European Journal of Internal Medicine 67 (2019) 89–96

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Acute heart failure and adverse events associated with the presence of renal dysfunction and hyperkalaemia. EAHFE- renal dysfunction and hyperkalaemia

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https://doi.org/10.1016/j.ejim.2019.07.010

Available online 20 July 2019

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ARTICLE INFO

Keywords:
Acute heart failure
Renal dysfunction
Hyperkalaemia
Outcomes

ABSTRACT

Objective: To study the outcomes of patients with acute heart failure (AHF) presenting renal dysfunction (RD) or hyperkalaemia (Hk) alone or in combination.
Method: We analysed the data of the EAHFE registry, a multicentre, non interventionist cohort with prospective follow-up of patients with AHF. Four groups were defined based on the presence or not of RD or Hk alone or in combination. The primary endpoint was 30-day all-cause mortality.
Results: A total of 11,935 of the 13,791 patients included in the EAHFE registry were analysed. Of these, 5088 (42.6%) did not have RD or Hk (NoRD-NoHk), 150 (1.3%) had no RD but had Hk (NoRD-Hk), 6012 (50.4%) had RD but not Hk (RD-NoHk) and 685 (5.7%) had both RD and Hk (RD-Hk). Thirty-day all-cause mortality was greatest in the RD-Hk group with an adjusted Hazard Ratio (HR) of 2.44 (confidence interval 95% [CI95%] 1.67–3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (CI95% 1.04–1.71; $p = 0.022$). There were no significant differences in in-hospital mortality and reconsultation at 30 days for HF. For the combined endpoint of 30-day all-cause mortality the adjusted HR was 1.33 (CI95% 1.04–1.70); ($p = 0.021$) for the RD-Hk group.
Conclusions: The association of 30-day all-cause mortality with the presence of RD and Hk in patients presenting AHF at admission is greater than in those without this combination.

1. Introduction

Heart failure (HF) is a syndrome which causes a high mortality and use of health care resources. Acute heart failure (AHF) is one of the main causes of hospitalization in patients with HF and generates the greatest expense among health care costs related to this disease [1]. In addition, AHF is associated with bad outcomes with a one-year mortality of 30% [2].

The presence of hyperkalaemia (Hk), defined as a potassium value ≥5.5 mEq/L and renal dysfunction (RD) in patients with HF has been related to an increase in adverse events including mortality and the need for hospital admission [3,4]. It has been estimated that the prevalence of Hk and heart failure with reduced ejection fraction (HFrEF) is 3.37% [5]. The European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) has reported that the presence of Hk in chronic HF is 2.64%, reaching 4.44% in patients with AHF [6], while in the EAHFE registry [2], the presence of Hk in patients with AHF was 5.6%. The cardiotoxic effects of Hk are severe and may potentially be lethal and difficult to diagnose because of the scarcity of clinical signs and symptoms. In the MEESSI-AHF scale, Hk is a variable associated with a greater risk of 30-day mortality [7]. Hk is also related to a greater use of drugs aimed at renin-angiotensin-aldosterone system inhibitors (RAASi), which is one of the therapeutic targets able to reduce the mortality of patients with HFrEF [8].

The prevalence of RD during an episode of AHF is elevated, reaching up to 60% [2], and is related to a worse outcome. Indeed, the higher the estimated glomerular filtration rate (eGFR) the worse the prognosis [3,6,9]. These results remain the same independently of the formula used to calculate the eGFR, although the Cockroft-Gault formula, which includes the weight of the patient, seems to be the most accurate [4].

Considering that the presence of RD is related to a greater presence of Hk, it is clear that this combination will have an added effect on the outcome of patients with AHF [10]. However, there are few studies on this effect in real life patient cohorts. We hypothesize that the presence of adverse events in patients with both RD and Hk is greater in patients with AHF than the presence of RD or Hk alone.

The aim of this study was to evaluate the outcomes of patients with AHF presenting RD and Hk alone or in combination.

2. Method

The present study analysed the data of the EAHFE registry (Epidemiology of Acute Heart Failure in Emergency departments), the methodology of which has been described elsewhere [7,11–13]. The EAHFE registry includes a multicentre, multipurpose, non interventionist cohort with prospective follow-up of patients presenting an episode of AHF in the Emergency Department (ED). The inclusion of patients was carried out in 5 phases: EAHFE-1 – from April 15 to May 15, 2007 (1 month, 10 Spanish EDs), EAHFE-2 - from June 1 to 30, 2009 (1 month, 19 EDs), EAHFE-3 – November 1 to December 31, 2011 (2 months, 29 EDs), EAHFE-4 – from February 1 to March 31, 2014 (2 months, 26 EDs) and EAHFE-5 - from January 1 to February 29, 2016 (2 months, 30 EDs). Forty-one Spanish EDs participated in the registry, recruiting a total of 13,791 patients. During the inclusion periods case detection was performed by the attending physician using the Framingham criteria [14], and patients provided signed informed consent to participate in the study. Thereafter, the principal investigator of each centre assigned the final diagnosis of each case. The diagnosis was confirmed by determination of natriuretic peptides or the presence of an echocardiogram according to the criteria of the European Society of Cardiology prevailing at the time of the different recruitment periods [8]. Patients with an acute coronary syndrome with an elevation of the ST segment were excluded from the study because the outcome depends on the coronary intervention performed. Since this was a non intervention study, the patients received care for the acute episode by the physicians based on internationally accepted protocols and according to the local reference strategies for the management of patients in each participating centre.

A total of 36 independent variables were collected which consisted in: 2 epidemiological variables (age and sex), 8 comorbidities arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic renal disease, atrial fibrillation, peripheral artery disease, cancer and previous episodes of acute cardiac insufficiency, 3 variables of basal status (Barthel index < 60 points, clase III - IV of the New York Heart Association [NYHA], Left ventricular ejection fraction < 40% [LVEF]), 7 variables of chronic home treatment (loop diuretics, thiazide diuretics, angiotensin converter enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], mineralocorticoid receptor antagonist [MRA], nitrates and oral anticoagulants), 9 variables of the clinical status of the patient at arrival to the ED (dyspnea, ortopnea, oedema, O2 saturation ≤90%, systolic blood pressure ≤100 mmHg, hyponatraemia with sodium values < 135 mmol/l, potassium, creatinine and eGFR < 60 ml/min/1.73 m^2), and 7 variables of treatment in the ED (oxygen, intravenous diuretics, intravenous nitrates, inotropic drugs or vasopressors, morphine, non invasive and invasive ventilation).

For this study, only the available values of eGFR and potassium were analysed at the time of arrival of the patient in the ED. For the

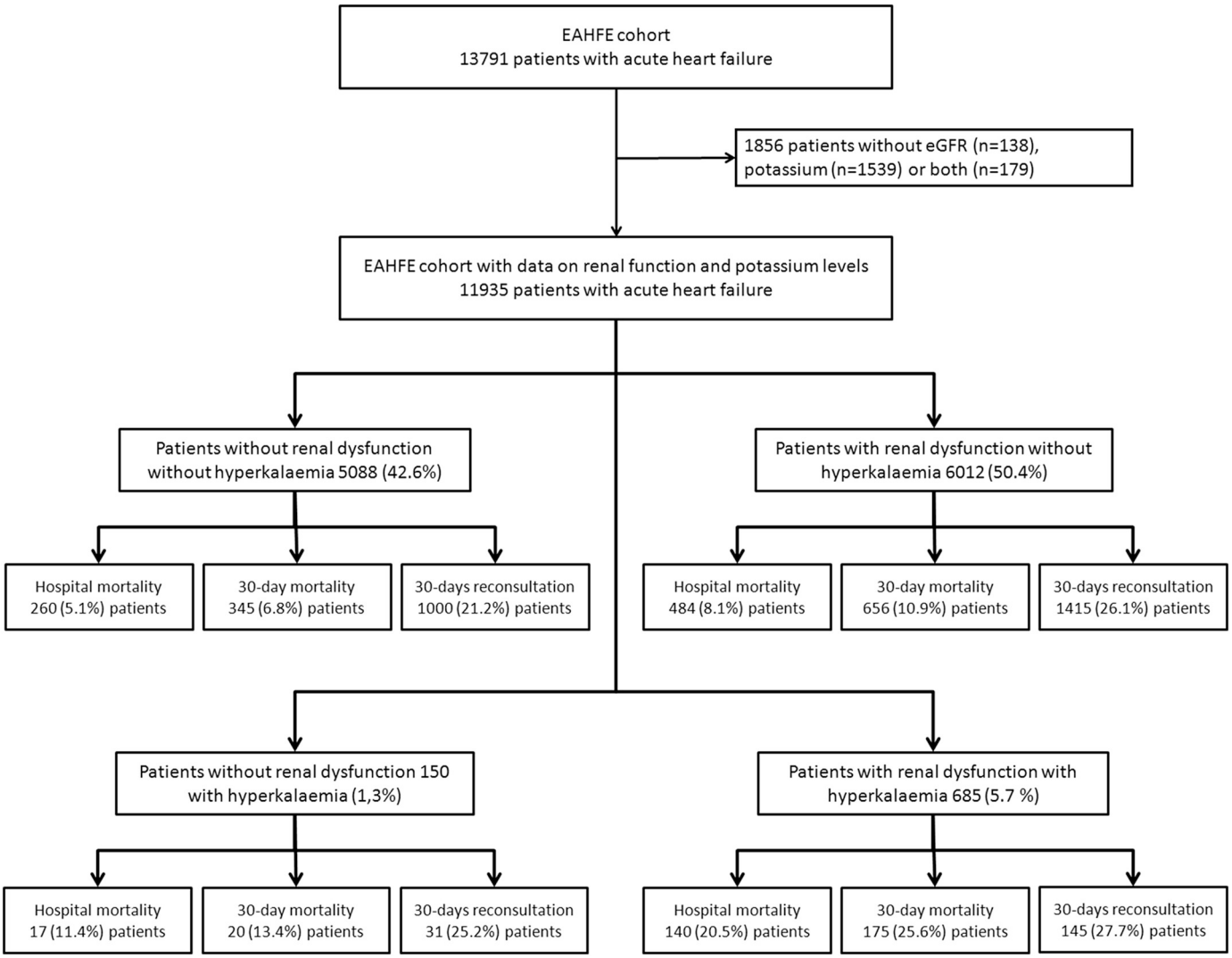

Fig. 1. Flowchart of patient inclusion in the present study. EAHFE: Epidemiology of Acute Heart Failure in Emergency departments.

comparative study, RD was defined as an eGFR < 60 ml/min/m^2 calculated at the time of admission with the MDRD-4 formula (Modification of Diet in Renal Disease), and Hk was defined as potassium levels ≥5.5 mmol/L at admission. Patients were classified into four groups based on these two variables: 1) absence of RD and Hk (NoRD-NoHk), 2) absence of RD but presence of Hk (NoRD-Hk), 3) presence of RD but absence of Hk (RD-NoHk), and 4) presence of RD and Hk (RD-Hk).

The principal endpoint of the study was all-cause mortality at 30 days. The secondary endpoints were: in-hospital mortality, reconsultation for AHF within 30 days after discharge and the combined variable of all-cause mortality or reconsultation for AHF within 30 days. Follow-up was made by a telephone call or by consultation of the hospital and primary care clinical histories of the patients at 30 days after the index episode.

The EAHFE registry was undertaken according to the Declaration of Helsinki of ethical principles for medical investigation in humans, and the patients provided informed consent to participate in the registry. The complete protocol was approved by the Committee of Ethics and Clinical Investigation of the *Hospital Universitario Central of Asturias*, which was the principal committee (protocols 49/2010, 69/2011, 166/13 and 160/15), as well as the committees of the other participating hospitals.

For the statistical analyses, qualitative variables were expressed as absolute values and percentages. Between group differences were analysed using the Chi-squared test (or the Fisher exact test, when appropriate). Quantitative variables were expressed as mean and standard deviation (SD). Differences among groups were determined with the one-way ANOVA test, to determine whether the distribution was normal, the Kolmogorov-Smirnov test was used, and if the distribution did not fulfill normality, the non parametric Kruskal-Wallis test was used. The 30-day all-cause mortality for the 4 groups was evaluated using survival tables and Kaplan-Meier curves and was adjusted by Cox regression with the variables showing significant

Table 1
Characteristics of the global cohort and the four groups classified according to the presence or not of renal dysfunction (RD) and hyperkalaemia (Hk).

	Total (*n* = 11,935)	NoRD-NoHk (*n* = 5088)	NoRD-Hk (*n* = 150)	RD-NoHk (*n* = 6012)	RD-Hk (*n* = 685)	P value
Demographic data (n, %)						
Age (years)[a]	80.1 ± 10.1	78.0 ± 11.1	77.2 ± 11.1	81.8 ± 9.0	81.4 ± 9.6	< 0.001
Age ≥ 75 years	9040 (75.7)	3512 (69.0)	98 (65.3)	4880 (81.2)	550 (80.3)	< 0.001
Male	5324 (44.6)	2565 (50.4)	79 (52.7)	2394 (39.8)	286 (41.8)	< 0.001
Personal history (n, %)						
Arterial hypertension	10,001 (84.0)	4015 (79.1)	119 (79.9)	5279 (88.0)	588 (86.0)	< 0.001
Diabetes mellitus	5053 (42.4)	1879 (37.2)	78 (52.3)	2712 (45.2)	384 (56.1)	< 0.001
Ischaemic heart disease	3452 (29.0)	1276 (25.1)	41 (27.5)	1940 (32.3)	195 (28.5)	< 0.001
Chronic kidney failure	3117 (26.2)	279 (5.5)	17 (11.4)	2494 (41.5)	327 (47.8)	< 0.001
Atrial fibrillation	5847 (49.1)	2421 (47.7)	76 (51.0)	3039 (50.6)	311 (45.5)	0.004
Peripheral artery disease	1089 (9.1)	366 (7.2)	16 (10.7)	626 (10.4)	81 (11.8)	< 0.001
Cancer	1508 (14.3)	640 (14.1)	22 (16.3)	762 (14.5)	84 (13.9)	0.844
Prior episode of heart failure	6979 (59.5)	2616 (52.4)	83 (56.8)	3848 (65.1)	432 (63.8)	< 0.001
Basal situation (n, %)						
Barthel Index < 60 points	1907 (18.2)	638 (14.4)	23 (17.8)	1100 (20.6)	146 (25.3)	< 0.001
NYHA functional class III–IV	2736 (24.5)	949 (20.0)	38 (27.7)	1554 (27.6)	195 (31.2)	< 0.001
LVEF < 40%	1397 (21.8)	518 (19.9)	23 (28.8)	762 (22.5)	94 (27.9)	0.001
Chronic treatments (n, %)						
Loop diuretics	7685 (66.5)	2872 (58.5)	83 (56.5)	4268 (73.3)	462 (69.0)	< 0.001
Thiazide diuretics	1687 (14.6)	727 (14.8)	14 (9.5)	856 (14.7)	90 (13.4)	0.264
ACEI or ARB	6638 (57.5)	2839 (57.8)	95 (64.6)	3293 (56.5)	411 (61.3)	0.023
MRA	1974 (17.1)	731 (14.9)	31 (21.1)	1048 (18.0)	164 (24.5)	< 0.001
Beta-blocker	4806 (41.6)	1899 (38.7)	68 (46.3)	2554 (43.9)	285 (42.5)	< 0.001
Nitrates	2073 (17.9)	677 (13.8)	26 (17.7)	1244 (21.4)	126 (18.8)	< 0.001
Oral anticoagulation	2168 (18.8)	920 (18.7)	34 (23.1)	1099 (18.9)	115 (17.2)	0.391
Data of the acute episode (n, %)						
Dyspnea	10,824 (91.0)	4635 (91.4)	132 (89.2)	5452 (91.0)	605 (88.8)	0.135
Orthopnoea	6617 (55.7)	2781 (54.9)	79 (53.4)	3361 (56.1)	396 (58.2)	0.271
Oedema	8068 (67.8)	3328 (65.6)	99 (66.9)	4162 (69.5)	479 (70.3)	< 0.001
O2 saturation ≤ 90%	3233 (28.1)	1312 (26.7)	47 (32.9)	1631 (28.1)	243 (37.1)	< 0.001
SBP ≤ 100 mmHg	650 (5.5)	180 (3.6)	12 (8.2)	382 (6.4)	76 (11.4)	< 0.001
Hyponatremia (< 135 mmol/l)	2175 (18.3)	860 (17.0)	55 (36.7)	1019 (17.1)	241 (35.5)	< 0.001
Potassium (mmol/L)[a]	4.42 ± 0.69	4.19 ± 0.51	6.04 ± 0.86	4.39 ± 0.54	6.00 ± 0.60	< 0.001
Creatinine (mg/dl)[a]	1.36 ± 0.85	0.85 ± 0.19	0.90 ± 0.18	1.70 ± 0.90	2.19 ± 1.21	< 0.001
eGFR (ml/min/m2)[a]	59.10 ± 27.65	84.15 ± 20.71	79.05 ± 17.89	40.45 ± 12.54	32.34 ± 13.10	< 0.001
Treatment in ED (n, %)						
Need for oxygen	8631 (73.1)	3650 (72.5)	105 (70.0)	4379 (73.6)	497 (73.5)	0.450
Need for intravenous diuretics[b]	10,214 (86.7)	4326 (86.1)	131 (87.3)	5163 (87.0)	594 (88.0)	0.345
Need for intravenous nitrates	1815 (15.4)	754 (15.0)	29 (19.3)	932 (15.7)	100 (14.8)	0.390
Need for inotropic or vasopressor	237 (2.0)	53 (1.1)	7 (4.7)	128 (2.2)	49 (7.3)	< 0.001
Need for morphine	644 (6.1)	238 (5.3)	11 (8.1)	333 (6.4)	62 (10.3)	< 0.001
Need for non-invasive ventilation	821 (7,0)	271 (5.4)	14 (9.3)	430 (7.2)	106 (15.7)	< 0.001
Need for invasive ventilation	315 (2.7)	138 (2.7)	3 (2.0)	157 (2.6)	17 (2.5)	0.930
Evolutive data (n, %)						
Hospital admission	9013 (75.6)	3647 (71.7)	118 (78.7)	4653 (77.5)	595 (86.9)	< 0.001
Stay (days)[a]	7.7 ± 12.3	6.9 ± 10.4	9.9 ± 25.5	8.1 ± 12.4	9.6 ± 18.1	< 0.001

[a] Values are mean ± SD, n (%).RD: renal dysfunction. Hk Hyperkalaemia. Chronic kidney failure (creatinine > 2 mg/dl), NYHA: New York Heart Association. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. SBP: Systolic blood pressure. ED: emergency department. eGFR: estimated glomerular filtration rate, calculated with the formula MDRD-4 (Modification of Diet in Renal Disease).

[b] Use of loop diuretics in perfusion, in bolus or both.

differences in the univariate study. The reference group was NoRD-NoHk. The results are expressed as hazard ratio (HR) with a confidence interval 95% (CI 95%). In all the cases statistical significance was accepted with a p value $< .05$ or if the CI95% of the HR excluded the value 1. The statistical analyses were performed using the statistical package SPSS 24.0 (IBM, North Castle, New York, USA).

3. Results

We analysed the data of 13,791 patients. Fig. 1 is a flowchart of patient inclusion. Of the 11,935 patients finally included in the study, 5088 (42.6%) were in the NoRD-NoHk group, 150 (1.3%) in the NoRD-Hk group, 6012 (50.4%) in the RD-NoHk group and 685 (5.7%) were in the RD-Hk group. The characteristics of the sample and the comparative study among the 4 groups are shown in Table 1. Twenty-eight of the 36 variables collected showed significant differences. Table 2 shows the results of the analysis of the crude and adjusted HR for the different groups based on the presence of RD and Hk in the acute episode, with the NoRD-NoHk group being the reference group for all the comparisons. The values of the beta coefficients for the multivariate analysis are presented in supplementary material, Table 1. The principal study variable, 30-day all-cause mortality was greatest in the RD-Hk group with an adjusted HR of 2.44 (CI95% 1.67–3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (1.04–1.71; $p = 0.022$). The combined variable of 30-day all-cause mortality and reconsultation for AHF was also significantly higher in the RD-Hk group with a HR of 1.33 (CI95% 1.04–1.70; $p = 0.021$), but not for the remaining groups. No significant differences were found in the crude or adjusted HR for the remaining variables studied. These results are shown in the survival curve for the principal variable (30-day all-cause death) in the different groups (Fig. 2).

Fig. 3 shows the results of the stratified analysis for the primary endpoint, 30-day all-cause death, based on the chronic treatments witch ACEI or ARB, MRA, LVEF < 40% or not, and hospital admission or not.

4. Discussion

The present study shows that the concomitant presence of RD and Hk at admission in patients consulting for AHF is associated with a worse outcome, especially 30-day all-cause mortality.

Patients with AHF have a high prevalence of RD which increases the risk of Hk, especially in those using RAAS inhibitors [15,16]. It is well known that the presence of RD is a predisposing factor for Hk [17]. In our study the presence of RD in the whole cohort was 56.1%, with Hk being present in 5.7%. It must be taken into account that the 30-day all-cause mortality in patients with RD and Hk is almost double that of patients with RD without Hk, and this has important implications. Physicians must be especially aware of the characteristics of patients with AHF [18,19]. Patients presenting RD and Hk during an acute episode have the worst prognosis, and therefore, have an elevated profile of risk for adverse events. This is likely because of the greater percentage of hospital admission in this group of greater risk.

The increase in 30-day all-cause mortality in the RD with Hk group is of note taking into account that the Hk without RD group did not present such an unfavorable outcome. On the other hand, the potassium levels in both groups were very similar. It was also of note that this association was not observed in any group in regard to in-hospital all-cause mortality. This was not found in other groups in which the presence of RD with Hk was associated with a worse outcome than Hk without RD [20], suggesting that patients with RD present greater tolerance or adaptation to Hk. One explanation for our results may be related to ED attendance. The ED physicians may have a more tolerant attitude to Hk in patients with RD. They may administer more treatment to reduce the potassium levels in patients not presenting RD, considering that the prognosis of this group is worse because the Hk is acute, while in RD, Hk is chronic and tolerance is greater. Nonetheless, we have no data on the treatment of Hk, and therefore, cannot make any firm conclusions, but the fact that more patients with RD and Hk are admitted than patients without RD but with Hk shows that physicians are more protective of this group.

High potassium levels are related to greater response to diuretics

Table 2
Crude and adjusted Hazard Ratios (HR) for the different groups based on the presence of renal dysfunction (RD) and hyperkalaemia (Hk) during the episode of acute heart failure.

	Crude HR (CI 95%)	P value	Adjusted HR (CI 95%)	P value
Primary endpoint				
30-day all-cause mortality				
NoRD-NoHk	Reference		Reference	
NoRD-Hk	2.06 (1.31–3.23)	0.002	1.17 (0.51–2.69)	0.714
RD-NoHk	1.64 (1.44–1.87)	< 0.001	1.34 (1.04–1.71)	0.022
RD-Hk	4.23 (3.52–5.07)	< 0.001	2.44 (1.67–3.55)	< 0.001
Secundary endpoint				
In-hospital all-cause mortality				
NoRD-NoHk	Reference		Reference	
NoRD-Hk	1.21 (0.74–1.97)	0.455	0.98 (0.40–2.40)	0.996
RD-NoHk	1.04 (0.89–1.21)	0.641	0.95 (0.70–1.29)	0.747
RD-Hk	1.31 (1.07–1.62)	0.010	0.95 (0.61–1.49)	0.831
30-day ED reconsultation for HF				
NoRD-NoHk	Reference	–	Reference	
NoRD-Hk	1.22 (0.85–1.75)	0.275	0.86 (0.47–1.57)	0.621
RD-NoHk	1.27 (1.17–1.38)	< 0.001	1.06 (0.92–1.23)	0.422
RD-Hk	1.35 (1.13–1.61)	0.001	1.06 (0.78–1.45)	0.703
30-day all-cause death or ED reconsultation for HF				
NoRD-NoHk	Reference	–	Reference	
NoRD-Hk	1.43 (1.08–1.91)	0.014	1.00 (0.62–1.63)	0.996
RD-NoHk	1.34 (1.25–1.44)	< 0.001	1.08 (0.95–1.23)	0.223
RD-Hk	2.01 (1.78–2.29)	< 0.001	1.33 (1.04–1.70)	0.021

Adjusted: male, age ≥ 75 years, personal history of arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic kidney failure, atrial fibrillation, peripheral artery disease or prior episode of heart failure; basal situation with Barthel Index < 60 points, NYHA functional class III–IV or left ventricular ejection fraction < 40%; chronic treatments with loop diuretics, angiotensin-converter enzyme inhibitor or angiotensin receptor blocker, mineralocorticoid receptor antagonist, beta-blocker or nitrates; acute episode with oedema, O2 saturation ≤ 90%, systolic blood pressure ≤ 100 mmHg or hyponatremia (sodium < 135 mmol/l); need in emergency department of inotropic or vasopressor, morphine or non-invasive ventilation, and hospital admission.

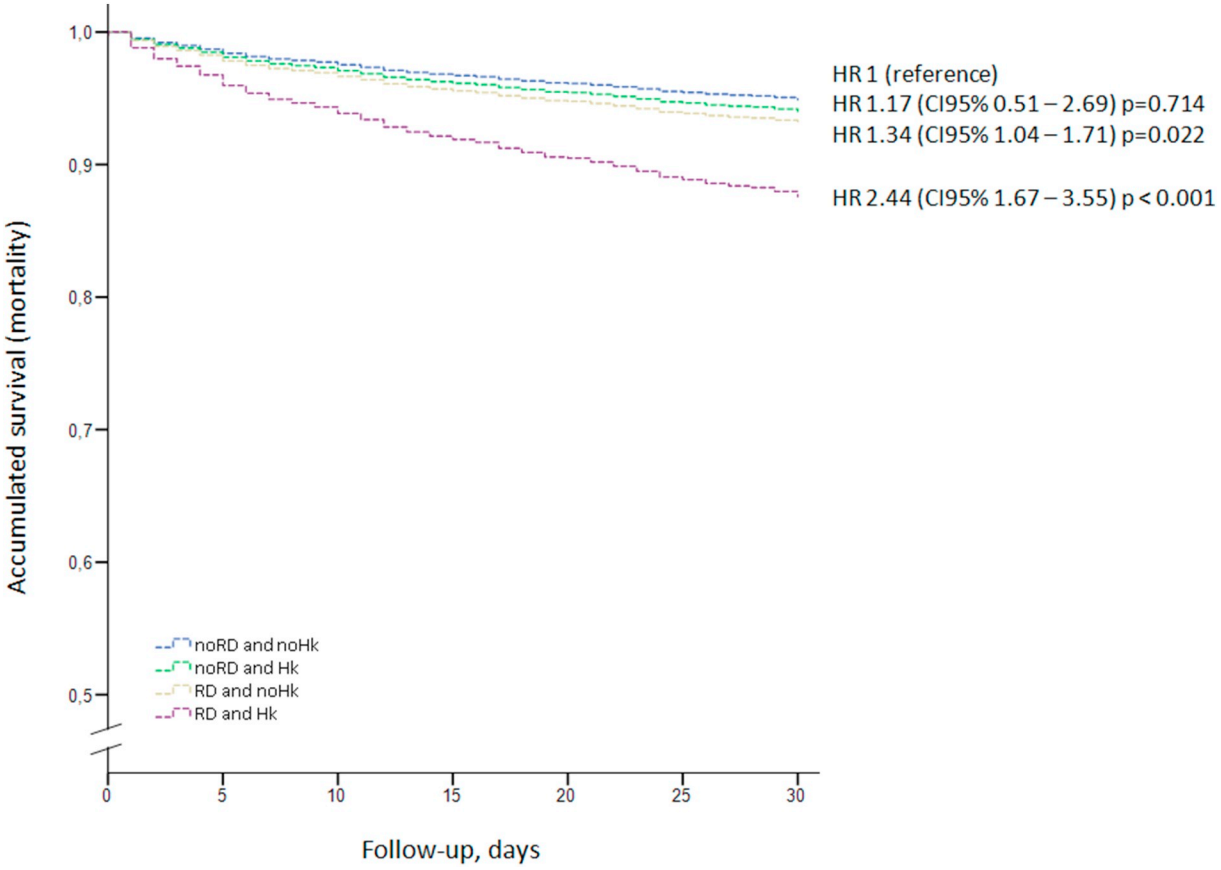

Fig. 2. Survival curve adjusted for the primary endpoint (30-day all-cause mortality) in the different study groups.

and the presence of RD is related to lower response to diuretics [21,22]. The data of the PROTECT and COACH studies showed an initially linear relationship between potassium levels and death, but this relation was not maintained after multivariate adjustment [23]. The authors concluded that the high potassium levels at the time of admission were associated with RD as well as greater response to diuretics, which could explain the lack of association with mortality. It should also be added that loop diuretics produce an elimination of potassium depending on the urine volume. In our study, there were no differences in the use of intravenous loop diuretics in the ED, but the dose of the diuretic or the volume of diuresis were not collected, and therefore, we cannot conclude that the response to diuretics influenced our results.

Our results show that the initiation of treatment with potassium binders should be evaluated in patients with AHF and the presence of Hk, especially if RD is also present. The new binders agents currently available are better tolerated and have demonstrated to be effective in reducing potassium levels [24–26], although it has not been demonstrated that they reduce the mortality of these patients [27]. Neither is there evidence of the benefits of emergency treatment of Hk [28] on patient outcome. Since we did not find any association with in-hospital all-cause mortality in any group, we believe that it is especially important to treat Hk with binders at hospital discharge following hospitalization or ED care.

Special attention is required by patients receiving RAASi. In the analysis by subgroups we found that, in patients with RD (either with or without concurrent Hk), the use of ACEI or ARB would avoid increases in 30-day mortality with respect to patients without RD and Hk (control group), a situation that it is not observed for patients not takind ACEI or ARB. Conversely, in patients with RD and Hk, the use of MRA is associated with a higher increase in 30-day mortality compared to control group patients than patients not taking MRA. Physicians should be especially sensitive to the MRA in the presence of RD and Hk.

Our study has several limitations. The most important being that it involved a registry of a prospective cohort, and therefore, conclusions are made on associations among variables. As mentioned previously, two variables which may influence the results of patient outcomes were not collected and these were the treatment of Hk and diuretic treatment and response to this treatment. However, the study has the strength of being a real life cohort with which points of improvement in daily clinical practice can be identified. Other limitation of the present analysis is the lack of adjustment for important potential confounders such as discharge treatment and doses.

In conclusion, the results of this study have important clinical applications. Taking into account the association between RD with Hk and mortality, clinicians must be especially aware of the presence of Hk in patients with RD. In this respect, potassium binders may improve the outcomes of these patients. Nonetheless, clinical studies are needed to study prognostic variables in patients with AHF.

Financial support

This study was partially supported by competitive grants from the Instituto de Salud Carlos III supported with funds from the Spanish Ministry of Health and FEDER (PI10/01918, PI11/01021, PI15/01019, PI15/00773, PI18/00393, PI18/00456), Catalonia Government (SGR 2009/1385, 2014/0313, 2017/1424), and Fundació La Marató de TV3 (2015/2510). The ICA-Research Group has received unrestricted funding from Novartis and Orion Pharma. The design of the study, patient inclusion, data analysis, discussion and final conclusions were exclusively carried out by the authors with no participation of the granters.

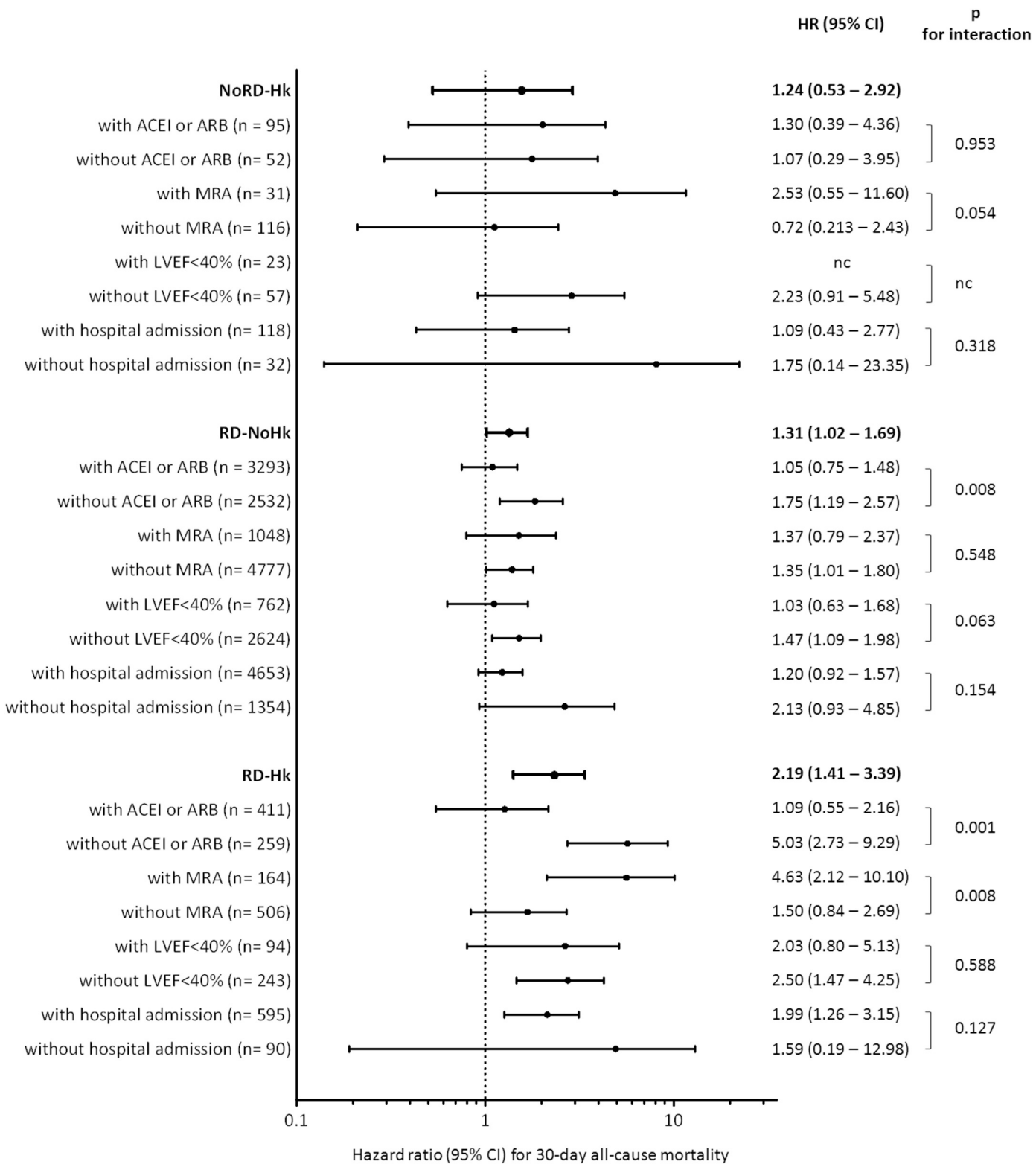

Fig. 3. Stratified analysis of the adjusted hazard ratios (HR) for primary endpoint (30-day all-cause mortality) the different groups based on the presence of renal dysfunction (RD), hyperkalaemia (Hk) or both during the episode of acute heart failure (reference group NoRD-NoHk).
RD: renal dysfunction. Hk Hyperkalaemia. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. nc: not calculated, because the sample size does not allow it.

Declaration of Competing Interests

JJ reports no conflict of interest.
LLL reports no conflict of interest.
PHP reports no conflict of interest.
FJMS reports no conflict of interest.
PLL reports no conflict of interest.
AR reports no conflict of interest.
VG reports no conflict of interest.
MF reports no conflict of interest.
FJLI reports no conflict of interest.
OM reports no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.07.010.

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