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► **To cite this version:**

Camille Roubille, Benjamin Eduin, Cyril Breuker, Laetitia Zerkowski, Simon Letertre, et al.. Predictive risk factors for death in elderly patients after hospitalization for acute heart failure in an internal medicine unit. *Internal and Emergency Medicine*, 2022, 10.1007/s11739-022-02982-2 . hal-03650078

**HAL Id: hal-03650078**

**<https://hal.science/hal-03650078>**

Submitted on 17 Nov 2023

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# **Predictive risk factors for death in elderly patients after hospitalization for acute heart failure in an internal medicine unit**

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## **Keywords**

Acute heart failure · Internal medicine · Hypoalbuminemia · Death · Prognosis

## **Abstract**

To determine the predictive factors of mortality after hospitalization for acute heart failure (AHF) in an internal medicine department. Retrospective observational analysis conducted on 164 patients hospitalized for AHF in 2016–2017. Demographic, clinical and biological characteristics were assessed during hospitalization. The primary endpoint was the occurrence

of all-cause death. Multivariate analysis was performed using the Cox model adjusted for age and renal function. The study population was mostly female (n = 106, 64.6%), elderly (82.9 years  $\pm$  10.0), with a preserved LVEF (86%). Mean Charlson comorbidity index was 6.5  $\pm$  2.5. After a median follow-up of 17.5 months (IQR 6–38), 109 patients (65%) had died with a median time to death of 14 months (IQR 3–29). In univariate analysis, patients who died were significantly older, had lower BMI and renal function, and higher CCI and NT-proBNP levels (median of 4944 ng/l [2370–14403] versus 1740 ng/l [1119–3503], p < 0.001). In multivariate analysis, risk factors for death were lower BMI (HR 0.69, CI [0.53–0.90], p = 0.005), lower albuminemia (HR 0.77 [0.63–0.94], p = 0.009), higher ferritinemia (HR 1.38 [1.08–1.76], p = 0.010), higher uricemia (HR 1.28 [1.02–1.59], p = 0.030), higher NT-proBNP (HR 2.46 [1.65–3.67], p < 0.001) and longer hospital stay (HR 1.25 [1.05–1.49] p = 0.013). In elderly multimorbid patients, AHF prognosis appears to be influenced by nutritional criteria, including lower BMI, hypoalbuminemia, and hyperuricemia (independently of renal function). These results underline the importance of nutritional status, especially as therapeutic options are available. This consideration paves the way for further research in this field.

## Introduction

Acute heart failure (AHF) is a major cause of unscheduled hospitalization in elderly patients and is associated with increased mortality [1].

The incidence of HF in Europe is approximately 5/1000 person-years in adults [2]. The prevalence of HF is estimated to be approximately 1–2% in adults in developed countries [3] and increases with age, with an estimated increase of more than 10% in those aged 70 years or older [4]. Although the prognosis of HF has improved in recent decades, it remains a public health issue, with a high risk for re-hospitalization following an admission for AHF [5]. Indeed, HF is characterized by episodes of acute decompensation, which may lead to repeated and prolonged hospitalizations [6], especially in the elderly and particularly in non-cardiologic units such as internal medicine departments. Moreover, due to the aging of the population in European countries, hospitalization for AHF in internal medicine units mainly involve multimorbid elderly patients.

Despite the improved survival of patients with HF, overall mortality remains a concern, with an estimated overall mortality rate of approximately 50% at 5 years, especially in elderly patients aged over 80 years [7]. Mortality rate at 5 years has also been reported to be higher, about 65% following diagnosis of HF [8].

Moreover, HF reduces the quality of life and increases the risk of hospitalization. In France, a cross-sectional survey reported a prevalence of HF of 2.3%, increasing to about 15% in people over

85 years of age, with 52.9% of people having an impaired quality of life [9]. In a French national cohort of 70,657 patients aged 65 years or older who survived after hospitalization for HF in 2015, 31.8% had at least one readmission for HF at 1 year [10].

Therefore, one of the challenges in the management of HF remains the identification of factors associated with poor prognosis and mortality. The aim of our study was to determine the predictive risk factors of mortality after hospitalization for AHF in an internal medicine unit.

## Methods

### Study population

The cohort included 180 patients who have been consecutively hospitalized in our medicine department between 2016 and 2017 for AHF. Of the 180 patients, 164 were included in the analysis after excluding those without any available data after hospitalization ( $n = 5$ ) and those who died during or immediately after hospitalization ( $n = 11$ ) (e.g., palliative care), to explore predictive risk factors associated with medium- and long-term mortality after hospitalization for AHF.

The diagnosis of HF was made on the basis of clinical signs of congestion, left ventricular ejection fraction (LVEF) less than 50% or signs of congestion on transthoracic echocardiography, with an elevated Nt-proBNP level without chronic renal failure [6]. AHF may be either acute de novo HF or acute exacerbation of chronic HF. According to the recognized terminology [6], HF patients with preserved ejection fraction (HFpEF) comprised HF patients with a LVEF  $\geq 50\%$ .

### Study outcomes

Demographic and clinical characteristics were assessed during hospitalization, including age, gender, weight (at admission and discharge), body mass index (BMI), and conditions being responsible for chronic HF such as valvular disease, ischemic heart disease, atrial fibrillation. Various comorbidities were collected at admission: hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease, chronic kidney diseases, sleep apnea–hypopnea syndrome, dementia, stroke, and peripheral artery disease. Comorbidities were declarative and defined as “presence” or “absence” at inclusion and were assessed by the Charlson Comorbidity Index [11]. At discharge, chronic heart failure treatment was collected by a pharmaceutical team during the medication reconciliation process, following a previously described validated protocol [12].

Regarding biological characteristics, the C-reactive protein (CRP) level, hemoglobin, ferritin, NT-proBNP, troponin-hs, creatin kinase, uric acid, protid, albumin, HDL, LDL, HbA1C, creatinine levels and transferrin saturation (TSAT) were determined at admission. Renal function was assessed by CKD-EPI ( $\text{ml}/\text{min}/1.73 \text{ m}^2$ ).

The primary endpoint was the occurrence of all-cause death, based on data from the national database [13]. We completed data collection by calling the patient's family physician. The protocol of this study was approved by the Institutional Review Board of Montpellier University Hospital (IRB-MTP\_2021\_04\_202100801).

**Table 1** Baseline demographic, clinical, and biological characteristics of the study population and comparison of factors associated with death during follow-up in univariate analysis

	Total n = 164	Alive n = 55	Deceased n = 109	p value
<i>Clinical</i>				
Female	106 (64.6)	39 (70.9)	67 (61.5)	0.299
Age (years)	82.9 ± 10.3	79.0 ± 11.7	84.8 ± 9	0.001
Weight (admission) (kg)	72.8 ± 20.7	79.3 ± 22.6	69.5 ± 18.9	0.004
Weight (discharge) (kg)	71.1 ± 19.4	77.6 ± 22.0	67.7 ± 17.0	0.002
BMI	28.4 ± 7.7	31.9 ± 8.6	26.6 ± 6.6	<0.001
Systolic blood pressure (mmHg)	139.4 ± 26.9	145.2 ± 28.8	136.4 ± 25.5	0.050
Heart rate (bpm)	84.7 ± 19.7	84.5 ± 18.4	84.7 ± 20.4	0.952
Duration of hospitalization (days)	14.0 ± 9.1	13.7 ± 8	14.18 ± 9.6	0.762
LVEF	47.2 ± 9	49 ± 6.8	46.3 ± 9.9	0.016
HFpEF	128 (86)	48 (92)	80 (83)	0.138
Coronaryopathy	13 (8)	7 (13)	6 (5.5)	0.126
Myocardial infarction	56 (34)	14 (26)	42 (39)	0.117
Hypertension	127 (77)	44 (80)	83 (76)	0.693
Atrial fibrillation	96 (59)	33 (60)	63 (58)	0.867
Left ventricular valvulopathy	109 (67)	33 (60)	76 (70)	0.225
Acute pulmonary oedema	72 (44)	23 (42)	49 (45)	0.741
<i>Comorbidities</i>				
Charlson comorbidity index	6.5 ± 2.5	5.7 ± 2.3	6.9 ± 2.5	0.003
Stroke	29 (18)	5 (9)	24 (22)	0.051
PAOD	31 (19)	9 (16)	22 (20)	0.674
CKD	64 (39)	20 (36)	44 (40)	0.735
Diabetes	60 (37)	20 (36)	40 (37)	1.000
COPD	24 (15)	7 (13)	17 (16)	0.815
Asthma	11 (7)	3 (6)	8 (7)	0.752
Dyslipidemia	45 (27)	18 (33)	27 (25)	0.354
Cancer	5 (3)	1 (2)	4 (4)	0.665
Cirrhosis	7 (4)	2 (4)	5 (5)	1.000
Dementia	22 (13)	6 (11)	16 (15)	0.630
<i>Biology</i>				
Hemoglobin (g/dl)	12.3 ± 7.1	11.9 ± 2.0	12.5 ± 8.6	0.608
TSAT (%)	16 ± 12	20 ± 15	14 ± 9	0.017
Ferritin (µg/l)	278 ± 299.2	261.7 ± 235.6	286.4 ± 327.6	0.687
Blood glucose (mmol/l)	7.0 ± 2.9	7.2 ± 3.2	6.9 ± 2.7	0.529
HbA1c (%)	6.5 ± 1.1	6.4 ± 1.1	6.6 ± 1.2	0.261
Creatinin (µmol/l)	127 ± 74	108 ± 59	136 ± 79	0.016
CKD-EPI (ml/min)	50 ± 26	56 ± 23	47 ± 28	0.044
Na (mmol/l)	139 ± 5.1	139.7 ± 4.2	139.3 ± 5.5	0.585
K (mmol/l)	4.1 ± 0.7	4.0 ± 0.6	4.2 ± 0.7	0.206
ASAT (U/l)	30 ± 23	30 ± 23	30 ± 23	0.981
ALAT (U/l)	24 ± 24	26 ± 23	22 ± 25	0.394
Uric acid (mmol/l)	454 ± 160	426 ± 135	468 ± 170	0.111
Proteins (g/l)	69 ± 8	69 ± 8	69 ± 8	0.666
Albumin (g/l)	36 ± 4	37 ± 4	35 ± 4	0.063
Creatin kinase (Ui/l)	186 ± 710	303 ± 200	128 ± 163	0.184
Troponins (ng/l)	103 ± 205	63 ± 80	122 ± 242	0.097
NT-proBNP (ng/l) (median, IQR)	3620 (1701–10,166)	1740 (1119–3503)	4944 (2370–14,403)	<0.001
HDLc (g/l)	0.46 ± 0.18	0.51 ± 0.21	0.4 ± 0.13	0.021
LDLc (g/l)	0.82 ± 0.38	0.94 ± 0.44	0.71 ± 0.29	0.024

**Table 1** (continued)

	Total n = 164	Alive n = 55	Deceased n = 109	p value
CRP (mg/l) (median, IQR)	22 (8–61)	19 (7–60)	22 (9–62)	0.787
<i>Discharge treatments</i>				
ACEI	68 (42)	19 (35)	49 (45)	0.241
ARB	26 (16)	8 (15)	18 (17)	0.824
MRA	17 (10)	7 (13)	10 (9)	0.588
Beta-blocker	101 (62)	33 (60)	68 (62)	0.865
Loop Diuretics	137 (84)	42 (76)	95 (87)	0.117
Amiodarone	32 (20)	13 (24)	19 (17)	0.405
Digitalis	3 (2)	2 (4)	1 (1)	0.261
Sacubitril-valsartan	0	0	0	
Anticoagulant	83 (51)	28 (51)	55 (51)	1.000
Antiplatelet	72 (44)	24 (44)	48 (44)	1.000
Statins	48 (29)	20 (36)	28 (26)	0.203

Data are expressed as n (%) or mean (S.D.) otherwise noted

*BMI* body mass index, *HFpEF* heart failure with preserved ejection fraction, *ACE-I* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta-blockers, *CKD* chronic kidney disease, *PAOD* peripheral artery obstructive disease, *COPD* chronic obstructive pulmonary disease, *MRA* mineralocorticoid receptor antagonist, *Na* natrium, *K* kaliemia, *CRP* C-reactive protein, *TSAT* transferrin saturation

## Statistical analysis

Continuous variables are expressed in mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR) in case of skewed distribution and were compared using Student's t test (Table 1). Qualitative variables are expressed as frequency and compared using Fisher's exact test. Cox proportional hazards regression model [expressed as hazard ratio (HR) with corresponding 95% confidence interval (CI) and p values] was used to assess the association between each clinical or biological outcome and the occurrence of death, adjusting on age and CKD-EPI, which are established risk factors of HF mortality. HR are expressed per SD for each continuous variable as computed in Table 1. Due to skewed distribution, CRP and NT-proBNP were log-transformed prior to analysis. The statistics were performed using IBM SPSS Statistics 25 software. p value < 0.05 was considered to be statistically significant.

## Results

### Study population

Baseline clinical and biological characteristics, including comorbidities and treatment at discharge, are shown in Table 1. The study population comprised 164 patients, including 106 women, mean age of  $82.9 \pm 10.3$  years, a mean BMI of  $28.4 \pm 7.7$ , a mean LVEF of  $47.2 \pm 9\%$ , and mostly HFpEF (86%). As regards comorbidities, 127 (77%) had hypertension, 60 (37%) had diabetes mellitus, 45 (27%) had dyslipidemia, and 64 (39%) had chronic kidney disease. Mean Charlson comorbidity index was  $6.5 \pm 2.5$ . Most of the patients (58%) received ACE-I or ARB, 62% received beta-blockers and 84% received loop diuretics.

### Outcomes

After a median follow-up period of 17.5 months (IQR 6–38), 109 (66.4%) patients died within a mean time of 14 months (IQR 3–29). Forty-nine patients (30%) died within the first year. In univariate analysis, patients who died during follow-up were significantly older, had lower BMI, lower LVEF,

and higher Charlson comorbidity index. These patients had a lower renal function, higher levels of NT-proBNP (median of 4944 ng/l [2370–14403] compared to 1740 ng/l [1119–3503],  $p < 0.001$ ), lower TSAT, and lower levels of HDL and LDL cholesterol compared with patients who survived (Table 1). Of note, 36 (22%) patients had both diabetes and CKD, of whom 24 died and 12 remained alive.

In multivariate analysis (Table 2), after adjustment for age and renal function, risk factors for death were weight at admission and discharge (respectively HR 0.76 [0.59–0.96]  $p = 0.022$  and HR 0.75 [0.59–0.96]  $p = 0.020$ ), BMI (HR 0.69, CI [0.53–0.90],  $p = 0.005$ ), albuminemia (HR 0.77 [0.63–0.94],  $p = 0.009$ ), ferritinemia (HR 1.38 [1.08–1.76],  $p = 0.010$ ), uricemia (HR 1.28 [1.02–1.59],  $p = 0.030$ ), NT-proBNP level (HR 2.46 [1.65–3.67],  $p < 0.001$ ) and longer hospital stay (HR 1.25 [1.056–1.49]  $p = 0.013$ ). We did not find any statistically significant association between mortality and the treatment for heart failure at discharge.

## Discussion

The present study explores, in a real-life setting, the long-term outcomes of elderly patients hospitalized for AHF in an internal medicine department. Patients hospitalized in France for AHF are now increasingly older, with preserved LVEF, and increasingly hospitalized in non-cardiologic units. In the OFICA (Observatoire Français de l'Insuffisance Cardiaque Aigue) nationwide survey, representing a single-day snapshot of all unplanned hospitalizations because of AHF in 170 French hospitals, 18% of the 1658 patients, nearly 50% of whom were octogenarians, were admitted to an internal medicine unit [10].

First, our study population, mostly female ( $n = 106$ , 64.6%), elderly ( $82.9 \pm 10.0$  years), with a preserved LVEF (86%), has similar characteristics as other published cohorts of patients hospitalized for AHF in internal medicine departments [14, 15]. For instance, Martinez et al.'s study population included primarily elderly women, with preserved ejection fraction and with multiple comorbidities, the main ones being cardiovascular risk factors, especially hypertension, chronic kidney diseases, respiratory diseases, and chronic anaemia [14]. In the present study, 22% of patients were diabetic with chronic renal failure, which are known to be at a very high cardiovascular risk [16] and for whom comprehensive risk factors control has been reported to improve cardiovascular outcomes and overall mortality [17]. AHF patients who are hospitalized in the internal medicine department are frequently older and affected by many comorbidities compared with patients hospitalized in cardiology units. As regards HF treatments, the French cohort study ODIN (Observatoire De l'Insuffisance Cardiaque) [18] reported that HT medications were less frequently prescribed with advancing age and with dosages lower than recommended. In the present study, we found a low rate of patients on ACE and ARB therapy (57%), without any reason other than age and comorbidities.

Second, we found a high mortality rate, with 65% of patients dying 5 years after hospitalization for AHF. A study based on data from the French national health insurance system in 2009, showed a 2-year mortality rate of 40% [19]. In the ESC-HF long term registry, which is a prospective observational study of 6,629 AHF patients enrolled from 2011 to 2015 in 21 European countries, Chioncelet al. reported a readmission rate of 25.9% at 1 year and an all-causes 1-year mortality rate of 26.7%, but

their study population was much younger with only 34% over 75 years of age [20] compared with 61.6% in our study.

**Table 2** Factors associated with death during the follow-up in multivariate analysis adjusted on age and CKD-EPI

	HR (95% CI)	<i>p</i> value
<i>Clinical</i>		
Female	0.72 (0.48–1.07)	0.103
Weight (admission) (kg)	0.76 (0.59–0.96)	0.022
Weight (discharge) (kg)	0.75 (0.59–0.96)	0.020
BMI	0.69 (0.53–0.90)	0.005
Duration of hospitalization	1.25 (1.05–1.49)	0.013
LVEF	0.83 (0.66–1.06)	0.128
HFpEF	0.68 (0.40–1.15)	0.155
Coronaropathy	0.70 (0.30–1.60)	0.395
Myocardial infarction	1.13 (0.77–1.67)	0.532
Hypertension	0.92 (0.59–1.43)	0.706
Atrial fibrillation	1.16 (0.78–1.71)	0.463
Left ventricular valvulopathy	1.26 (0.83–1.90)	0.272
Acute pulmonary oedema	0.97 (0.66–1.44)	0.897
<i>Comorbidities</i>		
Charlson score	1.13 (0.91–1.40)	0.271
Stroke	1.03 (0.65–1.63)	0.888
PAOD	1.39 (0.86–2.25)	0.175
Diabetes	0.99 (0.66–1.47)	0.949
COPD	1.15 (0.68–1.93)	0.607
<i>Biology</i>		
Hemoglobin (g/dl)	1.00 (0.84–1.20)	0.998
TSAT	0.83 (0.61–1.13)	0.240
Ferritin (µg/l)	1.38 (1.08–1.76)	0.010
Blood glucose (mmol/l)	1.02 (0.81–1.29)	0.872
HbA1c (%)	1.04 (0.79–1.38)	0.760
Uric acid (mmol/l)	1.28 (1.02–1.59)	0.030
Proteins (g/l)	0.98 (0.80–1.20)	0.855
Albumin (g/l)	0.77 (0.63–0.94)	0.009
Creatin kinase (Ui/l)	0.82 (0.54–1.27)	0.381
Troponins (ng/l)	1.16 (0.98–1.38)	0.077
NT-proBNP (ng/l)	2.46 (1.65–3.67)	<0.001
HDLc (g/l)	0.63 (0.37–1.05)	0.079
LDLc (g/l)	0.66 (0.41–1.06)	0.085
CRP (mg/l)	1.16 (0.83–1.62)	0.378
<i>Discharge treatments</i>		
ACEI	1.10 (0.75–1.60)	0.638
ARB	0.68 (0.41–1.14)	0.144
MRA	0.86 (0.44–1.65)	0.645
Beta-blockers	1.11 (0.75–1.63)	0.614

HR are expressed per SD for each continuous variable as computed in Table 1

HR hazard ratio, CI confidence interval, BMI body mass index, HFpEF heart failure with preserved ejection fraction, PAOD peripheral artery obstructive disease, COPD chronic obstructive pulmonary disease, ACE-I angiotensin converting enzyme inhibitors, ARB angiotensin receptor blockers, BB beta-blockers, MRA mineralocorticoid receptor antagonist, TSAT transferrin saturation



Indeed, various studies have shown that elderly patients with HF have a higher risk of poor prognosis [21, 22]. In another French study, the 5-year survival in elderly patients older than 80 years was reported at 19%, dramatically lower than the survival of the age- and sex-matched general population of 48% [22], consistently with our results. Female gender, hypertension, atrial fibrillation and comorbidities were reported to be more frequent in the elderly, as well as underuse and under dosage of medications recommended for HF management which may contribute to such a poor prognosis [22, 23].

As regards prognostic factors, especially in the elderly, albumin levels have been associated with mortality in the older patients with HF [24–26]. In one study including 438 patients, hypoalbuminemia predicted 1-year mortality (HR adjusted 2.05, 95% CI 1.10–3.81,  $p = 0.001$ ) [27]. Higher serum albumin levels (HR 0.67, 95% CI 0.53–0.85) were associated with longer survival in 1,120 patients with HFpEF [28]. Albumin level is a well-known marker of nutritional status, of utmost importance in elderly subjects. Hypoalbuminemia in HF patients is likely multifactorial, related to malnutrition due to decreased oral intake, as well as to increased catabolic activity, or chronic inflammation [28]. It may contribute to pulmonary edema and exacerbation of HF, due to decreased osmotic pressure. Hypoalbuminemia may provide additional prognostic criteria in elderly HF patients.

Furthermore, we found an inverse relationship between BMI and 5-year death. A higher BMI has been associated with reduced mortality in established HF patients, consistent with the “obesity paradox” [29]. This inverse relationship between obesity and prognosis in HF may be explained by the limitations of using BMI to define body composition [30]. On the other hand, cachexia has been associated with poor prognosis in HF [31], with a known association between lean body mass, muscle strength, and subsequent survival [30]. Of note, the Charlson comorbidity index was not independently associated with mortality in our population. More than the number of comorbidities per se, it may be more the profile of comorbidities that may have a different impact on the prognosis of elderly patients. Therefore, beyond the effect of the number of comorbidities, it may be more relevant to identify subsets of patients who are at higher risk of severe outcomes. In this line of thought, different frailty phenotypes have been associated with different impacts on mortality, as shown in the REPOSI study [32]. In the present study, our data highlight the importance of malnutrition over other comorbidities in the prognosis of elderly patients after AHF.

We also found an association between increased levels of uric acid and ferritin, and mortality. Consistently with our results, hyperuricemia has been associated with a higher risk of HF rehospitalization or death at 6 months [33]. This point seems important, given that some studies revealed a greater prognostic value of hyperuricemia in patients without chronic renal failure, suggesting that hyperuricemia may be predictive of poor outcome when it is a marker of increased xanthine oxidase activity, but not when it is related to impaired renal excretion of uric acid [34]. However, the association we found between ferritin levels and mortality is not in line with the previously reported association between iron deficiency and mortality in HF [6, 35]. It is possible that in our cohort, hyperferritinemia is rather related to the biological inflammatory syndrome. Indeed, the mean CRP level was elevated in our population, partly due to coexisting infection in several patients, but was not associated with mortality. Regarding TSAT, we found that deceased patients

had a lower TSAT, with an association with mortality in univariate analysis but not in multivariate analysis. This is consistent with recent studies recommending iron supplementation in these patients, especially the AFFIRM- HF study [36]. Further studies are needed to clarify this last point, especially in the acute phase of HFpEF.

### **Limitations**

The present study has several limitations. First, this is a retrospective analysis of a cohort of consecutive elderly patients admitted for AHF, based on the experience of a single internal medicine unit. However, as a tertiary center, this population could be considered representative of the large region (2 million inhabitants). Another limitation is a relatively small sample size, which may have implied relatively low power, and may not have identified significant associations. For example, the lack of association between discharge treatments and mortality should be taken with caution. Nevertheless, the sample size appears to be similar to other studies conducted in internal medicine departments, for example the study of Martinez et al. [14]. The exclusion of patients who died during or immediately after hospitalization may have created a bias. However, we believe that it allowed us to analyze the factors and comorbidities involved only in the medium- and long-term mortality of patients hospitalized for AHF. Moreover, we do not have information about muscle mass and body composition, which would have been of interest to further explore the association we found between malnutrition, BMI, and death. However, this appears to be related to the design of our study, which aimed to explore the association between non-selected comorbidities and death, without specifically focusing on malnutrition outcomes. Furthermore, all the criteria investigated here are widely available in clinical routine, which enables translation in clinical practice. In summary, in this retrospective study of a cohort of elderly patients with AHF hospitalized in an internal medicine unit, BMI, albuminemia, ferritinemia and uricemia may provide additive prognostic values after hospital discharge, given their association with mortality. These results highlight the need to consider nutritional support in elderly patients with HFpEF admitted for acute HF and paves the way **for interventional studies in the field.**

### **Author contributions**

All authors had full access to the data and reviewed and approved the manuscript for publication; CR, BE and PF take responsibility for the integrity of the data and the accuracy of the data analysis; concept and design, all authors; acquisition, analysis, or interpretation of data, all authors; drafting of the manuscript, CR; critical revision of the manuscript, all authors; agreement to be accountable for all aspects of the work, all authors; statistical analysis, PF. All authors have read and agreed to the **published version of the manuscript.**

### **Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### **Data availability**

Data could be available on reasonable request.

## Declarations

**Conflict of interest C.R.:** reports personal fees from Servier and Pfizer unrelated to this work; **L.Z.:** reports personal fees from Servier unrelated to this work; **S.L.:** reports personal fees from Servier unrelated to this work; **C.M.:** reports personal fees from Servier unrelated to this work; **F.R.:** reports grants, personal fees and non-financial support from Air Liquide, grants and personal fees from Abbott, AstraZeneca and Novartis, personal fees from Vifor, Servier, Abiomed, Zoll, Medtronic, Resmed, LVL, Eole, Pfizer, outside the submitted work; **P.F.:** has received travel and accommodation fees from Actelion, Johnson and Johnson, BMS, Pfizer, and Servier unrelated to this work. The remaining authors declare no conflict of interest.

## Institutional review board

The protocol of this study was approved by the Institutional Review Board of Montpellier University Hospital (IRB-MTP\_2021\_04\_202100801).

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