Clinical Research in Cardiology (2021) 110:993–1005
https://doi.org/10.1007/s00392-020-01710-0

ORIGINAL PAPER

Factors associated with in-hospital mortality and adverse outcomes during the vulnerable post-discharge phase after the first episode of acute heart failure: results of the NOVICA-2 study

Miguel Alberto Rizzi[1] · Ana García Sarasola[1] · Aitor Alquezar Arbé[1] · Sergio Herrera Mateo[1] · Víctor Gil[2] · Pere Llorens[3] · Javier Jacob[4] · Francisco Javier Martín-Sánchez[5] · Pablo Herrero Puente[6] · Rosa Escoda[2] · Begoña Espinosa[3] · Àlex Roset[4] · Raquel Torres-Gárate[7] · José Torres-Murillo[8] · Ana B. Mecina[9] · María Pilar López-Díez[10] · José María Álvarez Pérez[10] · Josep Tost[11] · Eva Salvo[12] · María Luisa López-Grima[13] · Cristina Gil[14] · María Mir[15] · Frank Rutzinska[14] · Ovidiu Chioncel[15] · Òscar Miró[2] on behalf of the ICA-SEMES Research Group

Received: 18 January 2020 / Accepted: 10 July 2020 / Published online: 21 September 2020

Abstract

Objective To identify patients at risk of in-hospital mortality and adverse outcomes during the vulnerable post-discharge period after the first acute heart failure episode (de novo AHF) attended at the emergency department.

Methods This is a secondary review of de novo AHF patients included in the prospective, multicentre EAHFE (Epidemiology of Acute Heart Failure in Emergency Department) Registry. We included consecutive patients with de novo AHF, for whom 29 independent variables were recorded. The outcomes were in-hospital all-cause mortality and all-cause mortality and readmission due to AHF within 90 days post-discharge. A follow-up check was made by reviewing the hospital medical records and/or by phone.

Results We included 3422 patients. The mean age was 80 years, 52.1% were women. The in-hospital mortality was 6.9% and was independently associated with dementia (OR = 2.25, 95% CI = 1.62–3.14), active neoplasia (1.97, 1.41–2.76), functional dependence (1.58, 1.02–2.43), chronic treatment with beta-blockers (0.62, 0.44–0.86) and severity of decompensation (6.38, 2.86–14.26 for high-/very high-risk patients). The 90-day post-discharge combined endpoint was observed in 19.3% of patients and was independently associated with hypertension (HR = 1.40, 1.11–1.76), chronic renal insufficiency (1.23, 1.01–1.49), heart valve disease (1.24, 1.01–1.51), chronic obstructive pulmonary disease (1.22, 1.01–1.48), NYHA 3–4 at baseline (1.40, 1.12–1.74) and severity of decompensation (1.23, 1.01–1.50; and 1.64, 1.20–2.25; for intermediate and high-/very high-risk patients, respectively), with different risk factors for 90-day post-discharge mortality or rehospitalisation.

Conclusions The severity of decompensation and some baseline characteristics identified de novo AHF patients at increased risk of developing adverse outcomes during hospitalisation and the vulnerable post-discharge phase, without significant differences in these risk factors according to patient age at de novo AHF presentation.

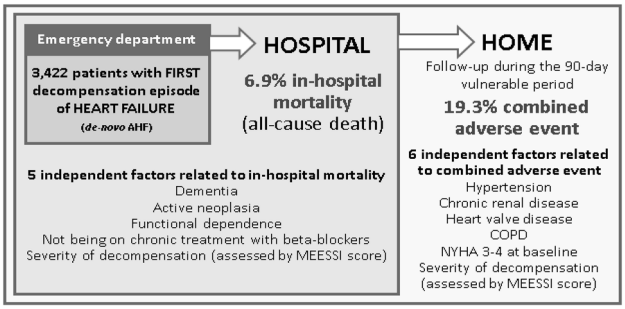
Miguel Alberto Rizzi and Ana García Sarasola have contributed equally to this study.

The members of ICA-SEMES Research Group is present in the Acknowledgements section.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-020-01710-0) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Graphic abstract



Keywords Emergency department · De novo acute heart failure · Vulnerable phase · Mortality · Rehospitalisation · Risk factors

Introduction

Background

Heart failure (HF) is one of the most common syndromes in adults, with a prevalence of 1–2% [1]. Exacerbations affect the natural history of HF. They often require urgent therapy and hospitalisation, and in-hospital mortality during the acute heart failure (AHF) episode remains high. In addition, despite most patients having symptomatic improvement in response to therapy received during hospitalisation [2], AHF patients have been identified as a group with extremely high post-discharge death and rehospitalisation rates, especially during the first 60–90 days after discharge. During this early post-discharge period with increased risk of adverse outcomes, termed "the vulnerable phase" [3], readmission for HF occurs in 15–30% of cases, and the mortality rate ranges from 7 to 11% [2–5].

Importance

The first episode of AHF (de novo AHF) usually marks a change in the natural history of this syndrome, as it usually represents the first step towards progressive patient deterioration and functional decline. Recently, it has been reported that this first decompensation is followed by a rate of 0.87 of subsequent hospitalisations per year, half of which are caused by new AHF episodes [6, 7]. In this scenario, the de novo AHF episode constitutes an essential step for the identification of patient- and episode-related risk factors associated with poor outcomes, as active actions on modifiable risk factors at this early moment could, in turn, improve patient prognosis [8–13]. Since patients seek medical care at the emergency department (ED) in most AHF episodes, EDs constitute a key setting for investigating AHF-related aspects. However, to the best of our knowledge, very few studies have analysed the natural history of patients after being diagnosed with de novo AHF, especially in unbiased patient samples from EDs.

The NOVICA (apocopate from the Spanish words "de NOVO *Insuficiencia Cardiaca Aguda*; in English, de novo AHF) project was designed to cover this gap in the literature. In two previously published studies, we described the characteristics and outcome of patients presenting their first AHF episode in the ED in comparison with patients with previous history of AHF (NOVICA-1) [14], as well as the natural history of a cohort of patients followed for a mean of 2.4 years after the de novo AHF episode (NOVICA-3) [7].

Goals of this investigation

In the present study (NOVICA-2), our objective was to identify risk factors associated with in-hospital mortality and poor outcomes (consistent with a combined endpoint formed by need for rehospitalisation or death) during the early post-discharge period (vulnerable phase) after the de novo AHF episode.

Methods

Setting

The EAHFE (Epidemiology of Acute Heart Failure in Emergency Department) Registry was initiated in 2007 and every 2–3 years carries out a 1- to 2-month recruitment period of all consecutive patients diagnosed with AHF in Spanish EDs participating in the project. To date, six recruitment phases (2007, 2009, 2011, 2014, 2016 and 2018) have been performed with the participation of 45 EDs from community

and university hospitals across Spain (representing about 15% of the Spanish public health care system hospitals), enrolling a total of 18,370 AHF patients. The NOVICA-2 study only included patients from the EAHFE registries 4 and 5 since the previous registries did not have the necessary information for the present analysis (rehospitalisation due to AHF was added from EAHFE-4 and is one of the outcomes assessed in the present study), and the EAHFE-6 follow-up was not completed at the time of the study design.

Design

Details of patient inclusion dynamics have been reported previously [15, 16]. In brief, any attending emergency physician in the participating EDs, who received specific study protocol instructions during a weekly ED meeting preceding patient recruitment, can enrol patients. These physicians are responsible for the detection of potential cases of patients with AHF. All suspected cases are confirmed by the principal investigator of each centre to ensure the patients meet the diagnostic criteria of AHF based on the Framingham clinical criteria [17]. If possible, the diagnosis is also confirmed by the measurement of plasma natriuretic peptide and/or echocardiography during ED or hospital stay following the current recommendations of the European Society of Cardiology (ESC) guidelines, and this was available in about 92% of cases. The principal investigator of each centre is responsible for the final diagnostic adjudication of the cases. All principal investigators are provided with a common dictionary of terms to have standard definitions at all the centres (Supplemental Table 1).

Selection of participants

We recruited patients in the ED by a face-to-face interview with them and their caregivers at admission to the emergency department. For the present study, we included patients with a first episode of AHF irrespective of whether they did or did not have a previous diagnosis or treatment of HF made by general practitioners or ambulatory specialists. The main condition was that the patient had never consulted to an ED or been hospitalised because of AHF. All patients with a final diagnosis of first episode of AHF after ED care were recorded and used to evaluate one of the co-primary outcomes (all-cause in-hospital mortality), and those discharged alive after the index AHF episode were followed up to 90 days to be included in the evaluation of the other co-primary outcome (the combined endpoint formed by rehospitalisation or death).

The only exclusion criterion for inclusion in the EAHFE Registry is a primary diagnosis of ST-elevation myocardial infarction (STEMI) while concurrently developing AHF (which occurs in 3% of AHF cases). The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the attending ED physician decisions.

Variables recorded

Trained clinical researchers extracted data from the initial interview with patients and their caregivers regarding functional class before admission according to the New York Heart Association [NYHA] classification and functional status (Barthel Index) in the 2 weeks before admission and was checked their medical history. We completed the data obtained from the initial interview by reviewing the hospital and primary care clinical report. We recorded data directly for each patient on a pre-established data collection form. We recorded the following variables: demography (sex, age and place of residence); cardiac history (HF, ischaemic cardiopathy, valvulopathy, LVEF) and preexisting comorbidities (hypertension, atrial fibrilation, diabetes mellitus, dyslipidemia, renal failure defined as creatinine ≥ 2 mg/dl, chronic obstructive pulmonary disease, stroke, peripheral artery disease, dementia) were assessed (yes/no) if they were recorded in the patient's medical records. HFpEF was defined as an ejection fraction $> 50\%$. We assessed the severity of the de novo AHF episode by (1) calculation of the MEESSI (Multiple Estimation of risk based on the Spanish Emergency department Score In patients with AHF) risk score [18], and (2) the need for hospitalisation during the index episode. We defined the index episode as "patients requiring ED care due to an episode of AHF".

Outcomes

The two co-primary outcomes in the present study were in-hospital all-cause mortality and 90-day post-discharge combined endpoint. The latter was considered if rehospitalisation due to AHF or all-cause death occurred during follow-up. These two components of the 90-day post-discharge combined endpoint were individually considered as the secondary outcomes. The follow-up was performed through telephone contact and consultation of medical records. We completed the data obtained in the initial interview and 90 days after discharge by reviewing the hospital and primary care clinical report. If we did not find information, patients, relatives, or caregivers were contacted by phone 90 days after ED discharge and data concerning mortality were recorded. We chose the 90-day time span for the vulnerable period based on the previous definition by Greene et al. [19].

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) or median [interquartile range (IQR)], and discrete variables as absolute values and percentages. Comparison among groups was carried out using the Student's *t* test, after checking with the Kolmogorov–Smirnov test to ensure that they fit a normal distribution, or the Mann–Whitney non-parametric test for non-normally distributed variables. The chi-square test (for trend, when needed) was used for comparing discrete variables.

The effect size of the independent variables on the risk of in-hospital all-cause mortality (co-primary outcome) was expressed by odds ratio (OR) calculated by logistic regression, while for the other co-primary outcome (90-day post-discharge combined endpoint) and for the secondary outcomes (90-day post-discharge readmission or death) it was estimated by hazard ratio (HR) calculated by Cox regression. All effect size estimations were calculated in adjusted multivariate models by entering all the variables showing a significant association in the univariate analyses. For calculations of adjusted OR and HR, missing values in the independent variables were replaced using the multiple imputation technique provided by SPSS software, generating five datasets in which there are no misses among all the variables included in the adjustment.

We also investigated if there was a significant different size effect according to patient age and the left ventricular ejection fraction (LVEF) for the risk factors that finally resulted independently associated with the primary outcomes. This was assessed by measuring the first-order interaction of age (dichotomised as ≤ 80 years or > 80 years) and LVEF (dichotomised as $< 50\%$—heart failure with reduced or mid-range ejection fraction or $\geq 50\%$—heart failure with preserved ejection fraction) with each risk factor in the multivariate adjusted logistic models.

Statistical significance was accepted if the 95% confidence interval (CI) of the OR or the HR excluded the value 1, or if the *p* value was less than 0.05. Since this was an exploratory study, a *pre-hoc* sample size calculation was not made. We used the SPSS, version 24.0 (SPSS Inc Chicago, USA) for all analyses.

Ethics

The EAHFE Registry 4 and 5 protocols were approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 166/13 and 160/15. Due to the non-interventional design of the registry, Spanish legislation allows central Ethical Committee approval, accompanied by notification to the local Ethical Committees. At admission, all participating patients gave informed consent (writing consent) to be included in the registry and to be contacted for follow-up. If a patient does not have the capacity to consent their participation in the study, to determine what his/her wishes would have been, we consult his/her close family or caregiver. The NOVICA-2 study was carried out in strict compliance with the Declaration of Helsinki principles. The authors designed the study, gathered, and analysed the data, vouch for the data and analysis, wrote the paper, and decided to publish.

Results

EAHFE-4 and 5 included 7946 patients with AHF, and 3422 patients met the inclusion criteria of the NOVICA-2 study (Fig. 1). The mean age of the patients was 80 (SD 11) years, and 52.1% were women. The main comorbidities were hypertension (79%), diabetes (37%) and atrial fibrillation (38%). Most patients had preserved left ventricular ejection fraction (72%), and nearly half had some degree of dependence in basic activities of daily living (Barthel Index of 90 or less; 48%). The most frequent precipitants of the index episode were infection (35%) and rapid atrial fibrillation (19%). With respect to the severity of the acute episode, 48% were classified as low risk by the MEESSI scale, 36% as intermediate risk and 16% as high/very high risk (distribution of patients in the 13 variables included in the MEESSI scale is presented in the Supplemental Table 1), and 2501 patients (73%) needed to be hospitalised during the index episode. Patient distribution according to the NYHA class recorded at patient arrival to the ED differed from that observed at baseline (Table 1), as few patients were in class I and II (1.7% and 14.1%, respectively) and most were in class III and IV (46.8% and 37.4%). The demographic, baseline and episode characteristics of the patients are summarised in Table 1. There were three variables (Barthel Index, left ventricular ejection fraction and classification of the severity of index episode by MEESSI scale that had more than 10% of missing values (comparison between patients with missing values for these three variables with the rest of patients in presented in Supplemental Table 2).

Two hundred and thirty-five patients died during hospitalisation (in-hospital mortality 6.9%). Table 2 shows the differences between survivor and non-survivor patients during the index AHF event. Patients who died were older, and more commonly had chronic kidney insufficiency, dementia and active neoplasia as comorbidities compared to survivor patients. In addition, they had a worse functional and NYHA baseline status and were less frequently on chronic beta-blocker treatment. The acute episode was more frequently triggered by infection and less frequently by hypertensive episodes, and the severity of decompensation was higher (Table 2). However, only five of these risk factors remained

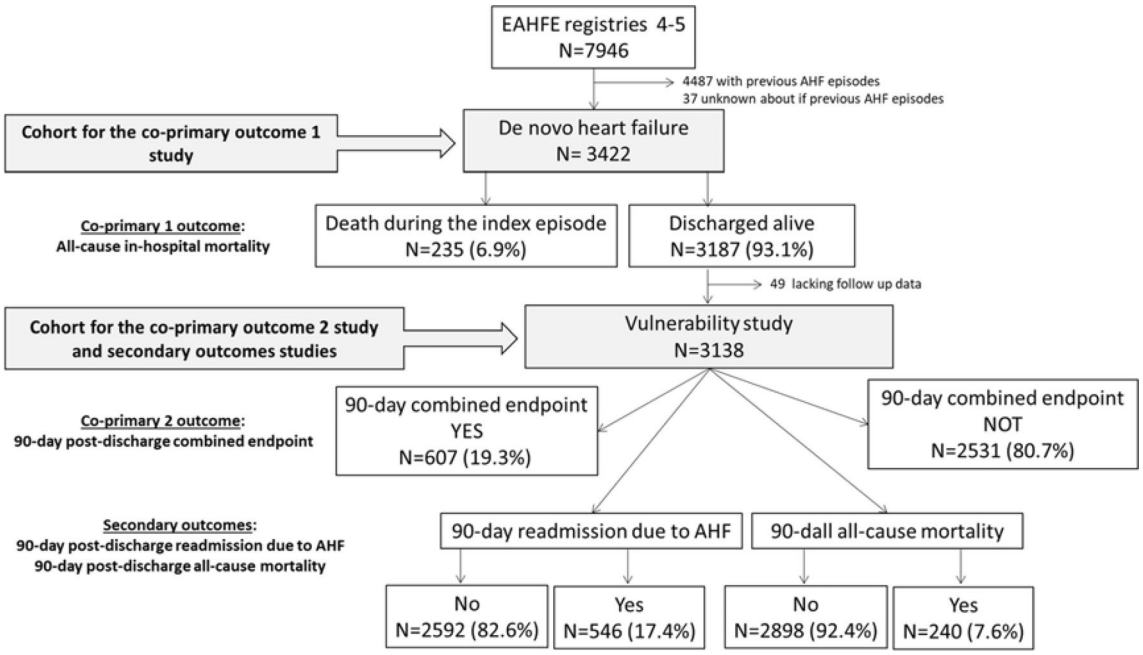


Fig. 1 Flowchart for patient inclusion

statistically significant in the adjusted analysis: two comorbidities (OR = 2.25, 1.62–3.14, for dementia and OR = 1.97, 1.41–2.76 for active neoplasia), the functional dependence at baseline (OR = 1.58, 1.02–2.43), being on chronic treatment with beta-blocker (OR = 0.62, 0.44–0.86), and the severity of decompensation (OR = 6.38, 2.85–14.26 for the high-/very high-risk patients compared to low-risk patients) (Fig. 2) (see Supplemental tables 3–6: Unadjusted analysis of risk factors related to outcomes during the first episode of acute heart failure).

The median length of stay for all patients discharged alive was 5 days (IQR = 1–9) and 7 days (IQR = 5–11) in the subset of patients that were hospitalised (i.e., excluding patients directly discharged from the ED without hospitalisation). The median length of stay for patients dying during the index event was 5 days (IQR = 2–11).

The vast majority of patients dying during the index event (221 out of 235, 94%) had been hospitalised, as only 14 died shortly after ED arrival before hospitalisation. By limiting the calculation of in-hospital mortality to only hospitalised patients, the percentage would increase from 6.9% (235 out of 3422 of index episodes) to 8.8% (221 out of 2501 hospital admissions).

Of the 3187 patients discharged alive, we obtained follow-up data on 3138 patients for the 90-day post-discharge analyses (Fig. 1). The 90-day combined endpoint was observed in 607 patients (19.3%) and six risk factors were independently associated with this outcome in the adjusted analysis (Fig. 3): four comorbidities (HR = 1.40, 1.11–1.76 for hypertension, HR = 1.23, 1.01–1.49 for chronic renal insufficiency, HR = 1.24, 1.01–1.51 for heart valve disease, and HR = 1.22, 1.01–1.48 for chronic obstructive pulmonary disease), the NYHA class 3 or 4 at baseline (HR = 1.40, 1.12–1.74) and the severity of decompensation (HR = 1.23, 1.01–1.50; and HR = 1.64, 1.20–2.25; for intermediate and high-/very high-risk patients, respectively). The secondary outcomes were observed in 546 patients (17.4%) for 90-day post-discharge rehospitalisation and in 240 patients (7.6%) for 90-day post-discharge death. Although many of the risk factors associated with the secondary outcomes coincided with the risk factors for the combined endpoint, different risk factors were observed for 90-day post-discharge rehospitalisation (hypertension, peripheral arteriopathy, chronic obstructive valve disease, NYHA 3–4, dietetic/therapeutic transgression as AHF trigger and severity of the de novo AHF episode) and death (chronic kidney insufficiency, NYHA 3–4, and severity of the de novo AHF episode) (Fig. 3).

The effect size of the risk factors found to be significantly associated with the two co-primary adverse outcomes in the adjusted models did not significantly differ according to age, with the exception of the relationship between active neoplasia and in-hospital mortality, which was significantly higher in patients ≤ 80 years of age (OR = 3.28, 1.80–5.96) than in patients with > 80 years (OR = 1.58, 0.62–4.05; *p*-for-interaction = 0.049). On the other hand, no interaction was found in the relationship between any of the risk factors and

Table 1 Baseline and acute heart failure episode characteristics corresponding to the 3422 patients included in the present study

	Total *N*=3422 *n* (%)	Missing values *n* (%)
Demographic data		
Age (years) [mean (SD)]	80 (11)	1 (0.0)
Age ≤80 years	1472 (43.0)	
Age >80 years	1949 (57.0)	
Female	1774 (52.1)	18(0.5)
Comorbidities		
Hypertension	2721 (79.6)	18 (0.5)
Atrial fibrillation	1310 (38.3)	2 (0.1)
Diabetes mellitus	1282 (37.5)	2 (0.1)
Ischaemic heart disease	787 (23.0)	3 (0.1)
Chronic obstructive pulmonary disease	674 (19.7)	4 (0.1)
Chronic kidney failure (creatinine >2 mg/mL)	646 (18.9)	3 (0.1)
Heart valve disease	615 (18.0)	4 (0.1)
Active neoplasia	515 (15.1)	2 (0.1)
Dementia	392 (11.5)	2 (0.1)
Cerebrovascular disease	379 (11.1)	3 (0.1)
Peripheral artery disease	260 (7.8)	5 (0.1)
Baseline status		
Barthel Index (points) [mean (SD)]	83 (24)	472 (13.8)
No or minimal dependence (Barthel Index >90 points)	1537 (52.1)	
Mild or higher dependence (Barthel Index ≤90 points)	1413 (47.9)	
NYHA class III–IV	513 (16.0)	224 (6.5)
Left ventricular ejection fraction (%) [mean (SD)]	53 (16)	1994 (58.3)
Reduced ejection fraction (<40%)	233 (16.3)	
Moderately reduced ejection fraction (40–49%)	162 (11.3)	
Preserved ejection fraction (≥50%)	1033 (72.3)	
Chronic treatments		
Diuretics (any)	1964 (59.5)	122 (3.6)
Renin–angiotensin system inhibitor	1722 (53.7)	123 (3.6)
Beta-blocker	1269 (37.6)	124 (3.6)
Mineralocorticoid-receptor antagonist	340 (10.3)	124 (3.6)
Digoxin	305 (9.3)	126 (3.7)
Triggering factor for the current AHF episode		
Infection	1138 (34.8)	149 (4.4)
Rapid atrial fibrillation	627 (19.1)	146 (4.3)
Anaemia	224 (6.8)	147 (4.3)
Hypertensive emergency	217 (6.6)	149 (4.4)
Dietetic or therapeutic transgression	88 (2.7)	146 (4.3)
Acute coronary syndrome	77 (2.1)	149 (4.4)
Severity of current decompensation [mean (SD)]		
Estimated by MEESSI scale*		1575 (46.0)
Low risk	893 (48.3)	
Intermediate risk	662 (35.8)	
High/very high risk	292 (15.8)	
Need for hospitalisation	2501 (73.1)	1 (0.0)

SD standard deviation

*Multiple estimation of risk based on the Spanish emergency department score in patients with AHF

Table 2 Comparison of the patients' baseline and acute heart failure episode characteristics depending on the presence or absence of the outcomes evaluated in the present study

	Death during the index event (in-hospital mortality)			Combined endpoint during the 90 days after discharge of the index event			Readmission during the 90 days after discharge of the index event			Death during the 90 days after discharge of the index event		
	No *N* = 3187 *n* (%)	Yes *N* = 235 *n*(%)	*p* value	No *N* = 2531 *n* (%)	Yes *N* = 607 *n* (%)	*p* value	No *N* = 2592 *n* (%)	Yes *N* = 546 *n* (%)	*p* value	No *N* = 2898 *n* (%)	Yes *N* = 240 *n* (%)	*p* value
Demographic data												
Age (years) [mean (SD)]	79 (11)	84 (10)	**< 0.001**	79 (11)	81 (10)	**< 0.001**	79 (11)	81 (10)	**< 0.001**	79 (11)	84 (10)	**< 0.001**
Female	1646 (51.9)	128 (54.9)	0.372	1294 (51.4)	325 (53.8)	0.281	1324 (51.3)	295 (54.4)	0.185	1496 (51.9)	123 (51.2)	0.849
Comorbidities												
Hypertension	2536 (79.6)	185 (78.3)	0.734	1987 (78.6)	513 (84.7)	**0.001**	2030 (78.4)	470 (86.2)	**< 0.001**	2314 (79.9)	186 (77.5)	0.368
Diabetes mellitus	1197 (37.6)	85 (36.2)	0.666	941 (37.2)	236 (38.9)	0.424	962 (37.1)	215 (39.4)	0.309	1091 (37.7)	86 (35.8)	0.572
Ischaemic heart disease	740 (23.2)	47 (20.0)	0.255	568 (22.5)	162 (26.7)	**0.025**	580 (22.4)	150 (27.5)	**0.010**	677 (23.4)	53 (22.1)	0.647
Chronic kidney failure (creatinine > 2 mg/mL)	583 (18.3)	63 (26.8)	**< 0.001**	426 (16.8)	145 (24.0)	**< 0.001**	442 (17.1)	129 (23.7)	**< 0.001**	505 (17.4)	66 (27.5)	**< 0.001**
Cerebrovascular disease	353(11.1)	25 (11.1)	0.991	266 (10.5)	78 (12.9)	0.093	275 (10.6)	69 (12.7)	0.160	316 (10.9)	28 (11.7)	0.702
Atrial fibrillation	1229 (38.6)	81 (34.5)	0.210	950 (37.5)	257 (42.4)	**0.027**	979 (37.8)	228 (41.8)	0.077	1107 (38.2)	100 (41.7)	0.292
Peripheral artery disease	252 (7.9)	16 (6.8)	0.540	185 (7.3)	60 (9.9)	**0.032**	188 (7.3)	57 (10.5)	**0.011**	228 (7.9)	17 (7.1)	0.658
Heart valve disease	574 (18.0)	41 (17.4)	0.821	434 (17.2)	129 (21.3)	**0.018**	448 (17.3)	115 (21.1)	**0.036**	512 (17.7)	51 (21.3)	0.168
Chronic obstructive pulmonary disease	628 (19.7)	46(11.6)	0.954	490 (19.0)	138 (22.8)	**0.035**	492 (19.0)	126 (23.1)	**0.028**	566 (19.6)	52 (21.7)	0.430
Dementia	312 (0.8)	84 (34.0)	**< 0.001**	235 (9.3)	69 (11.4)	0.121	246 (9.5)	58 (10.6)	0.420	252 (8.7)	52 (21.7)	**< 0.001**
Active neoplasia	455 (14.3)	60 (25.5)	**< 0.001**	348 (13.8)	96 (15.8)	0.192	362 (14.0)	82 (15.0)	0.526	401 (13.8)	43 (17.9)	0.082
Baseline status												
Barthel Index (points) [mean (SD)]	84 (23)	61(31)	**< 0.001**	85 (22)	81 (25)	**< 0.001**	85 (22)	82 (24)	**0.008**	86 (22)	71 (28)	**< 0.001**
NYHA class III–IV	449 (15.0)	64 (30.5)	**< 0.001**	326 (13.7)	109 (19.1)	**< 0.001**	336 (13.8)	99 (19.1)	**0.002**	381 (14.0)	54 (24.7)	**< 0.001**
Left ventricular ejection fraction (%) [mean (SD)]	53 (14)	51(16)	0.395	53 (14)	53 (14)	0.776	53 (14)	53 (14)	0.620	53 (14)	51 (14)	0.196
Chronic treatments												
Diuretics (any)	1821 (59.2)	142 (62.9)	0.270	1813 (73.5)	439 (76.2)	0.175	1846 (73.4)	406 (76.7)	0.111	2093 (74.0)	159 (73.3)	0.805
RAS inhibitor	1660 (54.0)	111 (49.6)	0.199	1222 (49.5)	264 (45.8)	0.110	1240 (49.3)	246 (46.5)	0.238	1404 (49.7)	82 (37.8)	**0.001**
Beta-blocker	1186 (38.6)	53 (23.7)	**<0.001**	1014 (41.1)	248 (43.1)	0,396	1032 (41.1)	230 (43.5)	0.306	1176 (41.6)	86 (39.8)	0.605
Mineralocorticoid-receptor antagonist	318 (10.3)	8.2 (9.8)	0.804	391 (15.8)	92 (16.0)	0,939	398 (15.8)	85 (16.1)	0.889	452 (16.0)	31 (14.3)	0.508
Digoxin	283 (9.2)	22 (9.8)	0.761	281 (11.4)	50 (8.7)	0,060	284 (11.3)	47 (8.9)	0.105	309 (10.9)	22 (10.1)	0.717
Triggering factor for the current AHF episode												
Infection	1038 (34.0)	100 (44.8)	**< 0.001**	823 (33.9)	203 (35.2)	0.567	846 (34.1)	180 (34.7)	0.785	940 (33.9)	86 (37.2)	0.307
Rapid atrial fibrillation	592 (19.4)	35 (15.7)	0.176	468 (19.3)	111 (19.2)	0.969	475 (19.1)	104 (20.0)	0.639	541 (19.5)	38 (16.5)	0.259
Anaemia	208 (6.8)	16 (7.2)	0.837	159 (6.6)	47 (8.1)	0.177	165 (6.6)	41 (7.9)	0.307	184 (6.6)	22 (9.5)	0.095
Hypertensive emergency	211 (6.9)	6 (2.7)	**0.014**	183 (7.5)	27 (4.7)	**0.015**	185 (7.4)	25 (4.8)	**0.032**	200 (7.2)	10 (4.3)	0.099
Dietetic or therapeutic transgression	86 (2.8)	2 (0.9)	0.087	76 (3.1)	10 (1.7)	0.070	78 (3.1)	8 (1.5)	**0.047**	83 (3.0)	3 (1.3)	0.138
Acute coronary syndrome	67 (2.1)	4 (1.7)	0.678	56 (2.2)	11 (1.8)	0.540	56 (2.2)	11 (2.0)	0.830	65 (2.2)	2 (0.8)	0.147

Table 2 (continued)

	Death during the index event (in-hospital mortality)			Combined endpoint during the 90 days after discharge of the index event			Readmission during the 90 days after discharge of the index event			Death during the 90 days after discharge of the index event		
	No $N=3187$ n (%)	Yes $N=235$ n(%)	p value	No $N=2531$ n (%)	Yes $N=607$ n (%)	p value	No $N=2592$ n (%)	Yes $N=546$ n (%)	p value	No $N=2898$ n (%)	Yes $N=240$ n (%)	p value
Severity of current decompensation [mean (SD)]												
Estimated by MEESSI scale*			**< 0.001**			**0.001**			**< 0.001**			**< 0.001**
Low risk	881 (52.5)	12 (8.9)		741 (53.8)	126 (40.8)		753 (53.3)	114 (41.5)		828 (53.1)	39 (30.5)	
Intermediate risk	624 (36.4)	38 (28.1)		496 (36.0)	124 (40.1)		507 (35.9)	113 (41.1)		568 (36.4)	52 (40.6)	
High/very high risk	217 (12.1)	85 (63.0)		141 (10.2)	59 (19.1)		152 (10.8)	48 (17.5)		163 (10.5)	37 (28.9)	
Need for hospitalisation		NA		1802 (71.2)	439 (72.3)	0.591	1849 (71.4)	392 (71.8)	0.839	2054 (70.9)	187 (77.9)	**0.021**

Bold p values denote statistical significance

AHF acute heart failure, *SD* standard deviation, *NA* not applicable, *RAS* renin–angiotensin system

* Multiple estimation of risk based on the Spanish emergency department score in patients with AHF

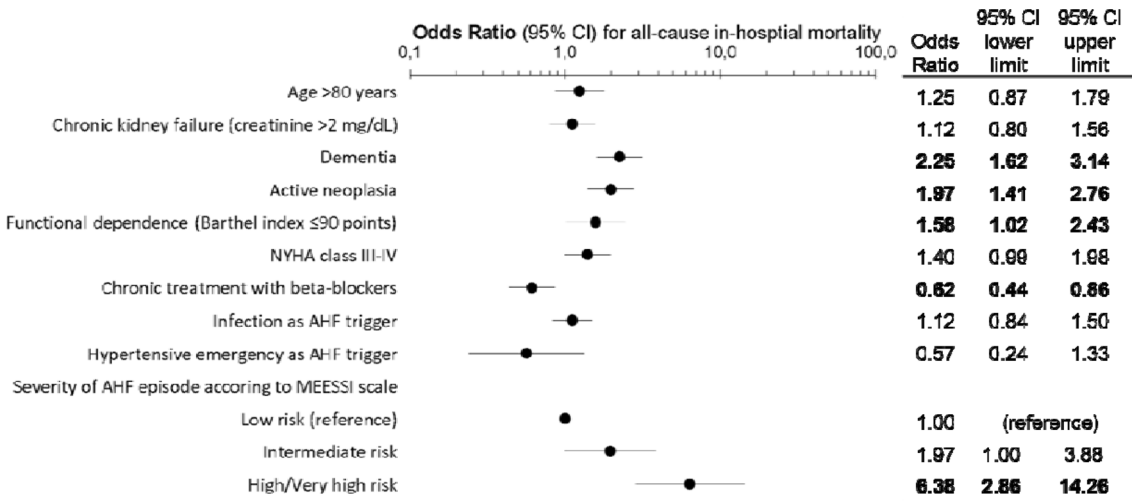
either of the two co-primary endpoints when the analysis was repeated and stratified by the LVEF.

Discussion

Our study provides further evidence on prognostic factors in patients presenting their first AHF episode and seen at the emergency department. We identified four factors which increased the risk of in-hospital mortality in patients with de novo AHF (dementia, neoplasia, functional dependence in basic activities of daily living, and severity of the de novo AHF index episode). During the vulnerable phase, six independent risk factors for combined endpoint were related to poor outcomes (hypertension, chronic kidney insufficiency, heart valve disease, chronic obstructive pulmonary disease, NYHA functional class III–IV, and severity of the index decompensation).

The main baseline characteristics of patients with de novo AHF were similar to those of other studies conducted in EDs, but differed from those reported for hospitalised patients (especially in cardiology departments) because our patients were older, fewer had previous history of coronary artery disease, and the most predominant type of HF according to left ventricular function was a preserved ejection fraction [11, 13]. In line with previous studies, we found an in-hospital mortality of 6.9% as well as 7.6% of mortality and 17.4% of readmission for AHF during the vulnerable post-discharge period (90 days post-discharge) [4, 11, 20, 21].

Our study has two major findings. The first was related to in-hospital mortality. We identified four factors which increased the risk of death (dementia, neoplasia, functional dependence in basic activities of daily living, and severity of the de novo AHF index episode) and one conferring protection against in-hospital death (being on chronic treatment with beta-blockers). Our findings highlight the importance of the initial clinical assessment in the ED including functional and cognitive evaluation of the patient. Dementia and activities of daily living have been proposed as the most representative prognostic indicators for survival in elderly patients in many chronic diseases [22, 23]. Multiple studies have highlighted their importance as factors of poor short-term prognosis in elderly patients who present at the ED with an episode of AHF [22, 24, 25]. It seems that beta-blocker treatment exerted a protective effect against adverse short-term outcomes during the de novo AHF episode [26]. We do not know the exact reason for the treatment with beta-blockers in our patients at the time of the debut of AHF (perhaps due to previous HF diagnosis without any previous decompensation, but also to other comorbidities such as hypertension or atrial fibrillation). An LVEF-stratified mortality analysis was not performed, and our study was not designed for this. Finally, the severity of the first



Bold numbers denote statistical significance.
AHF: acute heart failure.

Fig. 2 Adjusted analysis of risk factors related to all-cause in-hospital mortality in patients during the first episode of acute heart failure. Adjustment was performed by including in the multivariate logistic regression all variables with a significant different distribution in the univariate analysis (see Table 2). Bold numbers denote statistical significance. *AHF* acute heart failure.

decompensation, assessed by the MEESSI score designed to predict 30-day mortality, was associated with the risk of in-hospital mortality in de novo AHF patients.

The second major finding concerned factors related to poor outcomes during the vulnerable phase. We identified six independent risk factors for the combined endpoint (hypertension, chronic kidney insufficiency, heart valve disease, chronic obstructive pulmonary disease, NYHA functional class III–IV, and severity of the index decompensation). Many of these factors have been reported in previous studies [27–30], and underline the importance of comorbidity and functional status for identifying patients with the first episode of AHF with a poor short-term prognosis. Strikingly, dementia and functional dependence were not found to be markers of poor outcomes in our patients. We believe the differences found in our post-discharge model with respect to in-hospital mortality model may have been influenced by the organisation of the local health system and by the patients' clinical characteristics. Thus, it is likely that since the patients had a worse functional status and dementia, some of the consultations could have occurred in primary care (consultation with the on-call primary care physician) or other emergency health care providers for fragile patients or highly dependent patients (i.e., nursing home).

It is also of note that some variables classically related to short- and long-term prognosis in patients with HF were not related to the short-term prognosis of the de novo AHF episode. In this sense, the LVEF was not associated with any outcomes, while the presence of limited functional capacity assessed by the Barthel Index and, especially, advanced NYHA classes at baseline were. It is possible that this indicates that there is a subset of patients with a previous long history of well-compensated HF, although this aspect was not investigated in the present study. On the other hand, in the present study, hospitalisation during the de novo AHF episode was not related to outcomes, and this contrasts with the 2016 ESC Guidelines that recommend to admitting every patient in the first episode of AHF (26). Perhaps, if outpatient multidisciplinary pathways were well developed, all the study and therapeutic approaches needed after de novo AHF could be carried out in a subset of patients without hospitalisation. Finally, the lack of influence of age on any of the short-term outcomes of patients with de novo AHF is also highly remarkable. This finding seems to be consistent since age did not modify the effect on outcomes of the significant risk factors (with the exception of actual neoplasia on in-hospital mortality during the index AHF event, which was higher in younger patients).

The NOVICA-2 has a number of limitations. First, AHF was defined using Framingham criteria. These criteria were validated for chronic HF, but they have also shown good diagnostic accuracy for the diagnosis of AHF, with similar specificity for systolic and diastolic HF (89%) and higher sensitivity for systolic (97%) than for diastolic HF (89%) [31, 32]. Second, because of the observational nature of this study, not all patients had variables of interest, such as the LVEF or NT-pro-BNP, and some variables were not recorded (i.e., frailty). This could introduce some bias in our findings. However, the main clinical variables were systematically collected. Nevertheless, it should be kept in mind

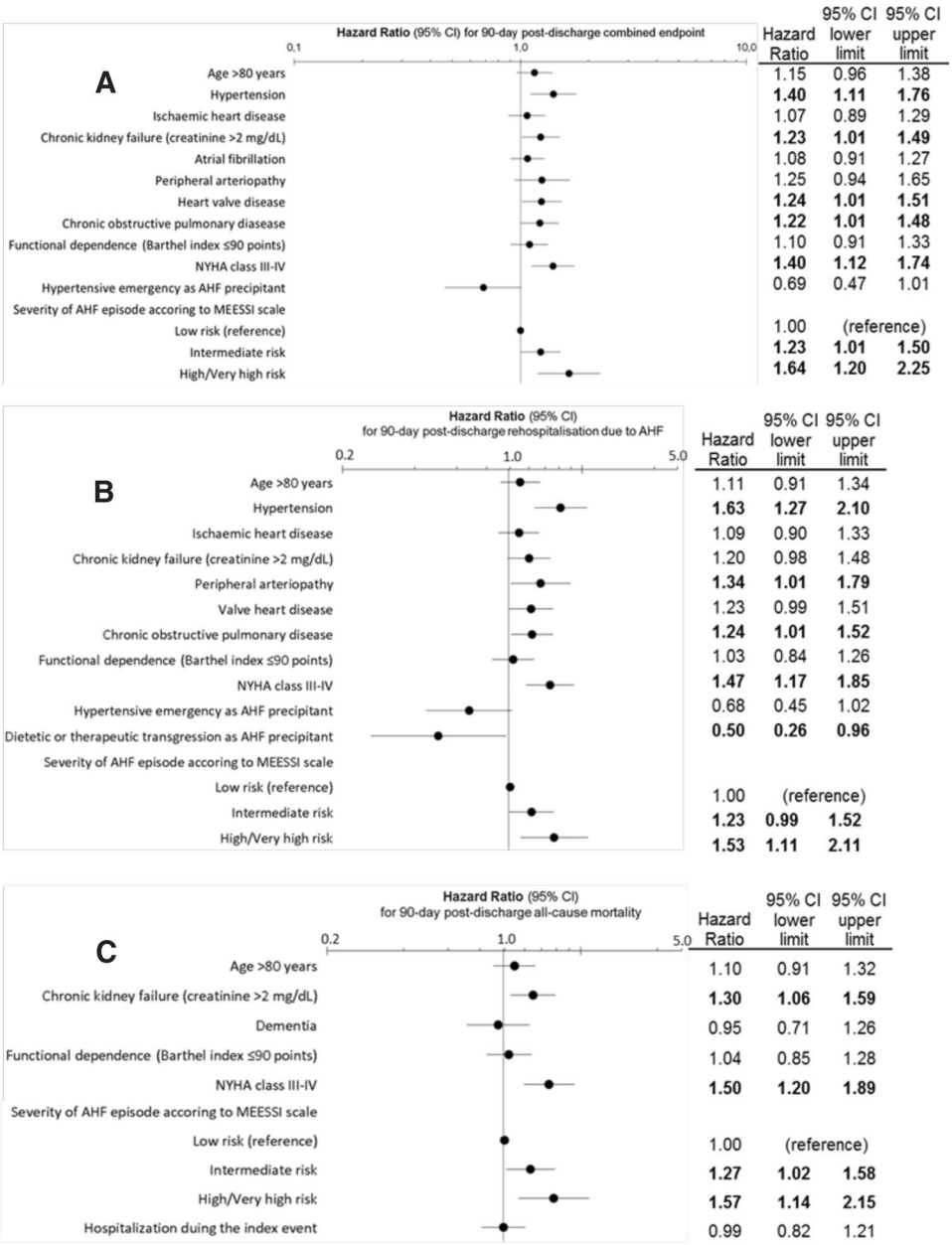


Fig. 3 Adjusted analysis of risk factors related to adverse events observed during the vulnerable post-discharge phase (90 days following the discharge after the index de novo acute heart failure event): **a** combined endpoint (panel A), rehospitalisation (panel B) and death (panel C). Adjustment of hazard ratios was performed by including in the multivariate Cox regression all variables with a significant different distribution in the univariate analysis (see Table 2). Bold numbers denote statistical significance. *AHF* acute heart failure.

Bold numbers denote statistical significance.
AHF: acute heart failure.

that our intention was to perform the study under conditions of routine clinical practice, mainly using the variables available to ED physicians in their daily decision-making processes. Third, by design, the study cannot distinguish patients with de novo AHF with known previous heart disease from patients without prior heart disease. Fourth, we excluded AHF in patients with STEMI. Fifth, we do not have the specific causes of death. Sixth, since there was no sample size calculation due to the exploratory nature of the study, a type II error cannot be excluded in some of the estimations made. The strength of the study is that, in contrast to most previous studies based on hospital patients, NOVICA-2 recruitment was done in the ED, providing a more global picture due to the inclusion of patients with different AHF profiles.

In conclusion, our findings highlight the importance of stratifying patients according to risk severity and assessing basal status with NYHA functional class and Barthel Index. In addition, it is important to assess some comorbidities and basic activities of daily living as well as the cognitive status of patients in the ED, as they are also related to in-hospital and vulnerable post-discharge phase adverse outcomes in patients with de novo AHF. Finally, the age of debut of AHF does not seem to influence in-hospital mortality or adverse outcomes during the vulnerable post-discharge phase.

Acknowledgements The members of Investigators of the ICA-SEMES (Research group on Acute Heart Failure of the Spanish Society of Emergency Medicine) are Marta Fuentes, Cristina Gil (Hospital Universitario de Salamanca), Héctor Alonso, Enrique Pérez-Llantada (Hospital Marqués de Valdecilla de Santander), Francisco Javier Martín-Sánchez, Guillermo Llopis García, Mar Suárez Cadenas (Hospital Clínico San Carlos de Madrid), Òscar Miró, Víctor Gil, Rosa Escoda, Carolina Xipell, Carolina Sánchez (Hospital Clínic de Barcelona), María José Pérez-Durá, Eva Salvo (Hospital Politénic La Fe de Valencia), José Pavón (Hospital Dr. Negrín de Las Palmas de Gran Canaria), Antonio Noval (Hospital Insular de Las Palmas de Gran Canaria), José Manuel Torres (Hospital Reina Sofía de Córdoba), María Luisa López-Grima, Amparo Valero, María Ángeles Juan (Hospital Dr. Peset de Valencia), Alfons Aguirre, Maria Angels Pedragosa, Silvia Mínguez Masó (Hospital del Mar de Barcelona), María Isabel Alonso, Francisco Ruiz (Hospital de Valme de Sevilla), José Miguel Franco (Hospital Miguel Servet de Zaragoza), Ana Belén Mecina (Hospital de Alcorcón de Madrid), Josep Tost, Marta Berenguer, Ruxandra Donea (Consorci Sanitari de Terrassa), Susana Sánchez Ramón, Virginia Carbajosa Rodríguez (Hospital Universitario Rio Hortega de Valladolid), Pascual Piñera, José Andrés Sánchez Nicolás (Hospital Reina Sofía de Murcia), Raquel Torres Garate (Hospital Severo Ochoa de Madrid), Aitor Alquézar-Arbé, Miguel Alberto Rizzi, Sergio Herrera (Hospital de la Santa Creu y Sant Pau de Barcelona), Javier Jacob, Alex Roset, Irene Cabello, Antonio Haro (Hospital Universitari de Bellvitge de Barcelona), Fernando Richard, José María Álvarez Pérez, María Pilar López Diez (Hospital Universitario de Burgos), Pablo Herrero Puente, Joaquín Vázquez Álvarez, Belén Prieto García, María García García, Marta Sánchez González (Hospital Universitario Central de Asturias de Oviedo), Pere Llorens, Patricia Javaloyes, Víctor Marquina, Inmaculada Jiménez, Néstor Hernández , Benjamín Brouzet, Begoña Espinosa (Hospital General de Alicante), Juan Antonio Andueza (Hospital General Universitario Gregorio Marañón de Madrid), Rodolfo Romero (Hospital Universitario de Getafe de Madrid), Martín Ruíz, Roberto Calvache (Hospital de Henares de Madrid), María Teresa Lorca Serralta, Luis Ernesto Calderón Jave (Hospital del Tajo de Madrid), Beatriz Amores Arriaga, Beatriz Sierra Bergua (Hospital Clínico Lozano Blesa de Zaragoza), Enrique Martín Mojarro, Brigitte Silvana Alarcón Jiménez (Hospital Sant Pau i Santa Tecla de Tarragona), Lisette Travería Bécquer, Guillermo Burillo (Hospital Universitario de Canarias de Tenerife), Lluís Llauger García, Gerard Corominas LaSalle. (Hospital Universitari de Vic de Barcelona), Carmen Agüera Urbano, Ana Belén García Soto, Elisa Delgado Padial (Hospital Costa del Sol de Marbella de Málaga), Ester Soy Ferrer (Hospital Josep Trueta de Girona). José Manuel Garrido (Hospital Virgen Macarena de Sevilla), Francisco Javier Lucas-Imbernón (Hospital General Universitario de Albacete), Rut Gaya (Hospital Juan XXIII de Tarragona), Carlos Bibiano, María Mir, Beatriz Rodríguez (Hospital Infanta Leonor de Madrid), José Luis Carballo (Complejo Hospitalario Universitario de Ourense), Esther Rodríguez-Adrada, Belén Rodríguez Miranda (Hospital Rey Juan Carlos de Móstoles de Madrid).

We would like to thank the Department of Medicine of the Autonomous University of Barcelona for its logistical and administrative support.

Compliance with ethical standards

Conflict of interest The authors state that they have no conflict of interests with the present work. The ICA-SEMES Research Group has received unrestricted support from Orion Pharma and Novartis. The present study was designed, performed, analysed and written exclusively by the authors independently of these pharmaceutical companies.

References

1. Lombardi CM, Ferreira JP, Carubelli V, Anker SD, Cleland JG, Dickstein K et al (2020) Geographical differences in heart failure characteristics and treatment across Europe: results from the BIOSTAT-CHF study. Clin Res Cardiol 109:967–977. https://doi.org/10.1007/s00392-019-01588-7
2. O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC et al (2010) Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. Am Heart J 159(841–9):e1
3. Krumholz HM (2013) Post-hospital syndrome–an acquired, transient condition of generalized risk. N Engl J Med 368:100–102
4. Farmakis D, Parissis J, Lekakis J, Filippatos G (2015) Insuficiencia cardiaca aguda: epidemiología, factores de riesgo y prevención. Rev Esp Cardiol 68:245–248
5. Llorens P (2018) Risk assessment in emergency department patients with acute heart failure: we need to reach beyond our clinical judgment. Emergencias 30:75–76
6. Allen CJ, Guha K, Sharma R (2015) How to improve time to diagnosis in acute heart failure-clinical signs and chest x-ray. Cardiac Fail Rev 1:69
7. Miró Ò, García Sarasola A, Fuenzalida C, Calderón S, Jacob J, Aguirre A et al (2019) Departments involved during the first episode of acute heart failure and analysis of emergency department revisits and rehospitalisations: an outlook through the NOVICA cohort. Eur J Heart Fail 21:1231–1244
8. Formiga F, Chivite D (2018) Acute heart failure: understanding the patient is essential. Emergencias 30:145
9. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG et al (2017) Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC heart failure long-term registry. Eur J Heart Fail 19:1242–1254
10. Tu JV, Donovan LR, Lee DS, Wang JT, Austin PC, Alter DA et al (2009) Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. JAMA 302:2330–2337
11. Franco J, Formiga F, Corbella X, Conde-Martel A, Llácer P, Rocha PÁ et al (2019) Insuficiencia cardiaca aguda de novo: características clínicas y mortalidad al año en el Registro Español de Insuficiencia Cardiaca Aguda. Med Clín 152:127–134
12. Miro O, Levy PD, Mockel M, Pang PS, Lambrinou E, Bueno H et al (2017) Disposition of emergency department patients diagnosed with acute heart failure: an international emergency medicine perspective. Eur J Emerg Med 24:2–12
13. Masip J (2019) Is the MEESSI-AHF score for multiple estimation of risk based on the Spanish emergency department score in

patients with acute heart failure an effective basis for discharging patients with AHF? Emergencias 31:3–4
14. García Sarasola AAAA, Gil V, Jacob J Llorens P, Rizzi MA et al (2019) NOVICA: características y evolución en los pacientes que presentan un primer episodio de insuficiencia cardiaca (de novo). Rev Esp Cardiol. 219:469–473
15. Llorens P, Javaloyes P, Martin-Sanchez FJ, Jacob J, Herrero-Puente P, Gil V et al (2018) Time trends in characteristics, clinical course, and outcomes of 13,791 patients with acute heart failure. Clin Res Cardiol 107:897–913
16. Miro O, Gil V, Rossello X, Martin-Sanchez FJ, Llorens P, Jacob J et al (2019) Patients with acute heart failure discharged from the emergency department and classified as low risk by the MEESSI score (multiple risk estimate based on the Spanish emergency department scale): prevalence of adverse events and predictability. Emergencias 31:5–14
17. Ho KK, Pinsky JL, Kannel WB, Levy D (1993) The epidemiology of heart failure: the Framingham study. J Am Coll Cardiol 22:6A–13A
18. Miro O, Rossello X, Gil V, Martin-Sanchez FJ, Llorens P, Herrero-Puente P et al (2017) Predicting 30-day mortality for patients with acute heart failure in the emergency department: a cohort study. Ann Intern Med 167:698–705
19. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M (2015) The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol 12:220–229
20. Miró Ò, Hazlitt M, Escalada X, Llorens P, Gil V, Martín-Sánchez FJ et al (2018) Effects of the intensity of prehospital treatment on short-term outcomes in patients with acute heart failure: the SEMICA-2 study. Clin Res Cardiol 107(4):347–361
21. Shoaib A, Farag M, Nolan J, Rigby A, Patwala A, Rashid M et al (2019) Mode of presentation and mortality amongst patients hospitalized with heart failure? a report from the first euro heart failure survey. Clin Res Cardiol 108(5):510–519
22. Leto L, Feola M (2014) Cognitive impairment in heart failure patients. J Geriatr Cardiol 11:316–328
23. Miró Ò, Llorens P, Martín-Sánchez FJ, Herrero P, Pavón J, Pérez-Durá MJ et al (2009) Short-term prognostic factors in elderly patients seen in emergency departments for acute heart failure. Rev Esp Cardiol (Engl Ed) 62:757–764
24. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC (2007) Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 9:440–449
25. Martin-Sanchez FJ, Rodriguez-Adrada E, Vidan MT, Diez Villanueva P, Llopis Garcia G, Gonzalez Del Castillo J et al (2018) Impact of geriatric assessment variables on 30-day mortality among older patients with acute heart failure. Emergencias 30:149–155
26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37:2129–2200
27. Chivite D, Formiga F, Pujol R (2011) La insuficiencia cardíaca en el paciente anciano. Rev Clín Esp 211:26–35
28. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI et al (2013) Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 309:355–363
29. Page RL 2nd, Lindenfeld J (2012) The comorbidity conundrum: a focus on the role of noncardiovascular chronic conditions in the heart failure patient. Curr Cardiol Rep 14:276–284
30. Trujillo-Santos AJ, Domingo-González S, Gonzalo-Blanquer J, Perea-Milla E, Jiménez-Puente A, García-Alegría J (2006) Indicadores de calidad relacionados con el reingreso y la muerte precoces tras la hospitalización por insuficiencia cardíaca. Med clín 126:165–169
31. Maestre A, Gil V, Gallego J, Aznar J, Mora A, Martin-Hidalgo A (2009) Diagnostic accuracy of clinical criteria for identifying systolic and diastolic heart failure: cross-sectional study. J Eval Clin Pract 15:55–61
32. Dodson JA, Chaudhry SI (2012) Geriatric conditions in heart failure. Curr Cardiovasc Risk Rep 6:404–410

Affiliation

Miguel Alberto Rizzi[1] · Ana García Sarasola[1] · Aitor Alquezar Arbé[1] · Sergio Herrera Mateo[1] · Víctor Gil[2] · Pere Llorens[3] · Javier Jacob[4] · Francisco Javier Martín-Sánchez[5] · Pablo Herrero Puente[6] · Rosa Escoda[2] · Begoña Espinosa[3] · Àlex Roset[4] · Raquel Torres-Gárate[7] · José Torres-Murillo[8] · Ana B. Mecina[9] · María Pilar López-Díez[10] · José María Álvarez Pérez[10] · Josep Tost[11] · Eva Salvo[12] · María Luisa López-Grima[13] · Cristina Gil[14] · María Mir[15] · Frank Rutzinska[14] · Ovidiu Chioncel[15] · Òscar Miró[2] on behalf of the ICA-SEMES Research Group

✉ Miguel Alberto Rizzi
MRizzi@santpau.cat

[1] Emergency Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain

[2] Emergency Department, Hospital Clínic, University of Barcelona, Barcelona, Spain

[3] Emergency Department, Short Stay Unit and Hospitalization at Home, Hospital General de Alicante, Miguel Hernandez University, Alicante, Spain

[4] Emergency Department, Hospital Universitari de Bellvitge, Barcelona, Spain

[5] Emergency Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Universidad Complutense de Madrid, Madrid, Spain

[6] Emergency Department, Hospital Universitario Central de Asturias, Oviedo, Spain

[7] Emergency Department, Hospital Universitario Severo Ochoa de Leganés, Madrid, Spain

[8] Emergency Department, Hospital Universitario Nuestra Señora de Valme, Sevilla, Spain

[9] Emergency Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain

[10] Emergency Department, Hospital Universitario de Burgos, Burgos, Spain

[11] Emergency Department, Hospital de Terrassa, Barcelona, Spain

[12] Emergency Department, Hospital Universitario La Fe, Valencia, Spain

[13] Emergency Department, Hospital Doctor Peset, Valencia, Spain

[14] Emergency Department, Hospital Universitario de Salamanca, Salamanca, Spain

[15] Emergency Department, Hospital Infanta Leonor, Madrid, Spain