principles of the Declaration of Helsinki.

### Categorization of LVEF

Patients were categorized according to the baseline LVEF at first visit in HFrEF (LVEF, <40%), HFmrEF (LVEF, 40%-49%), and HFpEF (LVEF, ≥50%), independently of how was the LVEF evolution during follow-up.

### Assessment of QOL

The QOL was assessed at the baseline visit using the Spanish version of an HF-specific questionnaire, the Minnesota Living with Heart Failure Questionnaire (MLHFQ),<sup>12</sup> which is widely used<sup>13</sup> and has been prospectively validated in Spain.<sup>14,15</sup> The MLHFQ consists of 21 questions and evaluates the impact of HF on the physical, psychological, and social aspects of patients' lives. The responses range from 0 (no limitation) to 5 (maximal limitation); thus, the global scores can range from 0 to 105, with higher scores reflecting worse QOL. Depending on the patient's reading and writing capabilities, an HF clinic nurse helped the patient complete the questionnaire<sup>13</sup> without altering the patient's response or compromising the patient's independence.

### Fragility Assessment

Fragility was assessed at baseline using a basic geriatric evaluation with 4 standardized geriatric scales.<sup>3,5,7</sup> The Barthel Index<sup>16</sup> evaluates independence in performing basic activities of daily living (range, 0-100); the Older Americans Resources and Services (OARS) Scale (the Instrumental Activities Daily Living subscale of the Multidimensional Functional Assessment Questionnaire)<sup>17</sup> evaluates autonomy in performing instrumental activities of daily living (range, 0-14); the Pfeiffer Test (Short Portable Mental Status Questionnaire)<sup>18</sup> evaluates cognitive function (range, 0-10); and the abbreviated Geriatric Depression Scale (GDS)<sup>19</sup> identifies possible emotional problems. Fragility was defined as having at least 1 abnormal evaluation on any of these 4 scales.

The predefined criteria for abnormal results for the scales were as follows<sup>3,5,7</sup>: Barthel Index,

less than 90; OARS, less than 10 in women and less than 6 in men; Pfeiffer Test score, more than 3 ( $\pm 1$ , depending on educational level); and 1 or more positive responses for depression on the abbreviated GDS. The OARS score was considered differently for men and women because of marked cultural and environmental differences, as recommended by others.<sup>20</sup> The presence of at least one abnormal evaluation identified fragile patients for the purpose of the study, as described previously.<sup>3,5,11,21,22</sup>

### Comorbidity Assessment

A comorbidity score that ranged from 0 to 7 was created. The score is a sum, with the presence of each of the following 7 conditions counted as 1: diabetes, hypertension, chronic obstructive pulmonary disease, renal failure (estimated glomerular filtration rate,  $<60$  mL/min per  $1.73$  m<sup>2</sup>), anemia (hemoglobin,  $<12$  g/dL; to convert to g/L, multiply by 10.0), peripheral artery disease, and atrial fibrillation.

### Follow-up and End-Point Assessment

All patients were seen regularly at follow-up visits at the HF clinic according to their clinical needs.<sup>5,9,11</sup> The follow-up visits included a minimum of one visit with a nurse every 3 months and one visit with a physician every 6 months (a cardiologist, internist, or family physician). There were also optional visits with geriatrics, psychiatry, and rehabilitation specialists, and, since 2014, with nephrology and endocrinology specialists.

The primary end points were all-cause death, HF-related hospitalization, and the composite end point of both. The number and causes of death and HF-related hospitalizations during follow-up were obtained from clinical records at the HF clinic, other hospital departments, or other hospital records or by contacting the patient's relatives. The data were verified using the Catalan and Spanish Health System databases. We lost 3 patients during follow-up for survival information and 18 for the HF-related hospitalization end point; these patients were censored in the corresponding analyses. Cardiac transplantation was performed in 6 patients during follow-up and was considered as a death for the analyses. However, no patient with HFmrEF received a cardiac transplant.

### Statistical Analyses

Categorical variables were expressed as frequencies and percentages. Continuous variables were described as means  $\pm$  SDs or as medians and 25th to 75th percentiles (Q1-Q3) for cases with skewed distribution. Normal distribution was assessed using normal Q-Q plots. Statistical differences between groups were assessed using the  $\chi^2$  test for categorical variables, the Student *t* test for continuous variables with normal distribution, or the Mann-Whitney *U* test for variables with nonnormal distribution. Follow-up for survival and event-free survival analyses starts at first visit. Univariate Cox regression analyses were performed for each variable of interest and for each end point. For the HF-related hospitalization end point, all-cause death was included in all the analyses as a competing risk, and the Gray method was used. Furthermore, separate multivariate Cox proportional hazards models were created that included all-cause death and the composite end point as the dependent variable and fragility, comorbidities, and QOL (per every 5 points in the score) and age, sex, New York Heart Association (NYHA) functional class, and ischemic etiology as covariates. Adjusted cumulative incidence curves up to 11 years were plotted for the composite end point in patients with HFmrEF according to the presence of fragility, the number of comorbidities (grouped into 4 groups: none, 1, 2-4, or 5-7), and the MLHFQ score (divided into quartiles). Statistical analyses were performed with SPSS 15 (SPSS Inc) and Stata 13.0 (StataCorp). A 2-sided *P* value of less than .05 was considered significant.

### RESULTS

The study included 185 patients with HFmrEF attended between August 1, 2001, and December 31, 2015. There were 127 men and 58 women with a mean age of  $67.7 \pm 11.7$  years, a median HF duration of 12 months (range, 2-44 months), 58% with ischemic etiology, and 119 (64.3%) and 59 (31.9%) in NYHA class II and III, respectively. [Table 1](#) compares the characteristics of patients with HFmrEF with those of 1058 patients with HFrfEF and 162 patients with HFpEF. Although there were some statistically significant differences between patients with

**TABLE 1. Baseline Demographic, Clinical, Biochemical, and Pharmacological Treatment Data of the Patients With Heart Failure (HF) During Follow-up<sup>a,b</sup>**

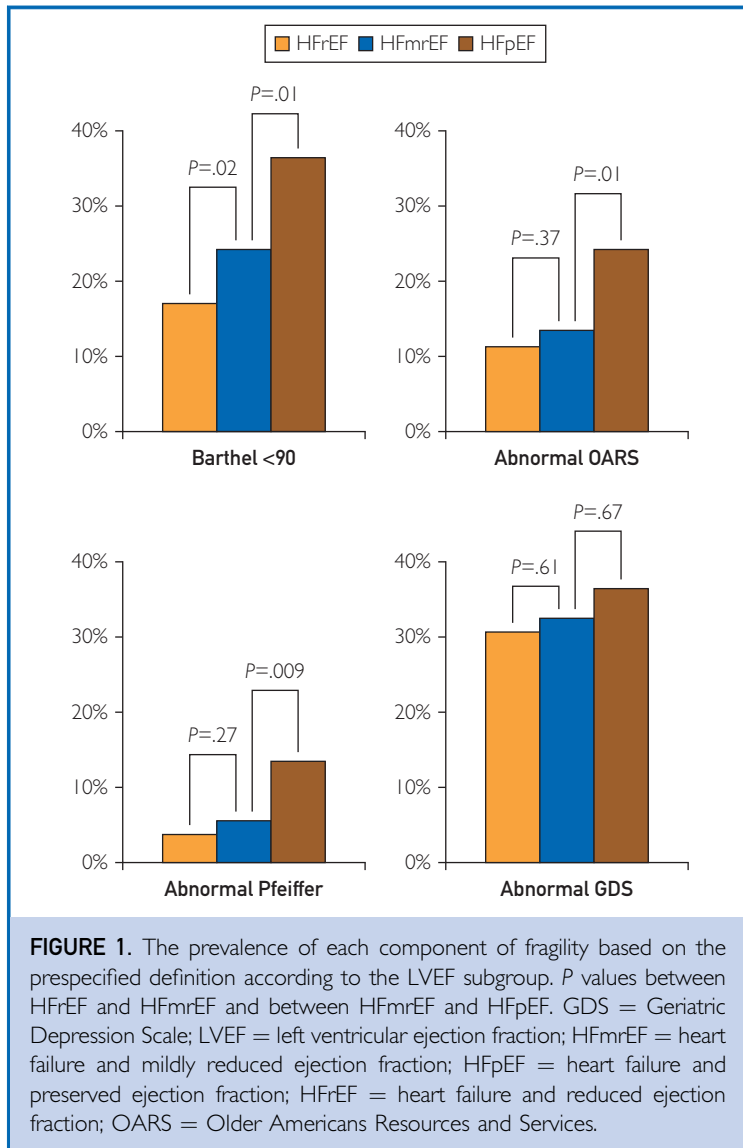
Characteristic	1. HFmrEF (n=185)	2. HFrEF (n=1058)	3. HFpEF (n=162)	P value	
				1 vs 2	1 vs 3
Age (y)	66.7±11.7	65.9±12.2	70.7±13.9	.07	.03
Female sex	58 (31.4)	234 (22.1)	98 (60.5)	.006	<.001
Etiology				.02	<.001
Ischemic heart disease	107 (57.8)	611 (57.8)	24 (14.8)	.98	<.001
Dilated cardiomyopathy	14 (7.6)	151 (14.3)	6 (3.7)	.03	.10
Hypertensive cardiomyopathy	17 (9.2)	69 (6.5)	48 (29.6)	.43	<.001
Alcohol cardiomyopathy	7 (3.8)	63 (6)	5 (3.1)	.41	.74
Drug-related cardiomyopathy	7 (3.8)	28 (2.6)	0	.34	.02
Valvular disease	21 (11.4)	63 (6)	48 (29.6)	.03	<.001
Other	12 (6.5)	73 (6.9)	31 (19.1)	.93	.001
HF duration (mo)	12 (2-44)	8 (1-50)	20 (4-60)	.56	.03
Number of HF admissions	0.97±1.2	1.03±1.3	1.45±1.6	.60	.001
LVEF	42.8%±2.8%	27%±7.2%	60.9%±7.7%	<.001	<.001
NYHA functional class				.52	.05
I	6 (3.2)	52 (4.9)	5 (3.1)		
II	119 (64.3)	687 (64.9)	86 (53.1)		
III	59 (31.9)	302 (28.5)	65 (40.1)		
IV	1 (0.5)	17 (1.6)	6 (3.7)		
Comorbidities	2.4±1.5	2.3±1.4	3±1.5	.31	<.001
Hypertension	119 (64.3)	623 (58.9)	113 (69.8)	.16	.28
Diabetes mellitus	68 (36.8)	419 (39.6)	64 (39.5)	.46	.60
COPD	22 (11.9)	202 (19.1)	33 (20.4)	.02	.03
Renal failure <sup>c</sup>	95 (51.4)	563 (53.2)	108 (66.7)	.64	.004
Anemia <sup>d</sup>	71 (38.4)	303 (28.6)	81 (50)	.008	.03
Peripheral vascular disease	32 (17.3)	177 (16.7)	19 (11.7)	.85	.14
Atrial fibrillation	39 (21.1)	142 (13.4)	72 (44.4)	.006	<.001
Treatments at baseline					
ACEI/ARB	139 (75.1)	840 (79.4)	77 (4.5)	.19	<.001
β-blockers	123 (63.5)	760 (71.8)	69 (42.6)	.14	<.001
MRA	40 (21.6)	323 (30.5)	31 (19.1)	.01	.57
Loop diuretics	128 (69.2)	811 (76.7)	134 (82.7)	.03	.003
Digoxin	36 (19.5)	252 (23.8)	49 (30.2)	.20	.02
Ivabradine	4 (2.2)	28 (2.6)	0	.70	.06
ICD	4 (2.2)	76 (7.2)	0	.01	.06
CTR	3 (1.6)	28 (2.6)	1 (0.6)	.41	.38
Treatments during follow-up					
ACEI/ARB	163 (88.1)	969 (91.6)	108 (66.7)	.13	<.001
β-blockers	156 (84.3)	956 (90.4)	105 (64.8)	.01	<.001
MRA	92 (49.7)	652 (61.6)	76 (46.9)	.002	.60
Loop diuretics	158 (85.4)	970 (91.7)	151 (93.2)	.007	.02
Digoxin	61 (33)	450 (42.5)	70 (43.2)	.02	.05
Ivabradine	13 (7)	148 (14)	4 (2.5)	.009	.05
ICD	8 (4.3)	169 (16)	2 (1.2)	<.001	.09
CRT	9 (4.9)	108 (10.2)	3 (1.9)	.02	.13

<sup>a</sup>ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; HFmrEF = heart failure and mildly reduced ejection fraction; HFpEF = heart failure and preserved ejection fraction; HFrEF = heart failure and reduced ejection fraction; ICD = implantable cardioverter device; LVEF = left ventricular ejection fraction; MRA = mineral corticoid receptor antagonist; NYHA = New York Heart Association.

<sup>b</sup>Data are expressed as means ± SDs, as medians (25th-75th percentiles), or as absolute numbers (percentage).

<sup>c</sup>Estimated Glomerular Filtration Rate <60 mL/min/1.73 m<sup>2</sup>.

<sup>d</sup>Hemoglobin <12 g/dL (to convert to g/L, multiply by 10.0).



HFmrEF and both patients with HFrEF and patients with HFpEF, the differences were greater between patients with HFmrEF and patients with HFpEF (Table 1). In summary, patients with HFmrEF were younger, predominantly men, and of ischemic etiology, had lower previous HF-related admissions, were treated more frequently with  $\beta$ -blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers than HFpEF patients, and received less  $\beta$ -blockers, mineral corticoid receptor antagonist, digoxin, ivabradine, and implantable cardioverter device than did patients with HFrEF. The number of comorbidities in patients with HFmrEF

( $2.41 \pm 1.5$ ) was similar to the number in patients with HFrEF ( $2.30 \pm 1.4$ ;  $P = .31$ ) and was significantly lower than the number in patients with HFpEF ( $3.02 \pm 1.5$ ;  $P < .001$ ).

In the HFmrEF cohort, 90 patients (48.6%) fulfilled the fragility criteria; 45 (24.3%) had a Barthel Index of less than 90; 25 (13.5%) had an anomalous OARS scale score; 10 (5.4%) had an abnormal score on the Pfeiffer Test; and 60 (32.4%) had a positive response for depression on the abbreviated GDS. The prevalence of fragility was not statistically different in patients with HFmrEF and in patients with HFrEF or HFpEF, although it was numerically slightly higher than in patients with HFrEF (41.9%;  $P = .09$ ) and lower than in patients with HFpEF (54.3%;  $P = .29$ ). Figure 1 shows the prevalence of each component of fragility according to the definition used in this study. Only Barthel Index of less than 90 was significantly more frequent in patients with HFmrEF than in patients with HFrEF ( $P = .02$ ). In contrast, the mean QOL score on the MLHFQ was  $30.1 \pm 18.3$  in patients with HFmrEF, which was similar to the mean score in patients with HFrEF ( $30.8 \pm 18.5$ ;  $P = .61$ ) and better than the mean score in patients with HFpEF ( $36.5 \pm 20.7$ ;  $P = .003$ ). Patients with fragility received less antineurohormonal and device treatments and more loop diuretics (Supplemental Table, available online at <http://mcpiqjournal.org/>).

The median follow-up was 5.6 years (Q1-Q3, 2.4-9.3). During follow-up, there were 104 deaths, 35 HF-related hospitalizations, and 112 composite end points. In univariate Cox regression analysis, the number of comorbidities was significantly associated with the 3 studied end points, whereas fragility and QOL were significantly associated with all-cause death and the composite end point (Table 2). The hazard ratios in patients with HFmrEF were higher for most of the end points than the hazard ratios in patients with HFrEF and patients with HFpEF, mainly for the number of comorbidities (Table 2). In separate multivariate analyses that also had age, sex, NYHA functional class, and ischemic etiology as covariates, the number of comorbidities remained strongly and independently associated with the 3 end points ( $P \leq .001$ ) as did fragility with all-cause death and the composite end point ( $P < .001$ ); however, QOL lost

**TABLE 2. Univariate Cox Regression Analyses<sup>a,b</sup>**

Variable	All-cause death			HF-related hospitalization			Composite end point all-cause death or HF hospitalization		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
No. of comorbidities <sup>c</sup>									
HFmrEF	1.56	1.36-1.78	<.001	1.90	1.50-2.40	<.001	1.61	1.42-1.83	<.001
HFrEF	1.45	1.37-1.53	<.001	1.31	1.20-1.42	<.001	1.44	1.36-1.52	<.001
HFpEF	1.52	1.31-1.76	.001	1.14	0.97-1.34	.12	1.44	1.26-1.64	<.001
Fragility									
HFmrEF	2.7	1.81-4.02	<.001	1.69	0.86-3.31	.13	2.53	1.73-3.71	<.001
HFrEF	1.89	1.62-2.22	<.001	1.27	0.99-1.61	.05	1.84	1.58-2.14	<.001
HFpEF	1.70	1.17-2.49	.006	1.99	1.15-3.45	.01	1.86	1.29-2.68	.001
Quality of life <sup>d</sup>									
HFmrEF	1.09	1.03-1.15	.002	1.07	0.99-1.14	.08	1.08	1.03-1.14	.002
HFrEF	1.06	1.04-1.08	<.001	1.05	1.02-1.08	<.001	1.07	1.05-1.09	<.001
HFpEF	1.06	1.02-1.11	.007	1.08	1.03-1.14	.003	1.09	1.04-1.13	<.001

<sup>a</sup>HF = heart failure; HFmrEF = heart failure and mildly reduced ejection fraction; HFpEF = heart failure and preserved ejection fraction; HFrEF = heart failure and reduced ejection fraction; HR = hazard ratio.  
<sup>b</sup>For HF-related hospitalization, death was included as a competing risk.  
<sup>c</sup>Comorbidities: hypertension, diabetes mellitus, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, renal failure (defined as a creatinine clearance rate of <60 mL/min), and anemia (defined as estimated glomerular filtration rate of <12 g/dL).  
<sup>d</sup>Per every 5 points on the Minnesota Living with Heart Failure Questionnaire.

statistical significance (Table 3). Figure 2 shows the adjusted cumulative incidence curves up to 11 years for the composite end point in patients with HFmrEF according to the presence of fragility, the number of comorbidities, and the MLHFQ score.

**DISCUSSION**

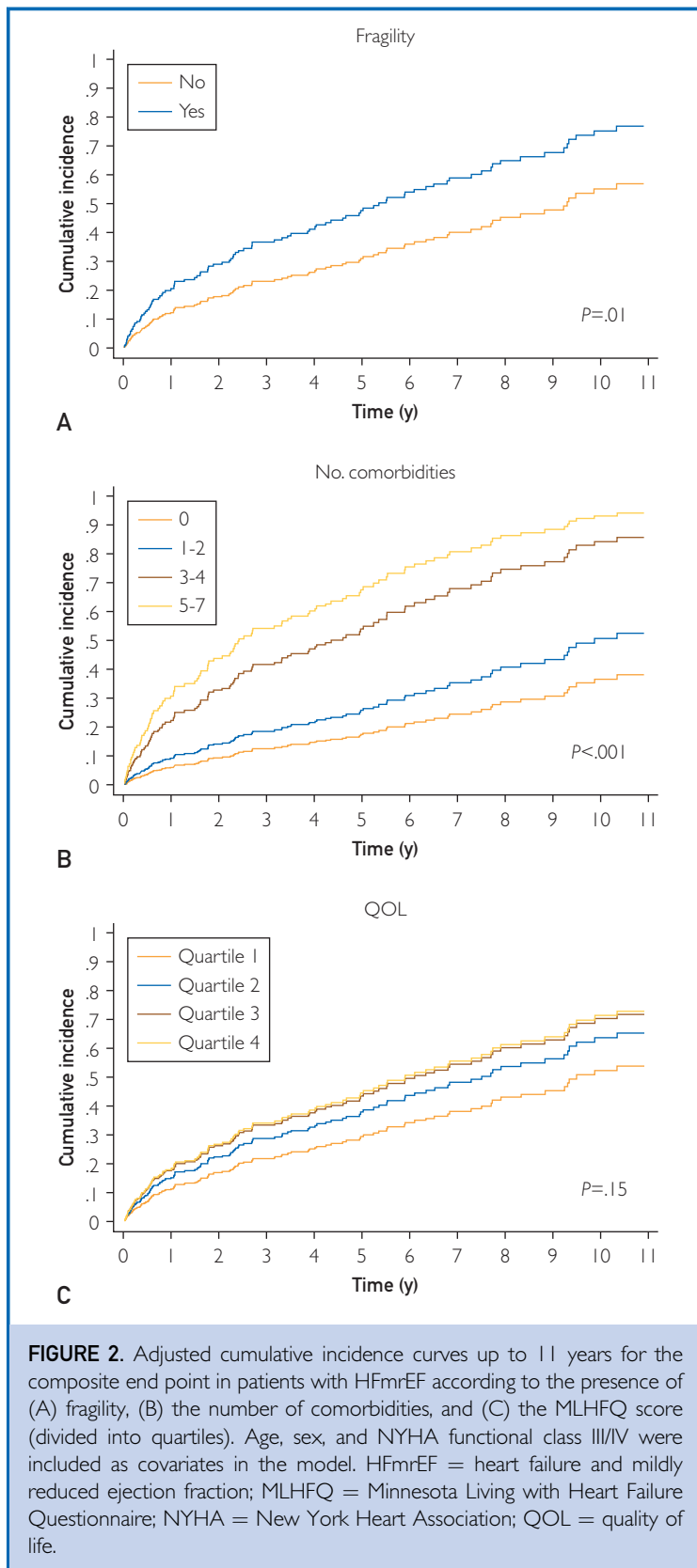
To our knowledge, this is the first study to assess and show together the prognostic value of fragility, comorbidities, and QOL in outpatients with HFmrEF. Our findings indicate that in these patients, fragility and

**TABLE 3. Multivariate Cox Regression Analysis of Patients With HFmrEF<sup>a,b</sup>**

Variable	All-cause death		HF-related first hospitalization		Composite end point	
	HR Cox (95% CI)	P value	HR Cox (95% CI)	P value	HR Cox (95% CI)	P value
Fragility						
Age	2.18 (1.43-3.33)	<.001	1.29 (0.57-2.91)	.54	2.10 (1.40-3.15)	<.001
Sex	1.09 (1.06-1.11)	<.001	1.02 (0.99-1.06)	.12	1.08 (1.06-1.11)	<.001
NYHA III/IV	0.95 (0.63-1.44)	.81	0.88 (0.42-1.86)	.74	0.95 (0.63-1.41)	.78
Quality of life <sup>c</sup>						
Age	1.25 (0.82-1.90)	.30	1.53 (0.70-3.32)	.29	1.22 (0.81-1.83)	.34
Age	1.05 (0.99-1.11)	.14	1.04 (0.95-1.12)	.40	1.05 (0.99-1.12)	.08
Sex	1.08 (1.06-1.11)	<.001	1.03 (1.00-1.06)	.09	1.08 (1.06-1.10)	<.001
Sex	0.94 (0.90-1.43)	.77	0.87 (0.41-1.86)	.72	0.92 (0.61-1.39)	.70
NYHA III/IV	1.39 (0.90-2.15)	.14	1.48 (0.71-3.11)	.30	1.34 (0.88-2.04)	.18
No. of comorbidities <sup>d</sup>						
Age	1.30 (1.12-1.51)	.001	2.00 (1.53-2.62)	<.001	1.35 (1.17-1.57)	<.001
Age	1.07 (1.04-1.10)	<.001	0.98 (0.94-1.02)	.34	1.06 (1.04-1.09)	<.001
Sex	0.93 (0.62-1.41)	.74	0.81 (0.39-1.68)	.57	0.91 (0.66-1.36)	.64
NYHA III/IV	1.61 (1.07-2.41)	.02	1.61 (0.83-3.11)	.16	1.57 (1.06-2.32)	.03

<sup>a</sup>HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HR = hazard ratio; NYHA = New York Heart Association.  
<sup>b</sup>For HF-related hospitalization, death was included as a competing risk.  
<sup>c</sup>Per every 5 points on the Minnesota Living with Heart Failure Questionnaire.  
<sup>d</sup>Comorbidities: Hypertension, diabetes mellitus, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, renal failure (defined as estimated glomerular filtration rate of <60 mL/min), and anemia (defined as a hemoglobin level of <12 g/dL [to convert to g/L, multiply by 10.0]).





comorbidities in particular importantly influenced patient outcomes (both morbidity and mortality). Remarkably and unexpectedly, this influence was greater in outpatients with HFmrEF than in patients with HFrEF and patients with HFpEF.

Fragility is a common problem in patients with HF, and it is present in both elderly and younger patients.<sup>3,4</sup> We previously demonstrated the profound impact of fragility on mortality in outpatients with HF in a small cohort (n=300) with only 1 year of follow-up,<sup>22</sup> and we confirmed the results after 5 years of follow-up.<sup>7</sup> In our previous study, fragile HF patient subgroups had a statistically significant higher LVEF than the nonfragile subgroups.<sup>7</sup> One explanation may be that HFpEF is more typically associated with older female patients. In fact, the fragile subpopulations of patients with HF have significantly more females.<sup>7</sup> In one study, most nondependent elderly patients who were hospitalized for HF showed a frailty phenotype at discharge that conferred a roughly 2-fold increased risk for mortality and readmission during the first year, independent of age, comorbidity, and classic HF prognostic factors.<sup>23</sup> The present study confirmed that the high prevalence of fragility goes beyond the severity of cardiac illness.

One of the most important reasons for assessing fragility in patients with HF is that it is, at least partly, a reversible condition. Interventions such as cardiac rehabilitation, physical exercise, polypharmacy reduction (especially the reduction of unnecessary medications), nutritional recommendations, and HF self-care and treatment optimization could be particularly useful for delaying the transition from fragility to disability and for reducing mortality after discharge in frail patients.<sup>23,24</sup> Our study found a high prevalence of fragility in HFmrEF (48.6%); the prevalence was nearly as high as that found in HFpEF and slightly higher than that in HFrEF. It is not clear why a higher proportion of patients with HFmrEF than patients with HFrEF have fragility, but it may be related to age and sex in this subgroup of patients.

Comorbidities are common in patients with HF.<sup>2,25</sup> Although HFpEF is associated with more comorbidities than is HFrEF, the patterns of co-occurring comorbidities are similar.<sup>25,26</sup>

The HFpEF has been suggested to be the result of several comorbidities that induce a systemic proinflammatory state.<sup>27</sup> There are several common comorbidities in patients with HF that have varying clinical relevance. In particular, hypertension, coronary artery disease, atrial fibrillation, and renal failure show direct causal associations with HF.<sup>25</sup> Anemia often develops along with HF<sup>25,28</sup> and has been linked to worse prognosis in HF.<sup>29</sup> The relationship between HF and diabetes is bidirectional, and the incidence of diabetes in patients with HF is significant.<sup>25</sup> Patients with diabetes have an increased risk of developing HF, and diabetes is associated with poor prognosis in patients with HF.<sup>30,31</sup> Renal failure is very common in patients with HF due to the interdependency of the kidneys and the heart,<sup>25</sup> and patients with both HF and renal insufficiency have a poor prognosis.<sup>9,32</sup> Even mild impairment of kidney function is associated with higher mortality compared with normal kidney function in these patients.<sup>33</sup> Other comorbidities, such as atrial fibrillation, can also influence the prognosis of patients with HF.<sup>34</sup> However, there is limited evidence that specific treatment of comorbidities is associated with a lower incidence of major cardiovascular events in HF regardless of LVEF. This may be because interventions are more often used in patients with more severe HF.<sup>25</sup> In view of our results, patients with HFmrEF may be the ideal group for targeted comorbidity treatment due to its effect on their prognosis and their less severe HF.

Earlier data suggested that QOL is related to fragility in elderly patients with HF, but in fact this is true for patients with HF of all ages.<sup>5</sup> The QOL of patients with HF can improve significantly over time in response to educational and monitoring programs, although it may decrease slightly when the programs end. Accordingly, improving patient QOL should be one of the main objectives of HF units or programs.<sup>11</sup> In the present study, the QOL of patients with HFmrEF was impaired and was similar to the QOL of patients with HFrEF and worse than that of patients with HFpEF. The literature shows a lack of correlation between QOL and LVEF.<sup>12,35-38</sup> However, Joyce et al<sup>39</sup> compared patients with reduced, preserved, and better LVEF (improvement in LVEF,  $\geq 50\%$ ) and found that fewer than one-half of patients

with ambulatory HF rated HF as the greatest limitation to their QOL. This suggested that it may be difficult to improve QOL using HF-targeted therapies alone, particularly in patients with higher LVEF and comorbidities.<sup>39</sup>

Our study has some limitations. Quantitative transthoracic 2-dimensional echocardiography was used to obtain LVEF values and was performed routinely in clinical practice. The left ventricle function could have been assessed more precisely using 3-dimensional echocardiography or cardiac magnetic resonance imaging. The classification of patients into 3 LVEF groups was based on LVEF as determined at admission to the HF clinic. The evolution of LVEF during follow-up was not taken into account in the analyses, which used baseline-based stratification, and we did not recategorize the patients during the follow-up period. We cannot discard that because of doing such recategorization the obtained results could not be modified. Fragility, comorbidities, and QOL were also determined at the first visit. Changes in QOL or the appearance of new fragility positive criteria or new comorbidities was not assessed. The term fragility may be used to describe slightly different settings; yet from a strict geriatric perspective, it means an increased risk of disability. Indeed, our approach has been included as the Comprehensive Geriatric Assessment instrument in a recent comprehensive review by McDonagh et al.<sup>6</sup> Most patients were referred from the cardiology department and had ischemic heart disease as the cause of HF, and the study population was relatively young, with a small percentage of women. Thus, it may not be possible to extrapolate our results to a general population of patients with HF. Indeed, because of the inclusion criteria of the HF unit, HFmrEF and even more HFpEF represent selected higher risk patients than general patients with HFmrEF and HFpEF.

## CONCLUSION

Comorbidities, fragility, and perceived QOL impairment are common in patients with HFmrEF. Comorbidities and fragility were key predictors of outcomes in ambulatory patients with HFmrHF to a greater extent than in patients with HFrEF and patients



with HFpEF. Our data highlight the importance of assessing frailty beyond a strictly geriatric syndrome and tackling comorbidities in all patients, including those with less severe ventricular dysfunction. Precisely in patients with HFmrEF, treatment and management of comorbidities might obtain higher clinical benefit. However, our results should be taken as hypothesis generating and should be confirmed in larger samples of patients with HFmrEF.

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### SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://mcpiqjournal.org/>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** **GDS** = Geriatric Depression Scale; **HF** = heart failure; **HFmrEF** = heart failure and mildly reduced ejection fraction; **HFpEF** = heart failure and preserved left ventricular ejection fraction; **HFrEF** = heart failure and reduced left ventricular ejection fraction; **LVEF** = left ventricular ejection fraction; **MLHFQ** = Minnesota Living with Heart Failure Questionnaire; **NYHA** = New York Heart Association; **OARS** = Older Americans Resources and Services; **QOL** = quality of life

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