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Fragility is a key determinant of survival in heart failure patients ☆

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ABSTRACT

Background: Heart failure (HF) is a chronic condition with poor prognosis, and has a high prevalence among older adults. Due to older age, fragility is often present among HF patients. However, even young HF patients show a high degree of fragility. The effect of fragility on long-term prognosis in HF patients, irrespective of age, remains unexplored. The aim of this study was to assess the influence of fragility on long-term prognosis in outpatients with HF.

Methods and results: At least one abnormal evaluation among four standardized geriatric scales was used to identify fragility. Predefined criteria for such scales were: Barthel Index, <90; OARS scale, <10 in women and <6 in men; Pfeiffer Test, >3 (±1, depending on educational grade); and ≥1 positive response for depression on the abbreviated Geriatric Depression Scale (GDS). We assessed 1314 consecutive HF outpatients (27.8% women, mean age years 66.7 ± 12.4 years with different etiologies. Fragility was detected in 581 (44.2%) patients. 626 deaths occurred during follow-up; the median follow-up was 3.6 years [P_{25}–P_{75}: 1.8–6.7] for the total cohort, and 4.9 years [P_{25}–P_{75}: 2.5–8.4] for living patients. Fragility and its components were significantly associated with decreased survival by univariate analysis. In a comprehensive multivariable Cox regression analysis, fragility remained independently associated with survival in the entire cohort, and in age and left ventricular ejection fraction subgroups.

Conclusion: Fragility is a key determinant of survival in ambulatory patients with HF across all age strata.

1. Introduction

Heart failure (HF) is a chronic condition with frequent hospital admissions and poor prognosis, and has a high prevalence among older adults. Due to older age, fragility is often present among HF patients. However, even young HF patients show a high degree of fragility [1,2].

There is no universal definition of fragility; therefore, there are no standardized methods for measuring it. The most frequent methods are based on questionnaires aimed at primary care patients [3,4] or acute care patients admitted to hospital [5]. To the best of our knowledge, there are no questionnaires specifically designed to detect fragility in ambulatory HF patients, and a set of validated geriatric scales may be used as surrogates of fragility [1,2]. Accordingly, the aim of the present study was to assess the relationship between fragility and HF prognosis, and whether a simple fragility assessment may be useful for patient risk stratification.

2. Methods

2.1. Study population

All consecutive outpatients, who were referred to a structured HF clinic of a university hospital between August 2001 and March 2012, were included. Clinical practice referral criteria to the HF unit have been reported elsewhere [2,6–8], and were irrespective of etiology (at least one HF hospitalization and/or reduced left ventricular ejection fraction [LVEF] <40%). Most patients were referred from cardiology and internal medicine departments, while fewer were from the emergency room/short-stay unit, or other hospital departments. Less than 10% of patients were admitted to the HF unit due to asymptomatic, reduced LVEF after acute myocardial infarction.

All patients were seen regularly in follow-up visits at the HF clinic, according to their clinical needs. Follow-up visits included a minimum of one visit from a nurse every three months and one visit from a physician every six months (cardiologist, internist, or family

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physician), as well as optional visits from specialists in geriatrics, psychiatry, and rehabilitation. During their baseline visit, patients provided written consent to obtain analytical samples and use their clinical data for research purposes. The study was performed in compliance with the principles of the Declaration of Helsinki.

2.2. Fragility assessment

Four standardized geriatric scales [2] were used to assess fragility in our ambulatory HF cohort: the Barthel Index [9], OARS Scale [10], Pfeiffer Test [11], and the abbreviated Geriatric Depression Scale (GDS) [12]. The predefined criteria for abnormal results [1,2] were: Barthel, <90; OARS, <10 in women and <6 in men; Pfeiffer Test >3 (±1, depending on educational grade); and ≥1 positive response for depression on an abbreviated GDS. The presence of at least one abnormal evaluation identified a fragile patient.

2.3. Death assessment

The number and causes of death during follow-up were obtained from clinical records at the HF unit, other hospital departments, other hospital records, or by contacting the patient's relatives. Data were verified using the databases of the Catalan and Spanish Health System. Five patients were lost during follow-up, and were adequately censored in the survival analysis.

2.4. Statistical analysis

Categorical variables were described by frequencies and percentages. Continuous variables were described by mean ± standard deviation (SD), and median and 25th–75th percentiles (P_{25}–P_{75}) for cases with skewed distribution. Normal distribution was assessed with normal Q–Q plots. Statistical differences between groups were assessed using the chi-square test for categorical variables, Student's-t test for continuous variables of normal distributions, or Mann–Whitney *U* test for non-normal distributions. Cox survival curves were plotted to ascertain the relationship between the baseline presence of fragility (and its components) and mortality. Furthermore, a multivariable Cox proportional hazards model was created, adjusting for classical confounders and the significant covariates in the univariate analysis (Table I in the online-only Data Supplement); treatments administered to less than 100 patients were excluded. Statistical analyses were performed using SPSS 15 (SPSS Inc., Chicago, IL). A two-sided $P < 0.05$ was considered significant.

3. Results

We prospectively enrolled 1314 consecutive ambulatory HF patients. Table 1 shows demographic, clinical, and biochemical data at enrolment, as well as treatment during follow-up. Median follow-up was 3.6 years [P_{25}–P_{75}: 1.8–6.7] for the total cohort and 4.9 years [P_{25}–P_{75}: 2.5–8.4] for living patients (minimum one year). Fragility was present in 44.2% of the studied population at baseline; Table 2 shows the prevalence of fragility and abnormal geriatric scores.

There were 626 deaths during follow-up. Causes of death were HF progression (30.2%), sudden death (13.1%), acute myocardial infarction (6.4%), stroke (2.7%), cardiovascular procedure (1.6%), other cardiovascular causes (5.6 %), non-cardiovascular cause (32.7%), and unknown causes (7.7%). Fragility was significantly associated with lower survival (Fig. 1A). Even after adjusting for other survival risk factors, fragility was independently associated with lower survival (Fig. 1B). Table 3 shows a comprehensive multivariate analysis for the total cohort and for the

Table 1
Baseline demographic, clinical, and biochemical data, as well as pharmacological treatment data during follow-up.

Characteristics	Total cohort	Fragile	Non-fragile	*P*-value
	n = 1314	*n* = 581	*n* = 733	
Age (years)	66.7 ± 12.4	69.3 ± 12.2	64.6 ± 12.2	<0.001
Female sex	364 (27.7%)	240 (41.3%)	124 (16.9%)	<0.001
Etiology				<0.001
Ischemic heart disease	706 (53.7%)	301 (51.8%)	405 (55.3%)	
Dilated cardiomyopathy	157 (11.9%)	65 (11.2%)	92 (12.6%)	
Hypertensive cardiomyopathy	121 (9.2%)	71 (12.2%)	50 (6.8%)	
Alcoholic cardiomyopathy	69 (5.3%)	19 (3.3%)	50 (6.8%)	
Medication-related cardiomyopathy	29 (2.2%)	19 (3.3%)	10 (1.4%)	
Valvular disease	122 (9.3%)	63 (10.8%)	59 (8.0%)	
Other	110 (8.4%)	43 (7.4%)	67 (9.1%)	
Heart failure duration (months)	12 (2–48)	10 (2–48)	12 (2–48)	0.849
	37.6 ± 59.8	37.5 ± 59.6	37.8 ± 59.9	
Number of HF admissions	1 (0–1)	1 (0–2)	1 (0–1)	<0.001
	1.07 ± 1.4	1.26 ± 1.5	0.92 ± 1.2	
LVEF	32.8% ± 13.2	34.3% ± 14.2	31.6% ± 12.2	<0.001
LVEF ≥40%	315 (24.0%)	166 (28.6%)	149 (20.3%)	0.001
NYHA functional class				<0.001
I	62 (4.7%)	11 (1.9%)	51 (7.0%)	
II	820 (62.4%)	289 (49.7%)	531 (72.4%)	
III	408 (31.1%)	262 (45.1%)	146 (19.9%)	
IV	24 (1.8%)	19 (3.3%)	5 (0.7%)	
Comorbidities	2.4 ± 1.4	2.8 ± 1.4	2.1 ± 1.4	<0.001
Hypertension	789 (60.0%)	383 (65.9)	406 (55.4%)	<0.001
Diabetes mellitus	505 (38.4%)	253 (43.5%)	252 (34.4%)	0.001
COPD	238 (18.1%)	119 (20.5%)	119 (16.2%)	0.047
Renal failure (CrCl <60 mL/min)	717 (54.6%)	375 (64.5%)	342 (46.7%)	<0.001
Anemia (Hb <12 g/dL)	422 (32.1%)	245 (42.2%)	177 (24.1%)	<0.001
Peripheral vascular disease	217 (16.5%)	115 (19.8%)	102 (13.9%)	0.004
Atrial fibrillation	237 (18.0%)	121 (20.8%)	116 (15.8%)	0.019
Treatments				
ACEI/ARB	1,156 (88.0%)	489 (84.2%)	667 (91.0%)	<0.001
Beta-blockers	1135 (86.4%)	464 (79.9%)	671 (91.5%)	<0.001
MRA	708 (53.9%)	305 (52.5%)	403 (55.0%)	0.370
Loop diuretics	1186 (90.3%)	537 (92.4%)	649 (88.5%)	0.018
Digoxin	509 (38.7%)	238 (41.0%)	271 (37.0%)	0.140
Statins	939 (71.5%)	375 (64.5%)	564 (76.9%)	<0.001
Ivabradine	93 (7.1%)	35 (6.0%)	58 (7.9%)	0.185
ICD	144 (11.0%)	53 (9.1%)	91 (12.4%)	0.058
CTR	85 (6.5%)	26 (4.5%)	59 (8.0%)	0.009

Data expressed as mean ± standard deviation, median (25th–75th percentiles) or absolute number (percentage).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRT, cardiac resynchronization therapy; Hb, haemoglobin; ICD, implantable cardioverter device; LVEF, left ventricular ejection fraction; MRA: mineral corticoid receptor antagonist; NYHA, New York Heart Association.