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Original Article

Lower admission blood pressure as an independent predictor of 1-year mortality in elderly patients experiencing a first hospitalization for acute heart failure☆

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ABSTRACT

Background: Systolic blood pressure (SBP) is an acknowledged prognostic factor in patients with heart failure (HF). Admission SBP should be a risk factor for 1-year mortality even in elderly patients experiencing a first admission for HF, and this risk may persist in the oldest subset of patients.
Design: Methods: We reviewed the medical records of 1031 patients aged 70 years or older admitted within a 3-year period for a first episode of acute heart failure (AHF). The cohort was divided according to admission SBP values in quartiles. We analyzed all-cause mortality as a function of these admission SBP quartiles.
Results: Mean age was 82.2 ± 6 years; their mean admission SBP was 138.6 ± 25 mmHg. A statistically significant association was present between mortality at 30 ($p < 0.0001$), 90 ($p < 0.0001$), and 365 days ($p < 0.0001$) after hospital discharge and lower admission SBP quartiles. One-year mortality ranged from 14.7% for patients within the upper SBP quartile to 41.4% for those in the lowest quartile. The multivariate analysis confirmed this association (HR: 0.884; 95% CI: 0.615-0.76; $p = 0.0001$), which remained significant when admission SBP was evaluated as a continuous variable (HR: 0.980; 95% CI: 0.975–0.985; $p = 0.0001$). The association between SBP and 1-year mortality remained when the sample was divided into old (70–82 years) and "oldest-old" (>82 years) patients.
Conclusions: Lower SBP at admission is an independent predictor of midterm postdischarge mortality for elderly patients experiencing a first admission for AHF.

1. Introduction

Heart failure (HF) is a growing public health problem with high prevalence and significant morbidity and mortality.[1] This is particularly true for the older population, which encompasses most cases of HF.[2]

Systolic blood pressure (SBP) is a well-known prognostic factor in patients with HF: an inverse association between SBP and mortality in patients with acute HF (AHF)[3–7] and even in older patients has been consistently found,[8] wherein patients presenting with lower admission SBP experience worse outcomes.

To further address the prognostic role of SBP, we developed the present study to investigate whether this association between SBP and mortality after an AHF episode remains when the evaluation is restricted to elderly patients experiencing a confirmed first-ever admission for AHF. We also evaluated whether this relationship extends to the oldest-old group of patients and also whether a differential clinical profile exists when these patients are stratified according to their admission SBP.

2. Methods

2.1. Study design

This retrospective study was performed at the Bellvitge University Hospital, a 750-bed tertiary-care public hospital located

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near Barcelona, Spain. The principles and procedures of the study have been previously described.[9] Briefly, we retrieved administrative data regarding all admissions to our hospital within a 36 month period (Jan 2012–Dec 2014) with HF as the primary discharge diagnosis. Following this first selection, we underwent a thorough review of all these patients' medical records to select only those who a) truly fulfilled the clinical criteria for AHF and b) were experiencing the first-ever admission due to a first episode of AHF. Those who had already been discharged ever before with a primary or secondary diagnosis of HF were excluded. For the present study, we selected only patients aged 70 years or older and excluded those in stage V chronic kidney disease (CKD) undergoing kidney replacement therapies, patients who had received a kidney or heart transplant, patients already receiving palliative therapy for any cause, patients whose AHF episode was secondary to an acute coronary syndrome, and patients discharged directly home within 24 hours or transferred to other acute care hospitals from the Emergency Department. All doubts regarding a patient inclusion were discussed within an investigators' review panel. The study conformed to the principles outlined in the Declaration of Helsinki, and the Ethics Committee of the Bellvitge University Hospital approved the overall protocol.

We ascertained the presence of HF using Framingham criteria. When echocardiographic data were available, we recorded the patients' ejection fraction (EF) values and coded HF as heart failure with preserved ejection fraction (HFPEF) type when the EF value was $\geq$50%. For all patients, we collected demographic data, medical history diagnoses, and all the clinical data related to HF history and AHF signs and symptoms. A basic blood chemistry panel was obtained at admission; in addition to kidney function, these data included ionic, lipid, and glycemic profiles and a complete blood count. The admission plasma concentration of NT-proBNP was not available in most patients, and for this reason, we did not include this biomarker in the patients' database. We also recorded the patients' index admission length of stay and the HF-related therapies prescribed upon discharge, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), beta-blockers, and diuretics.

2.2. Definitions of SBP

The primary independent variable was SBP, which was analyzed by categorizing into quartiles, as a continuous variable, and finally in groups (<90, 90–119, 120–149, 150–179, and >179 mmHg) as already used in other studies for risk estimation.[8] SBP data were retrieved from the first measurement obtained in the emergency department before any therapies were administered.

2.3. Procedure

We divided the sample according to SBP quartiles. To investigate whether the risk associated with admission SBP remained with advancing age, we also divided the sample according to the median age of our patients.

2.4. Outcome

The main outcome of the present study was 1-year all-cause mortality, defined as death measured as time-to-event within the year following discharge after the index AHF admission. Subjects were categorized as alive after 12 months of follow-up or as censored when they died. Secondary outcomes were in-hospital, 1-month, and 3-month all-cause mortality. Mortality status was determined by trained physician adjudicators from medical records obtained from hospitalizations, emergency room visits, death certificates, and autopsy and coroner's reports, when available. No patients were lost to follow-up.

2.5. Statistical analysis

We reported data as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. We categorized SBP at admission into quartiles as previously described and evaluated differences in patient characteristics. The Kolmogorov–Smirnov test was used to determine whether quantitative variables were normally distributed. The Student's t-test and ANOVA were used to compare continuous variables, with a previous Levene test for equality of variances, whereas either chi-square statistic or Fisher's exact test was used to compare categorical or dichotomous variables, respectively. For non-normally distributed continuous variables, we used the Wilcoxon rank sum test for independent variables and the Wilcoxon signed rank test for paired variables.

Kaplan–Meier survival curves were generated to assess prognostic differences in terms of mortality between groups and were compared by the log-rank test. To evaluate the hazard ratio (HR) between SBP quartiles and all-cause mortality, univariate and multivariate analyses were performed using forward stepwise Cox proportional hazard models. For multivariate analyses, we adjusted according to age, sex, and the covariates found to be associated with mortality in the univariate analysis ($p < 0.05$). We repeated the model using the five aforementioned categories of SBP and also using SBP as a continuous variable. Finally, we investigated the association by dividing the sample according to the median value of age comparing outcomes for "old" and "oldest-old" (>82 years) patients. The data were analyzed with the Statistical Package for Social Sciences (SPSS) program (IBM SPSS Version 21.0, Armonk, NY). Tests were two sided, and p-values <0.05 were considered as statistically significant.

3. Results

3.1. Baseline characteristics

A total of 1031 patients were included; their mean age was 82.2 ± 6 years (range 71–102 years), and 58.2% were women. The quartiles of age were 71–77, 77.1–82, 82.1–87, and >87 years; hence, the median value used for the age analysis was 82. The mean SBP for the entire cohort was 138.6 ± 25 mmHg. Baseline characteristics are shown in Table 1 according to SBP quartile values (<121, 121–137, 137–153, and >153 mmHg for Q1, Q2, Q3, and Q4, respectively). According to predefined SBP groups, the percentage of patients in each group was 0.8% (<90 mmHg), 21.7% (90–119 mmHg), 44.9% (120–149 mmHg), 24.5% (150–179 mmHg), and 8.1% (>179 mmHg). In total, 437 (42.4%) patients presented at admission with high SBP defined as >140 mmHg according to the current guidelines. The mean diastolic blood pressure (DBP) was 74.6 ± 15 mmHg. Regarding patients' baseline characteristics, most of the patients (86.8%) had a previous diagnosis of hypertension. No differences in age and gender were found between groups. There was a higher percentage of a previous diagnosis of hypertension and diabetes for Q3 and Q4 and higher percentages of a previous diagnosis of dementia and preserved EF for Q1 and Q2. Patients within the lower quartiles of SBP showed lower DBP, lower hemoglobin concentrations, and lower estimated glomerular filtration rates.

Table 1
Baseline characteristics, length of stay, discharge therapies, and cumulative mortality during index admission and 1 year of follow-up according to admission systolic blood pressure quartiles.

	SBP <121 mmHg (n = 276)	SBP 121–137 mmHg (n = 242)	SBP 137–153 mmHg (n = 257)	SBP >153 mmHg (n = 256)	p
Age (years), mean ± SD	81.95 ± 6	81.63 ± 5	82.9 ± 6	82.4 ± 6	0.100
Gender (female), n (%)	154 (55.8%)	139 (57.4%)	141 (54.9%)	167 (65.2%)	0.069
CAD, n (%)	66 (23.9%)	59 (24.4%)	53 (20.6%)	61 (23.8%)	0.733
Hypertension, n (%)	215 (77.9%)	207 (85.5%)	238 (92.6%)	235 (91.8%)	<0.0001
Diabetes mellitus, n (%)	88 (31.9%)	97 (40.1%)	103 (40.1%)	119 (46.5%)	0.007
Dyslipidemia, n (%)	152 (55.1%)	127 (52.5%)	140 (54.5%)	135 (52.7%)	0.916
Atrial fibrillation, n (%)	114 (41.3%)	108 (44.6%)	97 (37.7%)	90 (35.2%)	0.147
COPD, n (%)	69 (25%)	52 (21.5%)	68 (26.5%)	56 (21.9%)	0.483
CKD, n (%)	81 (29.3%)	60 (24.8%)	74 (28.8%)	62 (24.2%)	0.425
Dementia, n (%)	34 (12.3%)	12 (5%)	21 (8.2%)	24 (9.4%)	0.030
Stroke, n (%)	39 (14.1%)	38 (15.7%)	36 (14%)	44 (17.2%)	0.715
Known anemia, n (%)	59 (21.4%)	41 (16.9%)	56 (21.8%)	52 (20.3%)	0.525
HFpEF, n (%) (echocardiography, n = 377)	63 (80.8%)	74 (66.1%)	82 (64.6%)	78 (53.8%)	0.001
Charlson comorbidity index, mean ± SD	2.2 ± 1.6	2.1 ± 1.7	2.2 ± 1.8	2.1 ± 1.8	0.947
Chronic therapies, mean ± SD	8 ± 3	7.7 ± 3	8.2 ± 4	7.9 ± 4	0.486
Vital signs, mean ± SD					
SBP (mmHg)	109 ± 9	129 ± 4	145 ± 5	173 ± 16	<0.0001
DBP (mmHg)	64.8 ± 11	71 ± 11	76 ± 13	86 ± 16	<0.0001
Heart rate (bpm)	84.9 ± 20	85.6 ± 18	93.4 ± 20	85.3 ± 21	0.620
Laboratory tests, mean ± SD					
Hb (g/dL)	11.4 ± 1.8	11.8 ± 1.9	12.1 ± 4.7	12.8 ± 6.5	0.003
Na (mmol/L)	138 ± 5	137 ± 5	138 ± 3	138 ± 4	0.051
K (mmol/L)	4.2 ± 0.5	4.1 ± 0.6	4.2 ± 0.6	4.1 ± 0.5	0.220
Creatinine (μmol/L)	114 ± 68	104 ± 82	101 ± 54	105 ± 70	0.084
eGFR (MDRD) (mL/min)	50 ± 27	55.6 ± 32	57 ± 31	62.6 ± 37	<0.0001
Length of stay (days), mean ± SD	7.6 ± 12	5.8 ± 7	5.3 ± 4	4.7 ± 3	<0.0001
Medications at discharge, n (%)					
ACEI/ARBs	120 (48%)	104 (44.4%)	111 (44.8%)	108 (43.2%)	0.737
Beta-blocker	95 (38%)	117 (50%)	129 (52%)	135 (54%)	0.525
MRAs	18 (7.2%)	26 (11.1%)	39 (15.7%)	61 (24.4%)	<0.0001
Loop diuretics	240 (94.9%)	217 (92.3%)	231 (92.8%)	227 (90.8%)	0.506
Mortality, n (%)					
In-hospital	31 (51.7%)	12 (20%)	10 (16.7%)	7 (11.7%)	<0.0001
One month	53 (48.6%)	27 (24.8%)	20 (18.3%)	9 (8.3%)	<0.0001
Three months	71 (49%)	37 (25.5%)	23 (15.9%)	14 (9.7%)	<0.0001
One year	132 (41.4%)	71 (22.3%)	69 (21.6%)	47 (14.7%)	<0.0001

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HFpEF: heart failure with preserved ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; Na: sodium; K: potassium; eGFR: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; MRAs: mineralocorticoid receptor antagonists.

3.2. Hospitalization data (Table 1)

Length of stay was statistically longer for patients within the lowest quartiles of SBP ($p < 0.0001$). A total of 60 patients (5.8%) died during the index hospitalization; in-hospital mortality rate was higher among patients within the lowest quartiles of SBP ($p < 0.0001$).

3.3. HF-related discharge drug therapies

There were no statistically significant differences between quartiles with regard to discharge prescriptions of ACEI or ARB, beta-blocker agents, or loop diuretics. The only significant difference was for MRAs, more likely to be prescribed to patients in the upper SBP quartiles ($p < 0.0001$).

3.4. Follow-up

In total, 319 patients (32.8% of the 971 discharged) died during the follow-up period. One-year mortality ranged from 14.7% for patients within Q4 to 41.4% for those within Q1. A statistically significant association was present at 30 ($p < 0.0001$), 90 ($p < 0.0001$), and 365 days ($p < 0.0001$) after hospital discharge between higher mortality and the lowest quartiles of SBP (Table 1); this association is graphically shown in Fig. 1 as 1-year survival curves according to the SBP quartiles (log-rank test 11.71; $p < 0.001$).

The univariate logistic regression analysis (Table 2) identified SBP, both stratified by quartiles and as a continuous variable, to be independently associated with a higher risk of 1-year post-discharge mortality. The multivariate analysis confirmed this association (HR for SBP as quartiles 0.684; 95% CI: 0.615–0.761; $p = 0.0001$ and HR for SBP as a continuous variable 0.980; 95% CI: 0.975–0.985; $p = 0.0001$). The association also remained when we analyzed the five predefined categories of admission SBP (HR 0.611; 95% CI: 0.527–0.704; $p = 0.0001$) in addition to higher admission potassium values and higher number of chronic therapies. The remaining variables identified in the univariate analyses (history of hypertension and DBP) did not show significance for the association with mortality in the multivariate analyses.

When we evaluated only the 886 patients who were alive after 3 months of follow-up, the association between baseline SBP at admission and SBP at mortality after 9 months of further follow-up remained significant, by both baseline SBP quartiles ($p < 0.0001$) and predefined five SBP categories ($p = 0.005$).

3.5. Association of age and baseline SBP with mortality

Among patients aged 71–82 years, there was a significant association between baseline SBP and 1-year global mortality that persisted when adjusted in the multivariate analysis (HR 0.728; 95% CI: 0.629–0.843; $p = 0.0001$). In patients aged >82 years, there was

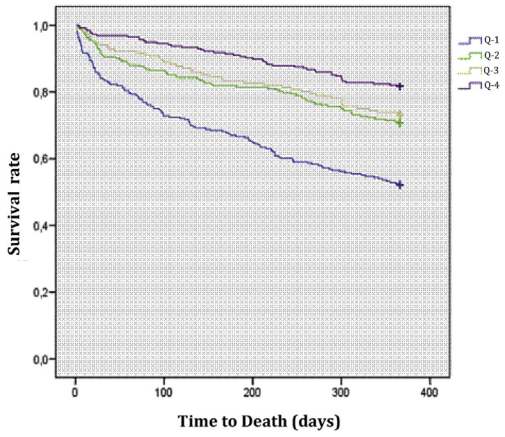

Fig. 1. Kaplan–Meier analysis of 1-year mortality according to admission systolic blood pressure quartiles. Log-rank test 67.65; p < 0.0001.

also a significant association between baseline SBP and 1-year global mortality that persisted when adjusted in the multivariate analysis (HR 0.773; 95% CI: 0.664–0.901; p = 0.001). Fig. 2 shows Kaplan–Meier curves for both age groups.

4. Discussion

The main finding of this study is that even when elderly patients experience a first-ever hospitalization for HF, patients with lower SBP exhibit worse outcomes in terms of higher midterm (1-year) mortality.

Our sample of "real-world" patients included many patients with prior diagnosed hypertension. Our reported figures of mean admission SBP (138 mmHg) and high (>140 mmHg) SBP (42%) are similar to those previously (140 mmHg and 47%) reported by Pérez-Calvo et al[6] in a cohort similar to ours. There were no significant differences in the profile of patients according to SBP quartiles, with neither sex nor age, in addition to the mentioned higher prevalence of previous hypertension and diabetes diagnoses among patients with higher admission SBP (Q3 and Q4) as well as higher prevalence of dementia and preserved HF among those with lower admission SBP (Q1 and Q2). Patients within the lower quartiles of SBP presented with lower DBP, lower hemoglobin levels, and lower estimated glomerular filtration rates; the study by Pérez-Calvo et al. found significantly higher hemoglobin levels in patients within the upper quartile of SBP.[6]

Mortality was significantly high in the lowest quartile of SBP across all evaluations, from in-hospital to 1-year mortality, the main outcome of our study. Although a history of high blood pressure is a well-established risk factor for the development of HF (actually most of our patients had a prior diagnosis of hypertension), once HF develops, the relationship between SBP, HF, and outcomes becomes even more complex.[6] Several studies report that low SBP is associated with high mortality, and conversely, a better prognosis has been described when SBP is increased,[6,10–12] as is the case of our cohort. When only older patients with acute HF are considered (mean age 79.7 years), higher SBP on admission is also associated with significant low 30-day and 1-year mortality.[8] Our study design does not allow, however, to confirm whether SBP relates to prognosis in a U-shaped curve when discharge SBP is very low or very high.[13]

It has been suggested that admission SBP reflects the interaction between vascular tone and myocardial pump function.[14] One possible explanation to this fact is that patients presenting with higher SBP possess hearts with a better pumping function, probably less affected by the course of the disease. In our study, patients were included regardless of the left ventricular ejection fraction and within their first hospital admission, in many cases at the time of diagnosis of the disease.

Chioncel et al.[14] evaluated the European Society of Cardiology Heart Failure Long-Term Registry and found that when patients were classified by SBP at initial presentation, 1-year mortality was 34.8% in patients with SBP <85 mmHg, 29.0% in those with SBP 85–110 mmHg, 21.2% in patients with SBP 110–140 mmHg and 17.4% in those with SBP >140 mmHg. These differences tended to diminish within the following months post discharge, and 1-year mortality for patients who survived at least 6 months post

Table 2
Baseline and admission risk factors for 1-year mortality.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.005 (0.098–1.023)	0.539		
Gender (female)	1.070 (0.856–1338)	1.338		
CAD	1.045 (0809–1.350)	0.734		
Hypertension	0.712 (0.529–0.959)	0.025		
Diabetes mellitus	0.469 (0.734–1.153)	0.469		
Dyslipidemia	0.982 (0.788–1.224)	0.873		
Atrial fibrillation	0.960 (0.766–1.203)	0.723		
COPD	0.877 (0.673–1144)	0.333		
CKD	0.979 (0.764–1.255)	0.869		
Stroke	0.889 (0.647–1.222)	0.468		
Dementia	1.258 (0.878–1.804)	0.211		
Known anemia	0.895 (0.676–1.185)	0.439		
Charlson Comorbidity Index	1.022 (0.962–1.085)	0.481		
Number of chronic therapies	1.041 (1.011–1.071)	0.006	1.047 (1.012–1.082)	0.008
HFpEF	0.739 (0.518–1.055)	0.096		
SBP quartiles (mmHg)	0.677 (0.611–0.750)	0.0001	0.684 (0.615–0.761)	0.0001
DBP (mmHg)	0.981 (0.974–0.989)	0.0001		
Heart rate (bpm)	1.002 (0.996–1.007)	0.555		
eGFR < 60 mL/min	0.883 (0.752–1037)	0.129		
Hb (g/dL)	0.977 (0.936–1.019)	0.277		
Na (mmol/L)	0.983 (0.958–1.009)	0.193		
K (mmol/L)	1.538 (1.279–1.850)	0.0001	1.568 (1.296–1.897)	0.0001

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HFpEF: heart failure with preserved ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; Na: sodium; K: potassium.

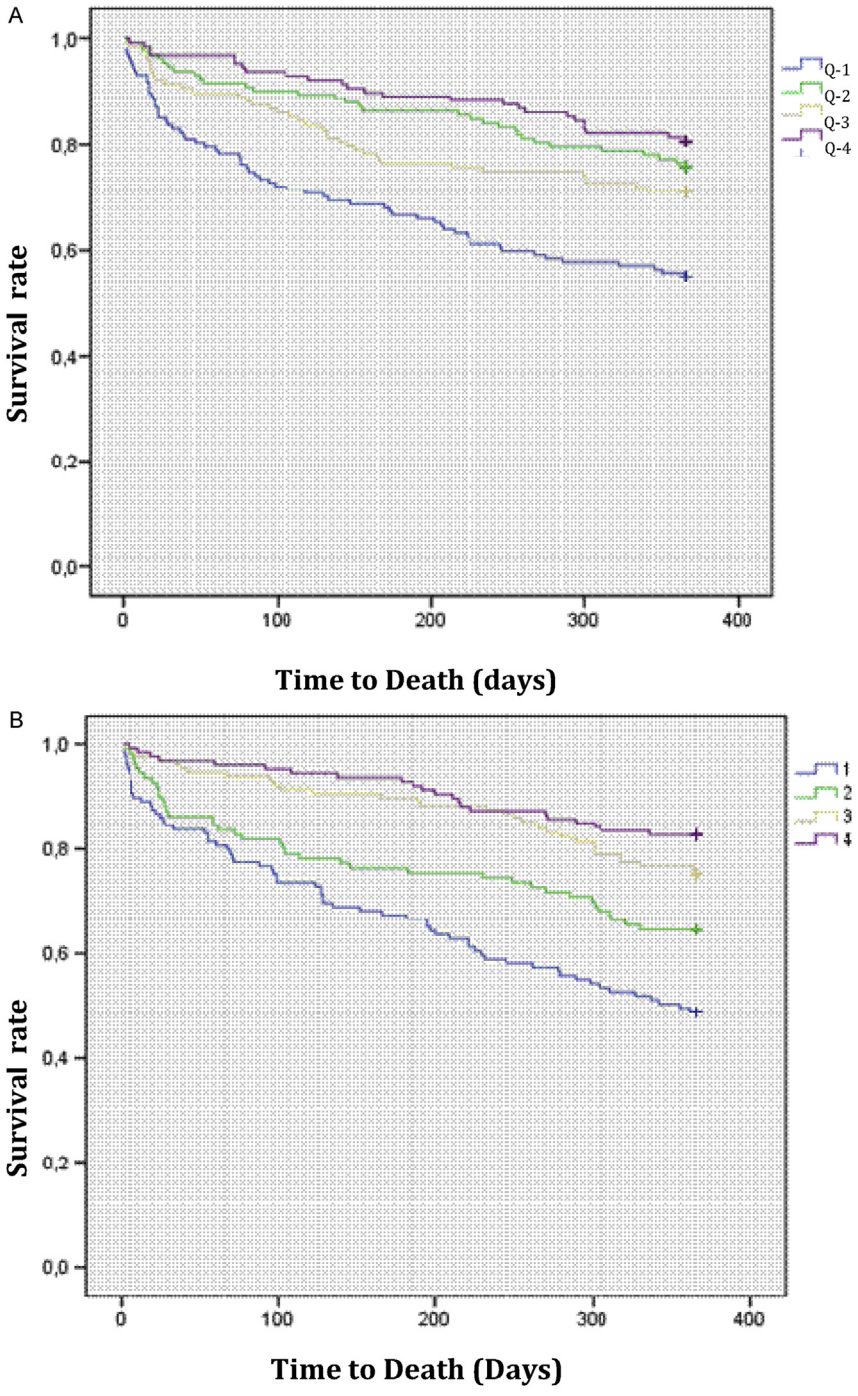

Fig. 2. Kaplan–Meier analysis of 1-year mortality according to systolic blood pressure; quartiles at admission; (A) Patients aged 71–82 years. Log-rank test 29.402; $p < 0.0001$ (B) Patients aged >82 years. Log-rank test 43.331; $p < 0.0001$.

discharge did not vary significantly by either clinical profile or SBP classification. In our cohort of older patients, however, the mortality in patients who survived at 3 months was still influenced by admission SBP.

Kajimoto et al.[15] reported, in patients hospitalized for acute HF, that the relationship between baseline SBP and all-cause mortality is markedly associated with increasing age (83 years or older) but not for "younger" old patients. In our study, however, baseline SBP influences 1-year global mortality even in the "younger" 70 to 82 year-old patients.

In our study, a history of hypertension is common among patients with HF (86.8%), and as previously reported, it did not affect mortality in patients hospitalized with HF.[16]

The main strength of this study is its focus on a well-defined subset of patients with AHF: those experiencing a first-ever admission, selected from a "real-life," unselected cluster of patients with HF whose disease is likely not to be influenced by long-term background chronic HF therapies or previous AHF episodes. Moreover, the individual chart review of all these patients before inclusion in the database adds robustness to the

diagnosis of both the HF and the comorbid conditions. However, some limitations are also present: First, the results should be interpreted with caution because the study is retrospective. Second, with regard to two basic tools for diagnosis, echocardiographic evaluation[17,18] was available only for few subjects and natriuretic peptides[19] were not available for most patients. Third, we did not collect SBP values before the decompensation or after emergency room stabilization, and therefore, we lack information about SBP before index hospitalization and before discharge. Fourth, we did not evaluate cardiovascular or HF-related deaths separately but only all-cause mortality as a whole. Finally, this is a single-center study.

5. Conclusions

Our study confirms that, even in elderly patients experiencing a first AHF episode, a low SBP upon admission is an independent risk factor for midterm all-cause global mortality both for “old” and “very old” patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

Statement of human and animal rights

The study has been approved by the ethics committee of the Bellvitge University Hospital.

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