

Predictors of long-term survival in patients with a first episode of acute heart failure

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ABSTRACT

Introduction: Acute heart failure (AHF) represents a critical event in heart failure progression, but data on long-term outcomes after first hospitalization remain scarce. The aim is to describe long-term survival and evaluate its predictors after the first episode of AHF.

Material and methods: Patients from five Spanish hospitals with a confirmed first diagnosis of AHF were categorized based on survival (≥ 5 or < 5 years). Thirteen independent variables were identified. Mortality was assessed using Kaplan–Meier curves after up to 10 years of follow-up. Adjusted odds ratios (OR) with 95% confidence intervals (CI) for mortality were calculated. Additionally, adjusted survival probabilities according to patient age and left ventricular ejection fraction (LVEF) were obtained using restricted cubic splines.

Results: A total of 1986 patients were included, with a median age 76 years (range: 68–82), 50% women, and 57% with preserved LVEF. Five-year mortality was 52%. Adjusted analysis showed that age (OR, 0.470 per 10-year increment; 95% CI, 0.421–0.525), New York Heart Association class III–IV vs. I (OR, 0.476; 95% CI, 0.341–0.666) and II vs. I (OR, 0.780; 95% CI, 0.627–0.969), chronic kidney disease (OR, 0.609; 95% CI, 0.452–0.820), coronary artery disease (OR, 0.657; 95% CI, 0.523–0.824), diabetes mellitus (OR, 0.658; 95% CI, 0.534–0.811), and male sex (OR, 0.774; 95% CI, 0.625–0.958) were associated with death within 5 years. LVEF at inclusion was not related to 5-year survival.

Conclusions: Survival after a first AHF episode is poor, with age, New York Heart Association class, kidney function, coronary artery disease, diabetes, and sex being key predictors of long-term mortality.

Key words: acute heart failure, long-term survival, mortality, outcome

INTRODUCTION

Heart failure (HF) is a heterogeneous syndrome resulting from a structural or functional abnormality of the heart [1]. In developed countries the prevalence of HF is 1%–2% [2], but it increases with age, reaching 10% in patients aged ≥ 70 years [3]. HF is usually divided into 2 clinical presentations: chronic heart failure and acute HF (AHF). An episode of AHF

involves the development of symptoms and signs of HF that prompt emergency department (ED) consultation and often unplanned hospital admission. AHF can be further classified into two categories: new onset HF or *de novo* AHF and acutely decompensated HF in patients with a history of HF. The first episode of AHF is a milestone in the natural history of patients with HF [4].

WHAT'S NEW?

This study provides long-term (up to 10 years) follow-up data on patients hospitalized for a first episode of acute heart failure in Spain. It identifies key clinical predictors of 5-year mortality, including age, New York Heart Association functional class, chronic kidney disease, coronary artery disease, diabetes mellitus, and male sex. Contrary to previous assumptions, left ventricular ejection fraction at admission was not associated with long-term survival. The findings contribute real-world evidence from a large, multicenter cohort, addressing the lack of long-term prognostic data. These results may help refine risk stratification for patients after their first acute heart failure hospitalization.

Numerous studies have evaluated the short-term prognosis of patients following their first admission for AHF. However, there is a paucity of studies analyzing the long-term prognosis after the first episode of AHF that requires hospitalization. In a Danish study [5], the 5-year mortality following the first admission for AHF was 61.3%, 63% in a Dutch study [6], 52% in a study from the United Kingdom [7], 60.3% in a Finnish report [8], and around 66% in Australia and New Zealand [9]. These variations in survival may be attributed to differences in healthcare services and population characteristics. Region-specific differences associated with patient outcomes have been described, but there is no information about long-term prognosis in patients from the Mediterranean area [10]. Additionally, previous studies have described the relationship between mortality and different prognostic factors such as age, renal function, diabetes, and ischemic heart disease, left ventricular ejection fraction (LVEF), and natriuretic peptide levels at admission [11–13]. The aim of this study was to describe long-term survival and analyze its predictors in patients with a first episode of AHF.

MATERIAL AND METHODS

Study design and population

The present study is a secondary analysis of patients included in two independent HF registries, the NOVICA and the Hospital Clínico Universitario de Valencia (INCLIVA) registries, which have been described in detail elsewhere [14–16]. In brief, the NOVICA (acronym of the Spanish “*de novo* insuficiencia cardiaca aguda”; in English: “*de novo* AHF”) cohort was designed as an exploratory study including patients diagnosed with a first episode of AHF of any etiology — excluding ST-elevation myocardial infarction — in 4 EDs located in Barcelona (Catalonia, Spain) between 2009 and 2014. The INCLIVA registry comprises all patients diagnosed with AHF of any cause — excluding myocardial infarction — admitted to a Department of Cardiology of a single tertiary care teaching hospital in Valencia (Spain). For the current study, patients recruited from 2007 to 2014 were included. All cases fulfilled diagnostic criteria according to the European Society of Cardiology guidelines based on clinical criteria plus natriuretic peptide and/or echocardiographic confirmation [17–19]. The primary cri-

terion was that patients had never consulted an ED or been hospitalized due to AHF, regardless of whether they had previously been diagnosed with HF or received treatment for HF from general practitioners or ambulatory specialists. The present study was named NOVICA-5 because it expands the data and knowledge provided by previously published studies including patients in the NOVICA cohort.

Data collection and outcomes

Thirteen independent variables were recorded, including demographic data (age, sex), comorbidities — hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, chronic kidney disease, heart valve disease, smoking habit (active), New York Heart Association (NYHA) functional class at baseline (within 15 days prior to the exacerbation episode), electrocardiographic findings (presence of atrial fibrillation, left bundle branch block), and LVEF assessed *via* quantitative echocardiography. LVEF was analyzed as a continuous variable and categorized as preserved ($\geq 50\%$), mildly reduced (40%–49%), or reduced ($< 40\%$).

The outcome of this study was survival. Information on patient survival status and date of death, if applicable, were recorded during follow-up assessments carried out by review of public healthcare medical records (nearly 100% of people living in Spain have universal public healthcare) or via telephone contact. The patients were classified into two groups according to their length of survival after inclusion in the study (first admission due to AHF): patients surviving ≥ 5 years were defined as long-term survivors (LTS), while those with a survival of < 5 years were defined as non-LTS. The follow-up period of all the patients included in the study was over 5 years. This classification, based on survival ≥ 5 years, is a commonly reported metric in studies evaluating long-term outcomes in heart failure [20]. Moreover, this threshold is clinically relevant, as approximately half of patients reach this long-term survival milestone [21].

Both registries received approval from their respective Ethics Committees. All the participating patients provided written consent for inclusion in the registry and for follow-up contact. In cases in which a patient lacked the capacity to consent, consultation was made with a close family member or caregiver. This study was carried out in strict compliance with the principles of the Declaration of Helsinki.

Table 1. Characteristics of the patients included in the study and comparison between long-term survivors and non-long-term survivors

	All patients n = 1986 n (%)	Missing values %	Long-term survivors n = 950 n (%)	Non-long-term survivors n = 1036 n (%)	P-value
Demographic data					
Age, years, median (IQR)	76 (68–82)	0.0	72 (63–79)	80 (73–85)	<0.001
Female sex	991 (49.9)	0.1	476 (50.1)	515 (50.2)	0.877
Comorbidity					
Hypertension	1562 (78.7)	0.0	704 (74.1)	858 (82.8)	<0.001
Dyslipidemia	947 (47.7)	0.0	441 (46.4)	506 (48.8)	0.281
Diabetes mellitus	850 (42.8)	0.0	360 (37.9)	490 (47.3)	<0.001
Coronary artery disease	650 (32.7)	0.0	252 (26.5)	398 (38.4)	<0.001
Chronic kidney disease	275 (13.8)	0.0	83 (8.7)	192 (18.5)	<0.001
Heart valve disease	469 (23.6)	0.0	237 (24.9)	232 (22.4)	0.181
Smoking habit (active)	229 (11.5)	0.0	134 (14.1)	95 (9.2)	<0.001
NYHA class at baseline ^a		2.4			<0.001
I	696 (35.9)		412 (44.1)	284 (28.3)	
II	1005 (51.9)		445 (47.6)	560 (55.8)	
III	231 (11.9)		76 (8.1)	155 (15.5)	
IV	6 (0.3)		2 (0.2)	4 (0.4)	
Electrocardiogram					
On atrial fibrillation	806 (40.8)	0.5	386 (40.8)	420 (40.8)	0.980
With left-bundle branch block on electrocardiogram	476 (24.1)	0.7	208 (22.0)	268 (26.0)	0.038
Echocardiography					
Left ventricular ejection fraction ^a		9.9			0.045
Preserved (≥50%)	1019 (56.9)		490 (54.9)	529 (59.0)	
Mildly reduced (40%–49%)	281 (15.7)		140 (15.7)	141 (15.7)	
Reduced (<40%)	490 (27.4)		263 (29.5)	227 (25.3)	

^aP-value obtained by χ^2 test for trendBold P-values denote statistical significance ($P < 0.05$)

Abbreviations: IQR, interquartile range; NYHA, New York Heart Association dyspnea classification

Statistical analysis

Quantitative variables were presented as median and interquartile range (IQR), and qualitative variables were expressed as counts and percentages. For comparisons, we used the Mann–Whitney U and the χ^2 tests, respectively. Survival tables were generated, and Kaplan–Meier curves were plotted for all-cause death. To identify factors independently associated with LTS multivariable analysis was performed using logistic regression. For this purpose, the 13 independent variables were included in the analysis, and the magnitude of association of each variable with LTS was expressed as the odds ratio (OR) with 95% confidence interval (CI). All independent variables were dichotomic, except for age, which was considered categorized (per each 10-year of increment) and assessed linearly, and LVEF, which was analyzed in three categories: preserved, mildly reduced, and reduced.

Additionally, we also explored the relationship between the quantitative variables of age and LVEF and LTS in a non-linear way using restricted cubic spline (RCS) curves obtained with logistic regression models considered in the present study. The RCS methodology allows the modeling of association between variables using linear and third-degree functions, without imposing linearity on their relationship. In the present study, knots were placed at the 10th, 50th, and 90th percentiles of marginal distribution of each continuous variable, following the recommendations of Harrell [22].

All statistical tests were two-sided, and significance was defined as a P -value < 0.05 . Statistical analyses were conducted using the SPSS package, version 24 (IBM, Armonk, NY, US), and the STATA package, version 13 (Stata Corp, College Station, TX, US). Figures were created using Microsoft Excel and PowerPoint 2016 (Microsoft Corporate Office, Redmond, WA, US).

RESULTS

A total of 1986 patients meeting the selection criteria were analyzed (first episode of AHF and followed for at least 5 years). The median age was 76 years (interquartile range 68–82), and 50% were women. The most prevalent comorbidities were hypertension (79%), dyslipidemia (48%), diabetes (43%), and atrial fibrillation (41%). Notably, an LVEF $\geq 50\%$ was observed in 57% of patients. Additional clinical characteristics are summarized in [Table 1](#).

The survival curve for the entire cohort showed a mortality of 20% within the first year, 52% at 5 years, and 76% at 10 years ([Figure 1](#)). Accordingly, 950 patients (48%) were classified as LTS. These patients were younger, had fewer comorbidities, better NYHA class at baseline, and higher LVEF compared to non-LTS ([Table 1](#)). Adjusted analysis showed that several variables were independently associated with a decreased likelihood of being a LTS ([Figure 2](#)). These variables included age (OR, 0.470 per 10-year increment; 95% CI, 0.421–0.525), NYHA class III–IV at baseline (OR, 0.476 compared to class I;

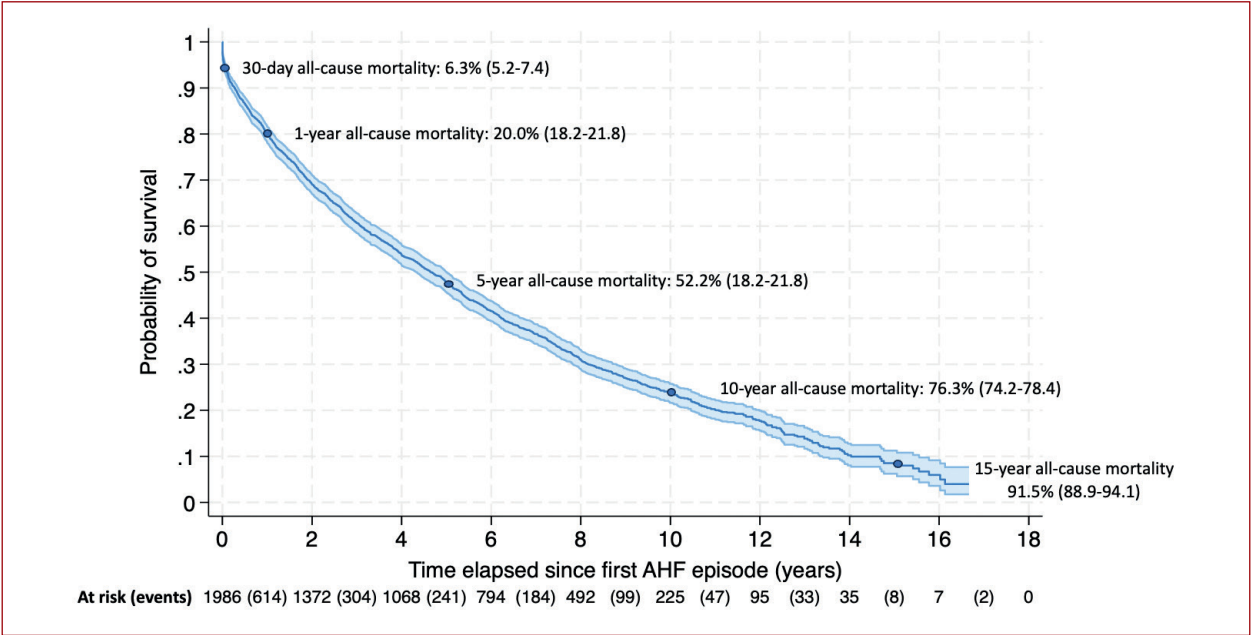


Figure 1. Survival curve for the entire cohort
Values between brackets indicate 95% confidence interval for the estimated probability of survival
Abbreviation: AHF, acute heart failure

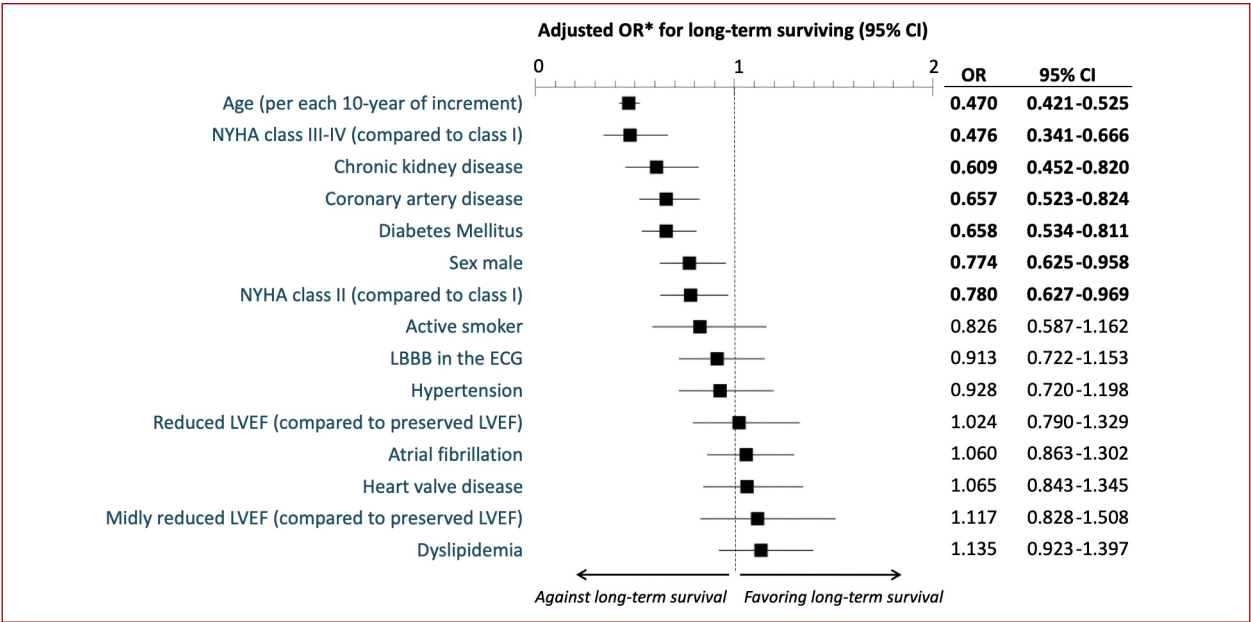


Figure 2. Adjusted analysis of factors associated with long-term survival
*Adjustment was performed by introducing all the variables in the multivariable model of logistic regression
Bold numbers denote statistical significance ($P < 0.05$)
Abbreviations: CI, confidence interval; ECG, electrocardiography; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio

95% CI, 0.341–0.666) and NYHA class II (OR, 0.780 compared to class I; 95% CI, 0.627–0.969), chronic kidney disease (OR, 0.609; 95% CI, 0.452–0.820), coronary artery disease (OR, 0.657; 95% CI, 0.523–0.824), diabetes mellitus (OR, 0.658; 95% CI, 0.534–0.811), and male sex (OR, 0.774; 95% CI, 0.625–0.958).
Non-linear analysis using RCS curves of the adjusted probability of being a LTS according to patient age

showed a sigmoidal curve, with the highest probability at the youngest ages and with a sustained decrease in older age, showing a rapid acceleration at around 70 years which slows beyond the age of 90 years. Conversely, there was no relationship between LVEF at inclusion and being a LTS, with an almost flat curve for the whole range of LVEF (Figure 3).

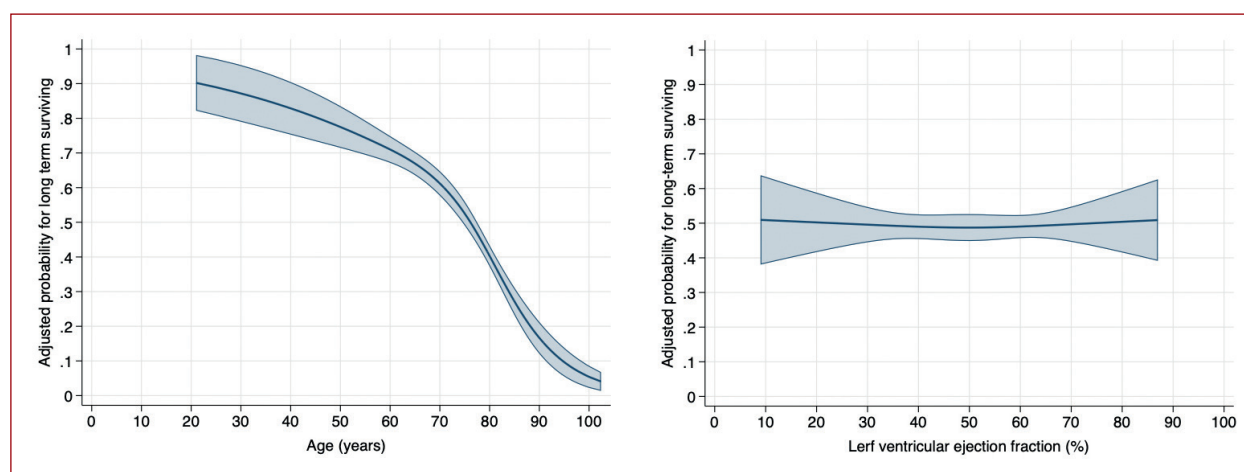


Figure 3. Adjusted probabilities for long-term surviving (>5 years) according to patient age (up) and left ventricular ejection fraction (down) at the first episode of acute heart failure. Curves have been obtained by restricted cubic spline methodology

DISCUSSION

This multicenter hospital-based study conducted among patients from the Spanish Mediterranean area analyzes long-term survival and its associated factors after a first AHF episode. Three main findings deserve to be highlighted. First, the survival curve was similar to that reported in other studies. Second, we identified risk factors against being a LTS: age, male sex, NYHA class at baseline ≥ 2 , chronic kidney disease, coronary artery disease and diabetes mellitus. Third, LVEF at inclusion was not associated with long-term survival. There are two novel aspects: firstly, the follow-up of the patients included is longer than in most previous studies; secondly, the analysis of the influence of age and LVEF by means of RCS allows the association of these variables to be studied without imposing linearity.

The profile of the patients included presented a number of characteristics that differed from those of other studies describing LTS [6–13]. Patients were recruited from EDs and cardiology wards of tertiary university hospitals in two Mediterranean cities (Barcelona and Valencia, Spain). The inclusion of patients diagnosed with AHF in the ED allows us to capture the diversity of decompensations by including those discharged home without hospitalization, those admitted to departments other than cardiology, and those managed in observation or short-stay units or through home hospitalization [15, 23]. This approach provides a real-world picture of AHF, as this is a syndrome in which many specialties participate in patient care [24]. Our cohort included older patients with a high prevalence of preserved LVEF (57%), a fact that may be explained by the exclusion of most patients with acute coronary syndromes (the INCLIVA cohort did not enroll any patient with acute coronary syndromes, whereas the NOVICA cohort excluded ST-segment elevation myocardial infarction patients). It is noteworthy that although the patients included had presented their first episode of AHF leading to an ED visit, many already had known previous heart disease, including previous coronary artery disease (33%), or valvular heart

disease (24%). Despite these particularities, the mortality during follow-up was similar to that reported in previous studies, with a high initial mortality, not only during admission but also in the post-discharge period, and progressively decreasing to 20% at 12 months and 52% at 5 years.

Regarding the factors associated with 5-year survival, certain aspects should be highlighted. As anticipated, age was associated with shorter survival. Chronological age is a well-established risk factor for mortality in patients with AHF [25]. Beyond age in itself, older patients had distinct clinical phenotypes from younger patients, received worse treatments, and these traits may contribute to a worse prognosis [26]. On the other hand, recent research has highlighted the relevance of biological age in patients with heart failure. Biological age refers to the functional and physiological state of an individual beyond their chronological age, and it may be potentially modifiable by optimizing management of comorbidities and lifestyle factors [27]. Moreover, biological age can be predicted using epigenetic analyses [28]. It should be noted that previous studies defined different age categories [6–10, 29]. This approach, based on categorizing a continuous variable, seems suboptimal [30]. Analysis of the relationship between age and mortality with RCS not assuming linearity, showed a sigmoid curve. This indicates that the probability of being a LTS after a first AHF episode decreases with age, but with a different magnitude according to patient age at debut. Indeed, there is a slow but gradual decrease in long-term survival among patients with the youngest age, followed by a clearly accelerated decrease which is maintained from 70 until 90 years of age, at which time the probability of being a LTS is <15%, and then this is followed by a slight decrease in this probability.

With regard to sex, our results align with previous studies reporting that being male was a risk factor in a broad spectrum of HF populations [31, 32]. The underlying cause of this difference in survival remains uncertain and has been inconclusively attributed to multiple factors [33]. The other

factors associated with a worse 5-year survival, including baseline dyspnea assessed by the NYHA classification, diabetes mellitus, previous ischemic heart disease, chronic kidney disease, are well known poor prognostic factors in the natural history of HF [34–36].

Our results confirm previous findings showing that renal function, diabetes, ischemic heart disease, and NYHA functional class are associated with the long-term prognosis of heart failure [11–13].

Lastly, the lack of association between LVEF and long-term survival in these *de novo* AHF patients was notable. Although prior authors have suggested a lower survival when LVEF is lower than 35%, other contemporary findings are in line with ours [37, 38]. The large improvement in medical therapy seen in patients with HF with reduced ejection fraction in contrast to HF with preserved ejection fraction may partially explain the irrelevant prognostic effect of LVEF reported in contemporary series in recent years.

Limitations

This study has several limitations. First, there is a lack of information on aspects that may influence survival (e.g., frailty), and no data were recorded regarding the triggers or the severity of the AHF episode. Additionally, information about medication was not recorded, although new drugs that modify the course of the disease have been introduced in recent years [39]. However, throughout most of the duration of the NOVICA-5 study, these drugs were not available in nearly all patients included in the study, and therefore, the impact on survival in this new therapeutic scenario cannot be inferred from the present results. Despite this limitation, the study provides long-term survival information in a real-life cohort. Second, the results were obtained from an elderly cohort with a predominance of preserved LVEF (mainly because of the absence of patients with ST-segment elevation myocardial infarction in our cohort); hence, the results should not be extrapolated to other populations. Third, by design, the study cannot differentiate patients with first AHF and known previous heart disease from those without prior heart disease. Fourth, we do not have information on the cause of death; however, based on previous studies [6, 7], we estimate that between 50% and 60% of deaths during follow-up would have been of cardiovascular origin. Fourth, at the time patients were enrolled, the use of natriuretic peptides was limited in Spain; consequently, N-terminal pro-B-type natriuretic peptide levels were available for only 969 out of 1986 patients (49%). Since data were missing in more than half of the cohort, and imputation would be required for over 50% of patients, this variable was not included.

Finally, we adjusted survival for a series of variables present in both cohorts that were recorded at decompensation. Unfortunately, we were unable to evaluate frailty and dependence, which are conditions that largely impact survival in general and in patients with AHF in particular, especially in older cohorts [40, 41].

CONCLUSION

Survival after a first AHF episode is poor, with age, NYHA class, kidney function, coronary artery disease, diabetes, and sex being key predictors of long-term mortality.

Article information

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