



Prevalence and outcome of diuretic resistance in heart failure

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Abstract

Diuretic resistance (DR) is common in patients with decompensated heart failure (HF), and is associated with adverse outcomes. To determine the prevalence of DR and its impact on survival among patients with decompensated HF, we prospectively evaluated the prevalence and influence on prognosis of DR (defined as persistent congestion despite ≥ 80 mg of furosemide per day) in a cohort of elderly patients from the Spanish HF registry (RICA) admitted for an acute decompensation of HF. Patients with new-onset HF were excluded. From the global cohort of 2067 patients, 435 (21%; 95% CI 19.3%–22.7%) patients met criteria for DR. Patients with DR had more comorbidities (hypercholesterolemia, diabetes mellitus, valvular disease, chronic kidney disease, and cancer) and a worse functional status compared to patients without DR. In addition, patients with DR had a higher proportion of ischemic etiology, more advanced functional class and lower left ventricular ejection fraction values. After 1 year of follow-up, all-cause mortality was higher in patients with DR with an adjusted hazard ratio of 1.37 (95% CI 1.06–1.79; $p=0.018$). The prevalence of DR in a cohort of elderly patients admitted for acute HF decompensation is 21%. DR is an independent predictor of 1-year mortality.

Keywords Heart failure · Diuretics · Furosemide

Introduction

Acute heart failure (AHF) is one of the leading causes of hospital admission worldwide, and loop diuretics are administered in up to 90% of patients hospitalized for AHF. Loop diuretics provide symptomatic benefit improving congestive symptoms, but do not improve long-term morbidity and mortality [1]. Poor response to diuretic therapy (that is, persistent signs and symptoms despite increasing doses of diuretic drug, known as diuretic resistance [DR]) occurs frequently

in patients during hospitalization for AHF, although the exact rate is unknown owing to the lack of a standard definition [2]. A poorer diuretic response has been associated with advanced heart failure (HF) and renal impairment and predicts mortality and HF rehospitalization [3].

A single accepted definition of DR is not available. Of the several definitions proposed, the most commonly used is “failure to decongest despite adequate and escalating doses of diuretics” [2]. Other definitions of DR have also been suggested: amount of sodium excreted as a percentage of

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filtered load < 0.2% [4]; failure to excrete at least 90 mmol of sodium within 72 h of a 160-mg oral furosemide dose [5]; and persistent congestion despite adequate doses of diuretic (> 80 mg furosemide per day) [6]. Not all these definitions include variables easy to determine in routine clinical practice.

The purpose of this study was to determine the prevalence of DR and to analyse its impact on survival among a real-world prospective cohort of elderly patients with chronic decompensated HF.

Methods

Study population (the RICA registry)

Patient data were collected from the Spanish National Registry on HF (Registro Nacional de Insuficiencia Cardíaca—RICA) supported by the Spanish Heart Failure Working Group of the Spanish Society of Internal Medicine. The RICA is a prospective, multicenter, cohort study including patients consecutively admitted to Spanish internal medicine departments for AHF. The registry began in 2008, and its organization and design have been extensively described elsewhere [7]. The RICA registry includes patients over the age of 50 years admitted for AHF according to the criteria of the European Society of Cardiology [8]. All discharged patients are registered, while those who die during the index admission are excluded. Patients are followed for 12 months after the index episode to determine mortality and re-admission rates. The registry complies with the Declaration of Helsinki. The local ethics committee from the University Hospital “Reina Sofía”, Córdoba, Spain approved the study protocols, and informed consent was obtained from all participating subjects.

Inclusion criteria

For this study, we included all patients enrolled in the RICA registry with an acute decompensation of previously diagnosed chronic HF (chronic decompensated HF). Patients with a first decompensation of AHF (new-onset HF) or with incomplete baseline information were excluded.

Study variables

The variables selected for this study were the following: past medical history related to HF, comorbidities (Charlson Comorbidity Index) [9], baseline functional status (using the Barthel Index scale for basic activities of daily living) [10], clinical parameters on admission (blood pressure, heart rate, weight and height), HF characteristics, and drug prescription before admission and at discharge. HF

was characterized in more detail according to New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) determined by 2-D echocardiography, and electrocardiogram. Blood chemistry values included kidney function, lipid and glucose profile, uric acid, and troponin and natriuretic peptides (when available). Glomerular filtration was estimated with the MDRD equation, and chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) lower than 60 ml/min/1.73 m².

Diuretic resistance

For the purposes of this study, we define DR as persistent congestion requiring hospitalization despite adequate doses of loop diuretic (≥ 80 mg furosemide per day). The assessment of congestion is not defined in the RICA protocol, is performed at investigator discretion, and according to their usual clinical practice (including clinical assessment, chest X-ray and/or lung ultrasound). We used this definition because it includes variables routinely collected in the RICA registry, and it is easily applicable in clinical practice.

In addition, a similar approach has been used in other studies. The DOSE trial enrolled patients with history of chronic HF with acute decompensation and a receipt of an oral loop diuretic before hospitalization at a dose between 80 and 240 mg of furosemide [11]. In a different setting, (stable patients with advanced chronic HF), a retrospective analysis of the PRAISE study (Prospective Randomized Amlodipine Survival Evaluation) used a similar “cut-off” of furosemide dose (80 mg) to compare high versus low diuretic dose [6].

Using this definition, we divided patients into three categories according to loop diuretic treatment before hospital admission. Patients were classified as having DR (group 1) if the daily dose of oral furosemide prior to admission was at least 80 mg (or equivalent doses of torasemide or bumetanide). Patients were classified as group 2 when their daily dose of furosemide was lower than 80 mg, and group 3 if they were not receiving loop diuretics before admission.

Follow-up and outcome

Follow-up consisted of four compulsory visits scheduled at 1, 3, and 6 months, and 1 year. Additional visits were allowed whenever necessary and according to clinical judgement. Primary end-points were first readmission due to acute decompensation of HF, and death for any cause, and survival time was the number of days between inclusion date and death. Readmissions during the follow-up period did not imply exclusion from the registry.

Statistical methods

Quantitative variables are expressed as median and interquartile range [IQR]. Qualitative variables are expressed as the number of patients and percentages. The Chi square or Fisher exact tests were used to compare qualitative variables. The Kolmogorov–Smirnov test was used to determine whether quantitative variables were normally distributed. The *t* test was used to compare normally distributed quantitative variables and the non-parametric Mann–Whitney *U* test was used when distribution was not normal. The one-way analysis of variance (ANOVA) and the non-parametric Kruskal–Wallis test were used to compare quantitative variables in more than two independent groups, and a Kaplan–Meier analysis was performed to compare survival between groups. Survival curves or distributions were compared using the log-rank test. The presence of DR was considered in a multivariate-adjusted logistic regression model that included those variables whose differences were significant in the univariate analysis: age, blood pressure, comorbidities (Charlson index), Barthel index, hemoglobin, creatinine, sodium, NYHA functional class, HF etiology, LVEF, and previous treatment with ACE inhibitors or beta-blockers. Finally, to analyse the independence of predictor variables we performed a collinearity analysis calculating the variance inflation factor (VIF) and tolerance statistics. The threshold to consider collinearity was set at > 10 and < 0.1 for VIF and tolerance statistics, respectively. Statistical significance was set at 0.05. Analyses were performed with the software Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, Illinois, USA).

Sample size

The required sample size for the present study was calculated based on previous findings in which prevalence of DR was 24–35%. With this assumption, a random sample of 779–972 individuals would be enough to estimate, with a confidence interval of 95% and a precision of ± 3 percentage units, a population percentage expected to be around 30%.

Results

Of the 2037 patients enrolled in this study, 435 were included in group 1 (daily dose of oral furosemide prior to admission ≥ 80 mg). Thus, the prevalence of DR in the RICA registry was 21% (95% confidence interval 19.3%–22.7%). The remaining 1632 patients were included in group 2 (740 patients with daily dose of furosemide lower than 80 mg),

and group 3 (892 patients not receiving loop diuretics before admission).

The baseline clinical characteristics for each of these groups are shown in Table 1. Some clinically significant differences are observed among the demographic characteristics. Patients with DR have lower blood pressure values, more comorbidities (hypercholesterolemia, diabetes mellitus, ischemic heart disease, CKD and cancer) and worse functional status (lower Barthel index scores). The analytical values also show differences, the most relevant being lower levels of hemoglobin, GFR, and sodium in patients with DR. In contrast, uric acid is higher in patients with DR, and glucose is higher in patients receiving diuretics (groups 1 and 2). We find no significant differences in natriuretic peptides and troponin levels. With regard to HF-related variables, the DR group has a higher proportion of ischemic etiology, more advanced functional class, higher systolic pulmonary artery pressure, and lower LVEF values. We find no relevant differences in factors triggering decompensation, except that anemia is more common in patients receiving diuretic treatment. Finally, radiographic alterations are more frequent in patients with DR, but none of these differences reach significance in the statistical analysis.

Pharmacological treatment prior to admission is shown in Table 2. Furosemide is the most frequently prescribed loop diuretic, followed far behind by torasemide. The proportion of patients receiving ACE inhibitors and digoxin is lower in the DR group. In contrast, these patients more frequently receive beta-blockers, ivabradin, and other types of diuretics.

After 1 year of follow-up, 634 (30.7%) deaths were reported. Mortality is significantly higher in patients with DR (163/453; 37%) in comparison with groups 2 (206/740; 28%) and 3 (265/892; 30%). The unadjusted hazard ratio for all-cause death in group 1 versus groups 2 and 3 is 1.47 (95% CI 1.18–1.84; $p = 0.002$). We also find differences in rehospitalization rates between the groups (58.3%, 52.9% and 56% for groups 1, 2 and 3, respectively) but these differences are not statistically significant ($p = 0.72$). Kaplan–Meier survival curves for all-cause mortality and rehospitalization are shown in Figs. 1 and 2. Using the log-rank test for comparison, we find differences in short- and long-term mortality (log-rank $p = 0.001$), but differences in rehospitalization are only apparent and significant after long-term follow-up (log-rank p value after 365 days of follow-up = 0.028).

The presence of DR is considered in a multivariate logistic regression model adjusted for the variables that are different among the three groups. After controlling for these variables, DR maintains statistical significance as a mortality predictor (adjusted hazard ratio for all-cause death: 1.37; 95% CI 1.06–1.79; $p = 0.018$). We also identify the following predictors of death, as described in Table 3: age, Charlson and Barthel index, haemoglobin and creatinine values, and NYHA functional class. Finally, we do find statistical

Table 1 Baseline characteristics of the study participants

	Group 1 furosemide ≥ 80 mg	Group 2 furosemide < 80 mg	Group 3 without furosemide	<i>p</i>
Number (%) of patients	435 (21%)	740 (36%)	892 (43%)	–
Age (years)*	81 (75–85)	81 (76–85)	80 (74–84)	< 0.001
Male sex [†]	203 (47%)	318 (43%)	433 (49%)	0.08
BMI	28.0 (24.6–32.0)	27.7 (24.6–32.0)	28.3 (24.8–32.3)	0.33
Systolic BP (mmHg)*	130 (114–150)	135 (120–151)	135 (120–154)	0.002
Diastolic BP (mmHg)*	70 (60–80)	70 (60–82)	73 (64–85)	< 0.001
Heart rate (bpm)*	80 (70–92)	80 (70–96)	80 (70–99)	0.11
Comorbidities [†]				
Hypertension	394 (91%)	656 (89%)	776 (87%)	0.15
Hypercholesterolemia	240 (55%)	397 (54%)	424 (48%)	0.01
Diabetes mellitus	266 (61%)	400 (54%)	494 (55%)	0.05
Atrial fibrillation	285 (66%)	462 (62%)	558 (63%)	0.51
Ischaemic heart disease	149 (34%)	214 (29%)	235 (26%)	0.01
Chronic kidney disease	256 (59%)	368 (50%)	399 (45%)	< 0.001
Peripheral arterial disease	69 (16%)	113 (15%)	111 (12%)	0.14
Cerebrovascular disease	74 (17%)	117 (16%)	126 (14%)	0.35
Dementia	20 (4.6%)	44 (5.9%)	59 (6.6%)	0.35
COPD	125 (29%)	206 (28%)	235 (26%)	0.62
Cancer	66 (15%)	83 (11%)	92 (10%)	0.03
Cirrhosis	11 (2.5%)	15 (2.0%)	19 (2.1%)	0.84
Charlson index	4 (2–6)	3 (2–5)	3 (1–4)	< 0.001
Barthel index	85 (65–100)	85 (60–100)	90 (70–100)	< 0.001
Laboratory parameters*				
Hemoglobin (g/dl)	11.5 (10.0–12.8)	11.8 (10.4–13.1)	11.9 (10.6–13.3)	0.002
Glucose (mg/dl)	120 (99–159)	122 (99–168)	115 (96–150)	< 0.001
Urea (mg/dl)	72 (49–106)	63 (46–86)	61 (47–84)	< 0.001
Creatinine (mg/dl)	1.3 (1.0–1.8)	1.2 (1.0–1.7)	1.2 (1.0–1.6)	< 0.001
eGFR MDRD (ml/min/m ²)	46 (32–64)	51 (36–68)	55 (39–70)	< 0.001
Sodium (mEq/l)	139 (136–141)	139 (136–142)	140 (136–142)	0.004
Uric acid (mg/dl)	8.4 (6.9–10.2)	7.9 (6.3–9.6)	7.9 (6.3–9.7)	0.043
BNP (pg/ml) <i>N</i> = 323	903 (408–2.177)	635 (338–1.010)	649 (331–1.354)	0.058
NT-pro-BNP (pg/ml) <i>N</i> = 878	3663 (1540–9000)	4517 (1969–9461)	3878 (1861–8590)	0.366
High Troponin level <i>N</i> = 679 [†]	8 (5.6%)	5 (1.8%)	9 (3.5%)	0.111
Characteristics of Heart failure [†]				
NYHA functional class				
Class I	8 (1.9%)	29 (4.0%)	46 (5.2%)	0.016
Class II	208 (48%)	367 (51%)	463 (52%)	0.364
Class III	197 (46%)	303 (42%)	344 (39%)	0.062
Class IV	19 (4.4%)	23 (3.2%)	32 (3.6%)	0.566
Heart failure aetiology				
Ischemic	147 (34%)	228 (31%)	244 (27%)	0.052
Valvular	98 (23%)	148 (20%)	189 (21%)	0.588
Hypertensive	140 (32%)	269 (36%)	322 (36%)	0.276
Hypertrophic	8 (1.8%)	18 (2.4%)	17 (1.9%)	0.704
Other	42 (9.7%)	76 (10%)	116 (13%)	0.097
Triggering factor				
Rapid atrial fibrillation	82 (19%)	139 (19%)	148 (17%)	0.427
Respiratory infection	142 (33%)	256 (35%)	283 (32%)	0.466
Hypertensive emergency	17 (3.9%)	42 (5.7%)	48 (5.4%)	0.391

Table 1 (continued)

	Group 1 furosemide ≥ 80 mg	Group 2 furosemide < 80 mg	Group 3 without furosemide	<i>p</i>
Poor therapeutic compliance	60 (14.3%)	80 (10.8%)	103 (11.6%)	0.401
NSAID consumption	7 (1.6%)	14 (1.9%)	16 (1.8%)	0.940
Acute coronary syndrome	19 (4.4%)	55 (7.5%)	50 (5.6%)	0.099
Anaemia	28 (6.4%)	40 (5.4%)	21 (2.4%)	< 0.001
Echocardiogram [†]				
LVEF	50 (35–60)	55 (40–64)	54 (40–62)	0.006
HErEF	193 (44%)	289 (39%)	361 (41%)	0.196
HFpEF	242 (56%)	451 (61%)	530 (59%)	0.196
PAP (mmHg) <i>N</i> = 1175*	50 (41–62)	45 (36–56)	49 (40–60)	< 0.001
Chest radiograph [†]				
Enlarged cardiac silhouette	400 (93%)	667 (91%)	789 (89%)	0.069
Pleural effusion	207 (48%)	337 (46%)	408 (46%)	0.765
Vascular redistribution	64 (15%)	93 (13%)	102 (12%)	0.231

BMI: body mass index; BP: blood pressure; COPD: chronic obstructive pulmonary disease; eGFR MDRD: estimated glomerular filtration rate (modification of diet in renal disease formula); BNP: B-type natriuretic peptide; NYHA: New York Heart Association; NSAID: nonsteroidal anti-inflammatory drugs; LVEF, left ventricular ejection fraction; HFpEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; PAP: systolic pulmonary artery pressure

*Results are expressed as median (IQR)

[†]Results are expressed and number and percentage

Table 2 Pharmacological treatment prior to admission

	Group 1 furosemide ≥ 80 mg	Group 2 furosemide < 80 mg	Group 3 with- out furosemide	<i>p</i>
Diuretic treatment [†]				
Loop diuretics	435 (100%)	740 (100%)	0 (0.00%)	< 0.001
Furosemide	433 (99%)	619 (84%)	0 (0.00%)	< 0.001
Daily furosemide dose (mg)*	80 (80–120)	40 (40–40)	–	< 0.001
Torsemide	2 (1%)	121 (16%)	0 (0.00%)	< 0.001
Daily torsemide dose (mg)*	10 (5–25)	10 (5–10)	–	0.651
Bumetanide	0 (0%)	0 (0%)	0 (0%)	–
Thiazide diuretics	31 (7%)	36 (5%)	35 (3.9%)	0.041
Aldosterone antagonists	128 (29%)	174 (24%)	69 (7.7%)	< 0.001
Other treatments [†]				
ACE inhibitors	179 (41%)	354 (48%)	451 (51%)	0.005
ARB	132 (30%)	260 (35%)	272 (30%)	0.091
Beta-blockers	304 (70%)	500 (68%)	567 (64%)	0.049
Nitrates	122 (28%)	189 (26%)	223 (25%)	0.480
Digoxin	101 (23%)	183 (25%)	257 (29%)	0.050
Antiaggregant	166 (38%)	297 (40%)	354 (40%)	0.793
Anticoagulant	240 (55%)	408 (55%)	531 (60%)	0.137
Ivabradine	23 (5.3%)	23 (3.1%)	24 (2.7%)	0.043

ACE: angiotensin-converting-enzyme; ARB: angiotensin receptor blockers

*Results are expressed as median (IQR)

[†]Results are expressed and number and percentage

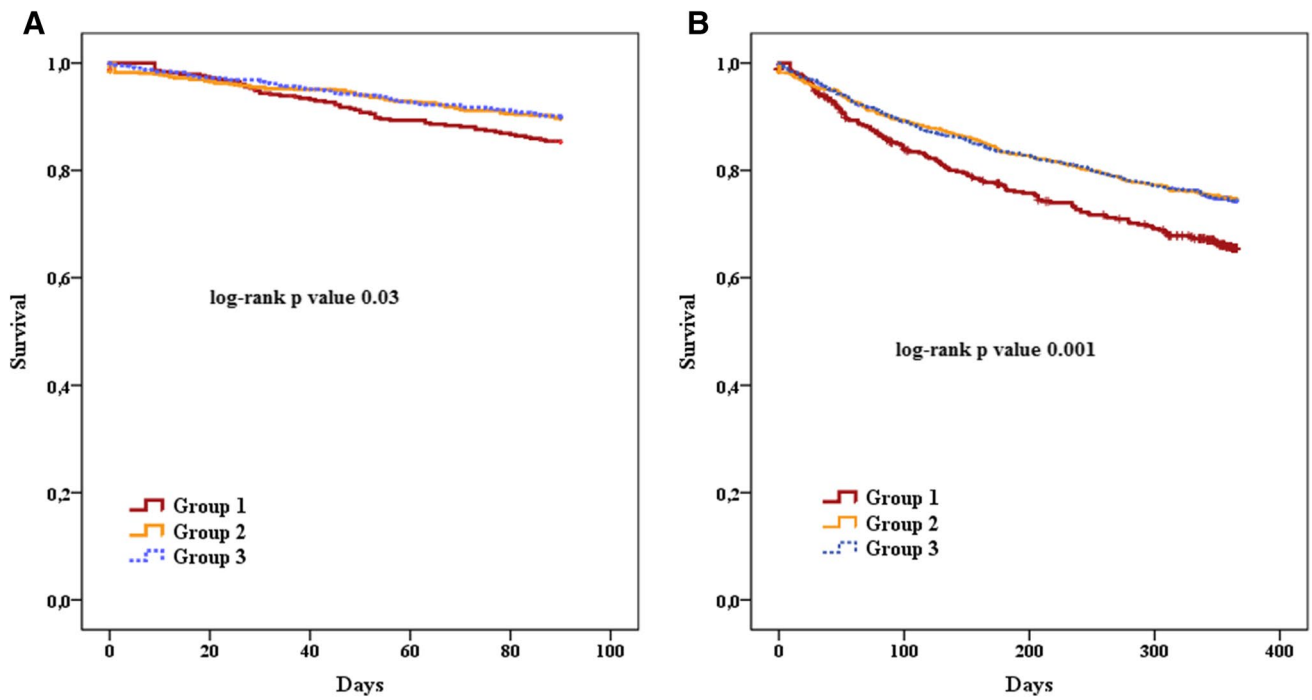


Fig. 1 Comparative survival analysis for all-cause mortality stratified by diuretic treatment group according to the Kaplan–Meier method, using the log-rank test for comparison. **a** Short-term follow-up (90 days); **b** long-term follow-up (365 days)

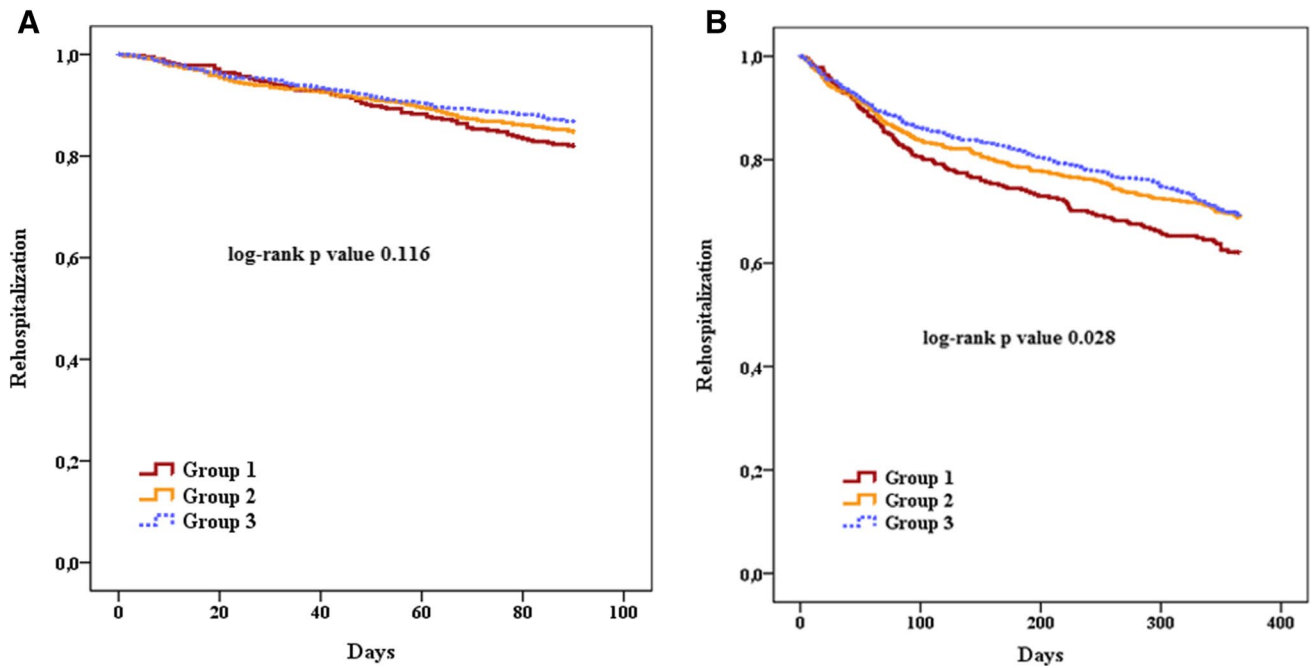


Fig. 2 Comparative survival analysis for hospitalization stratified by diuretic treatment group according to the Kaplan–Meier method, using the log-rank test for comparison. **a** Short-term follow-up (90 days); **b** long-term follow-up (365 days)

Table 3 Multivariate-adjusted logistic regression analysis for all-cause mortality

Variable	OR	95% CI	<i>p</i>
Age	1.022	1.007–1.037	0.004
Charlson index	1.098	1.049–1.149	<0.001
Barthel index	0.986	0.981–0.991	<0.001
Hemoglobin	0.942	0.889–0.998	0.043
Creatinine	1.237	1.049–1.459	0.011
NYHA*	1.547	1.239–1.930	<0.001
Diuretic resistance [†]	1.374	1.055–1.790	0.018

OR: Odds Ratio; CI: confidence interval; *p*: statistical significance; NYHA: New York Heart Association

*NYHA class III–IV versus I–II

[†]Diuretic resistance (group 1) versus groups 2 and 3

significance when analysing the collinearity between these variables.

Discussion

This is the first study to describe the prevalence of DR in a large cohort of elderly patients admitted for acute decompensation of chronic HF in a real-world setting, revealing a rate of 21%. Furthermore, we observe that the presence of DR independently increases the risk of death by 1.37-fold.

The real prevalence of DR is probably unknown, given the lack of a consensus definition and studies focusing on this question. The retrospective analysis of the PRAISE study finds a higher prevalence (35%) of DR using the similar definition (daily furosemide dose > 80 mg). However, the PRAISE study was performed in a different setting (stable patients with advanced chronic HF), and the baseline characteristics of patients are very different from those of the RICA registry: their patients are younger (65 years of age) with ischaemic aetiology and severe systolic dysfunction (mean LVEF 20%) [6]. To our knowledge, no other studies have analysed the prevalence of DR using the same definition.

The most extensive AHF registry in the world, the ADHERE registry (Acute Decompensated Heart Failure National Registry), has analysed DR with a focus on insufficient symptom relief and loop diuretic dosing during the first 24 h after admission. The patients enrolled in the ADHERE registry have more in common with those included in the RICA registry: they have a median age of 75 years and a significant comorbidity burden, and a similar proportion (53%) of patients have preserved LVEF. Among more than 50,000 patients enrolled in this study, only 33% lost ≥ 2.27 kg and 16% gained weight during hospitalization [12]. As for loop diuretic dosing, 23.8% of patients required

high-dose intravenous loop diuretics, defined as a total intravenous furosemide dose ≥ 160 mg, during the first 24 h [13].

In the light of these results, and regardless of the definition used, it seems clear that DR is a common problem in clinical practice.

We also find that patients with DR more often present an ischaemic aetiology of HF, lower values of LVEF, more advanced functional class, and worse kidney function. These findings are also described in patients receiving high doses of diuretics in the PRAISE study [8]. In addition, patients with DR have more comorbidities and a poor functional status measured with the Barthel index. The Barthel index is well known to be a key outcome predictor of mortality in patients with HF in the chronic [10] and the acute setting [14], but to our knowledge, it is the first time that it has been directly associated with DR.

Differences in treatment before admission are also found between groups, which can be justified, in part, by the above-mentioned differences in baseline characteristics. For example, the lower proportion of ACE inhibitors and digoxin could be explained by the greater prevalence of CKD in patients with DR. Moreover, the higher proportion of patients treated with beta-blockers and ivabradine can be justified by the predominant ischemic aetiology of HF. It is interesting and important to note that patients receiving loop diuretics before admission (groups 1 and 2) are more frequently treated with additional diuretics, including thiazides or potassium-sparing diuretics. Sequential nephron blockade by addition of a second diuretic class (combination diuretic therapy) is an attractive strategy to overcome DR, but the optimal timing of this sequential blockade in HF remains uncertain [15–17].

Finally, we find that DR was independently associated with overall mortality. Various observational studies have demonstrated an association between higher doses of diuretics and worse outcomes. These findings may be confounded by indication: patients who receive higher doses of diuretics may do so because of greater disease severity compared with patients who can be successfully treated with lower dose [18]. Although most of these studies have found a persistent adverse effect of loop diuretics even after multivariable adjustment for other known predictors of mortality, such adjustment may be insufficient to completely eliminate confounding [18]. In our study, after adjusting for possible confounders including comorbidities and functional status, DR persists as an independent risk factor for mortality. However, even these results do not confirm that diuretics are harmful per se. The pathophysiology of DR is a complex interaction between multiple factors (pharmacokinetic and pharmacodynamic factors, CKD, renal adaptation mechanisms with nephron remodeling, neurohormonal activation, etc.) that cannot be completely controlled in clinical studies [2, 19–21]. In the future, carefully controlled studies will

be required to clarify whether there is a causal relationship between diuretic use and adverse outcomes, or alternatively, if diuretic dosage is just a surrogate for disease severity.

Early identification of a poor diuretic response might allow the initiation of therapies to modify this response. Different objective methods to evaluate diuretic response have been introduced (metrics of diuretic response) and suggest that diuretic response should be determined based on the effect of the diuretic dose administered (e.g. weight loss or net fluid loss per milligramme of loop diuretic). The use of such metrics of diuretic response could help identify patients who might benefit from alternative decongestive therapies and guide treatment selection [3, 22–25].

We are aware that our study has some limitations. First, the RICA registry does not include patients who died during the index hospitalization. Assuming that a high proportion of these patients had more severe HF and some degree of DR, their exclusion could lead to an underestimation of DR. Second, the RICA registry does not collect information regarding interventional procedures during hospitalization (like coronary revascularization) that might have influence on prognosis. Third, loop diuretic doses are probably a surrogate marker of DR, and it would be desirable to confirm and compare our results using other metrics of diuretic response that are not included in the RICA registry. Finally, the heterogeneity about the DR definition is a limitation for external validation of these results, and for this reason, we have to be cautious before extending these results to the general HF population.

In summary, we frequently find patients who require hospitalization for chronic heart failure decompensation despite receiving high dose (at least 80 mg) of oral furosemide. This clinical scenario could be a surrogate marker of diuretic resistance with a higher risk for mortality.

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Compliance with ethical standards

Conflict of interest The authors declare that have no conflicts of interest.

Statements on human and animal rights The registry complies with the Declaration of Helsinki. The local ethics committee from the University Hospital "Reina Sofia" (Córdoba, Spain) approved the study protocols.

Informed consent Informed consent was obtained from all participating subjects.

Appendix

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