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Hyperkalemia in Acute Heart Failure: Short Term Outcomes from the EAHFE Registry

Zubaid Rafique[1,*], Maria José Fortuny[2,*], Dick Kuo[1], Lukasz Szarpak[1], Lluís Llauger[3], Begoña Espinosa[4], Víctor Gil[5], Javier Jacob[6], Aitor Alquézar-Arbé[7], Juan Antonio Andueza[8], José Manuel Garrido[9], Alfons Aguirre[10], Marta Fuentes[11], Héctor Alonso[12], Francisco Javier Lucas-Imbernón[13], Carlos Bibiano[14], Guillermo Burillo-Putze[15], Julio Núñez[16], Wilfried Mullens[17], Pedro Lopez-Ayala[18,19], Christian Mueller[18,19], Pere Llorens[4], Frank Peacock[1,19], Òscar Miró[5,19] (on behalf of the ICA-SEMES Research Group*)

[1] Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, Texas, USA
[2] Emergency Department, Hospital de Gandía, Alicante, Spain
[3] Emergency Department, Hospital Universitari de Vic, Barcelona, Catalonia, Spain
[4] Emergency, Short Stay and Hospitalization at Home Departments, Hospital General Dr. Balmis de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Universidad Miguel Hernández, Alicante, Spain
[5] Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Catalonia, Spain
[6] Emergency Department, Hospital Universitari de Bellvitge, l'Hospitalet de Llobregat, Barcelona, Catalonia, Spain
[7] Emergency Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Catalonia, Spain
[8] Emergency Department. Hospital General Universitario Gregorio Marañón, Madrid, Spain
[9] Emergency Department. Hospital Virgen Macarena, Sevilla, Spain
[10] Emergency Department. Hospital del Mar, Barcelona, Catalonia, Spain
[11] Emergency Department. Hospital Universitario de Salamanca, Salamanca, Spain
[12] Emergency Department, Hospital Marqués de Valdecilla, Santander, Spain
[13] Emergency Department, Hospital General Universitario de Albacete, Albacete, Spain
[14] Emergency Department, Hospital Infanta Leonor, Madrid, Spain
[15] Hospital Universitario de Canarias, Santa Cruz de Tenerife, Tenerife, Spain
[16] Ca Cardiology Department, Hospital Clínico Universitario de Valencia, Universidad de Valencia, INCLIVA, Valencia, Spain, CIBER Cardiovascular
[17] Cardiology Department, Ziekenhuis Oost-Limburg, Genk, Hasselt University, Diepenbeek, Belgium
[18] Cardiology Department and Cardiovascular Research Institute Basel (CRIB), University Hospital of Basel, Basel, Switzerland
[19] The GREAT (Global REsearch in Acute conditions Team) network, Rome, Italy

**Both authors equally contributed to this paper and should be considered as first author.*

Address for correspondence:

Zubaid Rafique, MD
Baylor College of Medicine
Ben Taub General Hospital
1504 Ben Taub Loop
Houston, TX 77030
Phone: (713) 873-2626
E-mail: zubaidrafique@gmail.com

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

Key words: Acute heart failure, potassium, outcome, mortality, emergency department, revisit, hospitalization.

ABSTRACT

Objective: Both hyperkalemia (HK) and Acute Heart Failure (AHF) are associated with increased short-term mortality, and the management of either may exacerbate the other. As the relationship between HK and AHF is poorly described, our purpose was to determine the relationship between HK and short-term outcomes in Emergency Department (ED) AHF.

Methods: The EAHFE Registry enrolls all ED AHF patients from 45 Spanish ED and records in-hospital and post-discharge outcomes. Our primary outcome was all-cause in-hospital death, with secondary outcomes of prolonged hospitalization (>7 days) and 7-day post-discharge adverse events (ED revisit, hospitalization, or death). Associations between serum potassium (sK) and outcomes were explored using logistic regression by restricted cubic spline (RCS) curves, with sK =4.0 mEq/L as the reference, adjusting by age, sex, comorbidities, patient baseline status and chronic treatments. Interaction analyses were performed for the primary outcome.

Results: Of 13,606 ED AHF patients, the median (IQR) age was 83 (76-88) years, 54% were women, and the median (IQR) sK was 4.5 mEq/L (4.3-4.9) with a range of 4.0-9.9 mEq/L. In-hospital mortality was 7.7%, with prolonged hospitalization in 35.9%, and a 7-day post-discharge adverse event rate of 8.7%. Adjusted in-hospital mortality increased steadily from sK ≥4.8 (OR=1.35, 95%CI=1.01-1.80) to sK=9.9 (8.41, 3.60-19.6). Non-diabetics with elevated sK had higher odds of death, while chronic treatment with mineralocorticoid-receptor antagonists exhibited a mixed effect. Neither prolonged hospitalization nor post-discharge adverse events was associated with sK.

Conclusion: In ED AHF, initial sK >4.8 mEq/L was independently associated with in-hospital mortality, suggesting that this cohort may benefit from aggressive HK treatment.

Key words: Acute heart failure, potassium, outcome, mortality, emergency department, revisit, hospitalization.

INTRODUCTION

Hyperkalemia (HK) is a potentially life-threatening electrolyte disorder, occurring in 3.6-8.8% of emergency department (ED) patients (1,2). It is more common in patients with chronic kidney disease (CKD), diabetes mellitus (DM) and heart failure (HF), and it is associated with increased morbidity and mortality, most frequently due to cardiac dysrhythmias (3–6).

Hyperkalemia, HF and kidney disease are closely related. The Acute Decompensated Heart Failure National Registry (ADHERE) has shown that approximately 30% of patients admitted to hospitals for acute HF (AHF) have kidney dysfunction(7). Furthermore, among the predictors of mortality in AHF, renal dysfunction (BUN > 43 mg/dL, or creatinine > 2.75 mg/dL) is the most significant (8). This is because HF affects the kidneys in multiple ways (9). Chronic HF can cause kidney dysfunction, called cardiorenal syndrome, which is classified into 5 subtypes (10), and may ultimately present as HK. Conversely, an AHF exacerbation may need aggressive diuretic treatment which can also cause acute kidney injury (11) and affect potassium regulation (12–16). Lastly, medications commonly used to treat HF (e.g., renin-angiotensin-aldosterone inhibitors and beta blockers) disrupt potassium metabolism and thus elevate serum potassium (sK), which is one of the major reasons for discontinuing guideline-based therapy in HF (17–19). Hence, HF failure and HK are intimately related, each of which are known to be an independent risk factor of mortality (20–22).

Prior studies on HK have reported a U-shaped mortality curve (1,6,23,24). Einhorn *et al.* (24), evaluating the records of 245,808 veterans, reported an increased one-day odds ratio of mortality in patients with HK. An inpatient based study by Goyal *et al.* (6), evaluating 38,689 patients with acute myocardial infarction, found that mortality was lowest when sK was between 3.5 and 4.5 mEq/L, with arrhythmia and death increasing rapidly outside that range. In another study, Collins *et al.* (23) investigated the relationship of sK with all-cause mortality over an 18-month period and found a similar U-shaped relationship in CKD, DM and HF. However, HK was more common in the HF population (25.8%) and the OR for mortality was higher in this cohort. While these studies evaluated HK in various settings with different outcomes and follow up periods, none evaluated the short-term effects of initial sK in AHF in the ED.

The goal of the current study is to determine the effect of initial sK in AHF. Our primary objective is to identify the rate of all-cause in-hospital morality in patients presenting to the ED for AHF with an elevated sK. Our secondary objective is to evaluate the incidence of prolonged hospitalization (>7 days) and 7-day post-discharge adverse events (ED revisit, hospitalization, or death) in this cohort.

METHODS

Setting and patient selection

This is a retrospective chart analysis of the EAHFE registry, the methodology of which has been extensively presented elsewhere (25–27). Briefly, EAHFE is a prospective multicenter dataset which includes patients presenting with AHF to 45 Spanish EDs. Diagnosis of HF is based on clinical criteria and, if available, confirmed by natriuretic peptides or echocardiographic criteria, as recommended by the ESC guidelines (28). Patients have been included in the database over multiple periods, with the registry undergoing 7 recruitment periods (in 2007, 2009, 2012, 2014, 2016, 2018 and 2019). During 1 or 2 months of every period, all consecutive adult patients diagnosed with AHF are included in the registry. Patients presenting with ST elevation myocardial infarction are excluded since they bypass the ED and go directly to the coronary angiography suite.

For the current study we included all patients from the registry. Exclusion criteria were missing sK values at index visit. Patients were also excluded if the sK <4.0 mEq/L since our objective is to focus on HK and a range of 3.5 to 4.5 has been previously reported to have the optimal outcome in cardiac patients(6).

Data collection

We recorded demographic data (age, sex), 11 comorbidities (hypertension, DM, coronary artery disease, heart valve disease, peripheral artery disease, cerebrovascular disease, CKD [defined as creatinine >2 mg/mL], chronic obstructive pulmonary disease, dementia, active neoplasia, and liver cirrhosis), 2 variables corresponding to baseline status (functional class according to Barthel index, and respiratory class according to New York Heart Association), 6 chronic treatments related to HF and potentially impacting on renal function (loop diuretics, thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, betablockers, and mineralocorticoid receptor antagonists [MRA]), and results of 3 laboratory tests obtained in the ED (creatinine, sodium, and potassium).

Endpoints

Our primary outcome was all-cause in-hospital mortality after ED presentation. Secondary outcomes included prolonged hospitalization (>7 days) and 7-day post-discharge adverse events which included ED revisit, hospitalization due to AHF, or all-cause death. Outcomes were collected by site-level principal investigators by consulting the Spanish public healthcare insurance registry, which includes more than 99.5% of people living in Spain and by reviewing medical records and contacting patients (or their relatives) over the telephone.

Statistical analysis

Quantitative variables are expressed as median and interquartile range (IQR), and qualitative variables as numbers and percentages. A restricted cubic spline (RCS) function was used to model the continuous association of sK and outcomes. Potassium values available on arrival to the ED were used for this analysis. Five spline knots were placed at the 5, 27.5, 50, 72.5 and 95 centiles of each continuous variable marginal distribution, following the recommendations of Harrel(29). The magnitude of the effect of each sK unit change on unadjusted outcomes was graphically represented and assessed by curves. The unadjusted and adjusted associations were expressed in a dose-response manner for probability or odds ratio (OR), with 95% confidence intervals (CI) for each outcome of interest. A sK of 4.0 mEq/L was used as the reference value to generate an OR for the dose-response plots. Adjustment was performed for all independent baseline and comorbid conditions which included 21 independent covariates (listed in Table 1) in the final adjusted model. First-degree interaction for these 21 independent variables on the relationship between sK and the primary outcome (in-hospital mortality) was investigated.

Hypothesis testing was two-tailed, and p values <0.05, or odds ratio (OR) with a 95% CI excluding 1, were considered statistically significant. Data analysis was performed using Statistical Package for Social Sciences version 23.0 (IBM, Armonk, NY, USA) and Stata version 16.1 (Stata Corp, College Station, TX, USA), and some graphs were produced using Microsoft Office Power Point version 2019 (Microsoft Corporate Office, Redmond, Washington, USA).

Ethics

The EAHFE Registry protocol was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 49/2010, 69/2011, 166/13, 160/15 and 205/17. All patients

provided informed consent to be included in the registry and to be contacted for follow-up. The present study was carried out in strict compliance with the principles of the Declaration of Helsinki.

RESULTS

Of the 19,945 patients in the registry, 6,339 were excluded because of missing sK (n=2,088) or having sK <4.0 mEq/L (n=4,251) (Figure 1). In the remaining 13,606, the median age was 83 (IQR= 76-88), 54% women, and the median sK was 4.5 (IQR=4.3-4.9), with a maximum of 9.9 mEq/L (Figure 2). Common comorbid conditions were hypertension (83.4%), DM (43.5%), CKD (29.2%), coronary artery disease (28.5%), valvular disorder (25.5%) and chronic obstructive pulmonary disease (23.8%). This cohort of AHF patients had a median Barthel Index of 90 (IQR= 65-100) with more than 25% in NYHA class of III or IV at baseline (Table 1). Missing values are shown in a supplemental table (S1).

Overall, an in hospital all-cause mortality event occurred in 1,051 (7.7%) patients. In the unadjusted model, this was associated with change in sK in an exponential manner, with significant mortality odds noted at a sK of 4.7 mEq/L (OR=1.32; 95% CI 1.02-1.72) or higher. After adjustment for 21 covariates, an elevated mortality odds was found with a sK as low as 4.8 mEq/L (OR 1.35; 95% CI of 1.01-1.80). The OR rose to 2.09 (95% CI 1.53-2.86) at a sK of 5.2 mEq/L and then to 8.4 (95% CI 3.6-19.5) at a sK of 9.9 mEq/L in an almost linear fashion (Figure 3).

Analysis of interaction in the adjusted model between sK and in-hospital all-cause mortality for all independent variables only showed significant interactions with the comorbid condition of DM (p=0.007) and the use of MRAs (p=0.015) (Figure 4). Separate ROCS curve analyses showed higher odds of in-hospital mortality associated with sK in the absence of DM (OR of 3.13 vs. 1.75 at sK = 5.5 mEq/L of 5.61 vs. 2.32 at sK = 7 mEq/L, and of 12.1 vs. 3.39 at sK = 9 mEq/L). A more complex relationship was noted with the use of MRA. Patients on chronic MRAs had a lower odds of death when sK was moderately elevated (OR of 1.09 vs 3.00 at sK = 5.5 mEq/L), but turned into a higher odds when sK was severe (OR of 11.2 vs 5.74 at sK = 9.0 mEq/L) (Figure 4).

Of the 12,543 patients discharged alive after the index AHF episode**,** 238 were excluded because of unknown length of stay, and 677 due to missing adverse event records (Figure 1). Secondary outcomes of prolonged hospitalization and 7-day post discharged adverse event occurred in 4,423 (35.9%) and 1,032 (8.7%), respectively.

The unadjusted model of prolonged hospitalization and sK showed a significant association, which mostly disappeared when controlling for demographics, comorbidities, functional status, and chronic medications. There was no association between sK and 7-day post discharge adverse events neither in unadjusted nor adjusted model (Figure 5).

DISCUSSION

We have found that in-hospital mortality in AHF starts rising at a sK of 4.8 mEq/L and doubles by 5.2 mEq/L. Furthermore, DM and the use of MRAs significantly modify the relationship between sK and in-hospital mortality. However, even though prolonged hospitalization occurred in almost 36%, and post-discharge adverse events occurred in approximately 9%, there was no association with HK.

This is the largest study evaluating the short-term outcomes of initial sK in an AHF cohort presenting to the ED. Prior studies have evaluated the effect of HK in all-comers to the ED (1), or long-term mortality in HF patients (21–23), which may not be helpful to the acute care physician managing HF in the ED. A study by Collins *et al.* (23) evaluated outpatient mortality (18-month follow-up) in a cohort of 50,202 patients with HF and 338,297 controls. They found that HK is more common in HF and the mortality rises with incremental change in sK. More importantly, both EHMRG and MEESSI-AHF tools derived from large data sets have correlated sK with poor outcomes. Miro et al.(25) while using the EAHFE registry to derive MEESSI-AHF (Multiple Estimation of risk based on the Emergency department Spanish Score In patients with Acute Heart Failure) found a correlation of sK with 11 different outcomes including in-hospital mortality. A similar trend was also noted by Lee et al. (30) with EHMRG (Emergency Heart failure Mortality Risk Grade, to predict 7-d mortality based on vital signs, mode of transportation and laboratory data available upon presentation to the ED. These tools, while comprehensive and helpful to the acute care physician in risk stratification of HF patients do not isolate the level at which sK starts affecting mortality. Distinctively, our study evaluated the mortality odds associated with the initial sK and found that the in-hospital mortality starts rising at 4.8 mEq/L in AHF, which may help an acute care physician in managing HF and deciding on the disposition.

Our findings are similar to those derived from large databases. Einhorn *et al.* (24) initially described the U-shaped relationship of sK and mortality and reported that HK occurred more frequently in patients with CKD and that there was significant short-term (within one day) associated mortality when compared to normokalaemia. Goyal *et al.* (6) evaluated the effect of sK in hospitalized acute myocardial infarction and reported that a post-admission sK level formed a U-shaped in-hospital mortality that started rising at a sK as low as 4.0 mEq/L. Lastly, Jacob et al.(21) have described the effect of sK on mortality in AHF using the EAHFE registry. They analyzed the effect of sK ≥ 5.5

mEq/L on in-hospital all-cause mortality and found a numerical increase but not a statistically significant effect (HR 1.21; 95% CI 0.74–1.97, p=0.455). Here, we evaluated initial sK in a continuous manner and found that in-hospital mortality starts rising at sK of 4.8 mEq/L in AHF patients.

The effect of DM and MRA use on in-hospital mortality is novel and perplexing. Diabetes mellitus is a risk factor for HK and an independent risk factor for mortality (23,31–33). However, the effect of DM on short term mortality in HK and AHF has not been analyzed to our knowledge. Diabetes mellitus is known to cause kidney injury and in turn increases risk of HK (33,34). However, in the short term, patients with DM are prone to higher blood sugar level (35) and this may lower their sK. In fact, administration of dextrose as an effective treatment for HK has been reported previously (36). So, it is plausible that patients with DM had a higher circulating serum insulin level, either released endogenously or administered as treatment in response to high blood sugar, and thus lowered sK during their hospital stay and in turn lowered mortality. As for MRA use, it is expected that MRAs elevate sK which is an independent risk factor of mortality in all-comers (6,23,24). However, MRAs have a mortality benefit in HF patients (37,38). So, it is plausible that the beneficial effects of MRAs are appreciated at mild to moderate HK and counterbalanced in severe HK. However, these hypotheses need to be evaluated more thoroughly in future studies.

More than one third of patients in our study stayed in the hospital longer than seven days. This rate of prolonged hospitalization can be a regional phenomenon as reported previously (39,40) or may reflect the severity of illness found in this population. Our cohort was of advanced age with a high proportion of comorbid disease which may have influenced the length of stay. It is plausible that this cohort took a longer time to clinically improve before safe discharge. Moreover, frailty, as evidenced by the low Barthel Index in this cohort, is also a well-recognized factor linked to adverse outcomes (41,42). On the other hand, it is possible that HF management and discharge practices vary among regions and countries, and this is a regional anomaly. In any case, neither prolonged hospitalization nor 7-day adverse event, which included ED revisit or hospitalization due to AHF or all-cause mortality, was found to be associated with sK. Lastly, it is also plausible that since HK is relatively easy to correct, most patients had a normal sK during their hospital stay and at discharge and therefore there was no association noted between initial sK and length of stay or post-discharge adverse events. In any case, we believe that future

studies will need to include multi-national data to evaluate the effect of sK on prolonged hospitalization and short-term adverse events.

Limitations

Our study has several limitations. Since this is an observational study, despite all the statistical adjustments, there is a possibility of residual confounding. In fact, the relationship between sK and outcomes may represent reverse causation and thus the results should be considered as hypothesis generating. Second, data collection and outcome adjudication were performed by site principal investigators without external overview. However, we used easily identifiable data points and outcomes to overcome the need for external adjudication. Third, our analysis is based on the first measured sK in the ED and we did not monitor efforts to correct abnormal values. It is plausible that correcting abnormal sK may improve odds of in-hospital mortality, but that effect is not captured in our study. Fourth, even though this is a multicenter registry, HF treatment is not uniform in all Spanish territories(43–45), and the outcomes and associations may be different at a particular site and more so in a different country. Fifth, our study included a high percentage of elderly AHF patients, with high proportion of advanced NYHA score and low functional status, and these may have inflated the primary outcome.

Conclusion

We have found that the in-hospital mortality in AHF started rising at a sK of 4.8 mEq/L and doubled at a sK of 5.2 mEq/L, suggesting that AHF patients may benefit from aggressive HK treatment in the ED. Prospective studies are indicated to further understand the effect of initial sK on mortality in AHF and the interactions with DM and MRA use.

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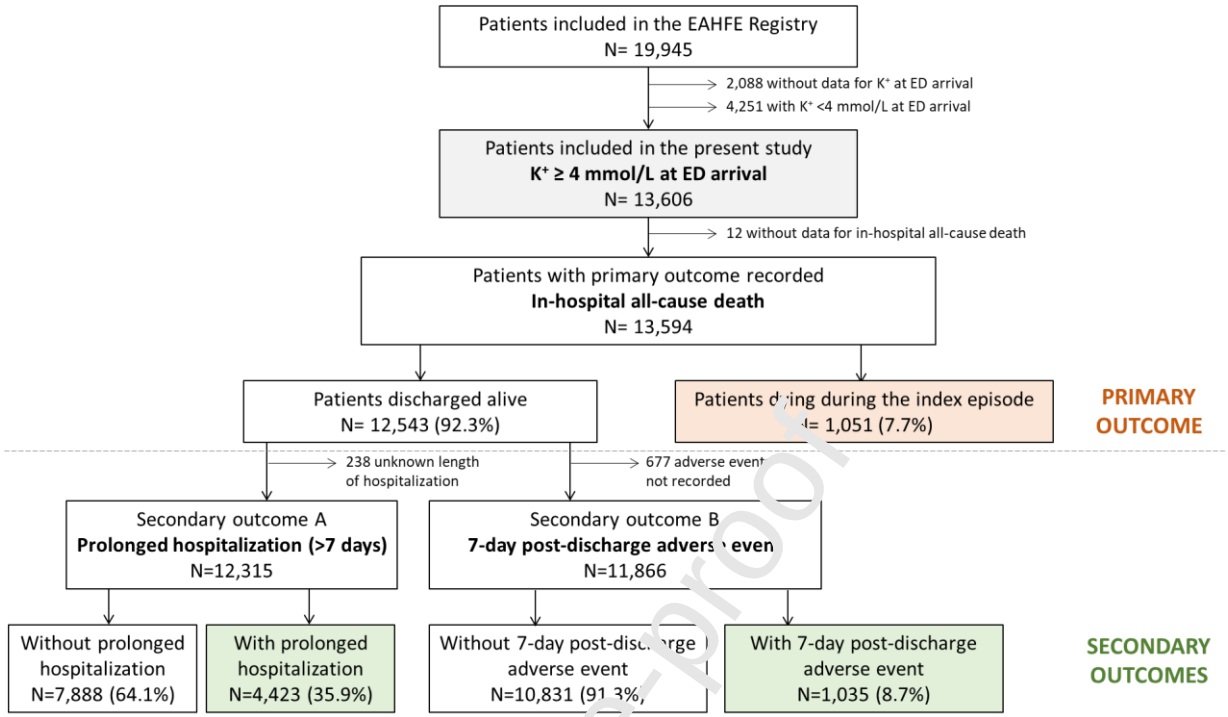
Table 1: Patients characteristics.

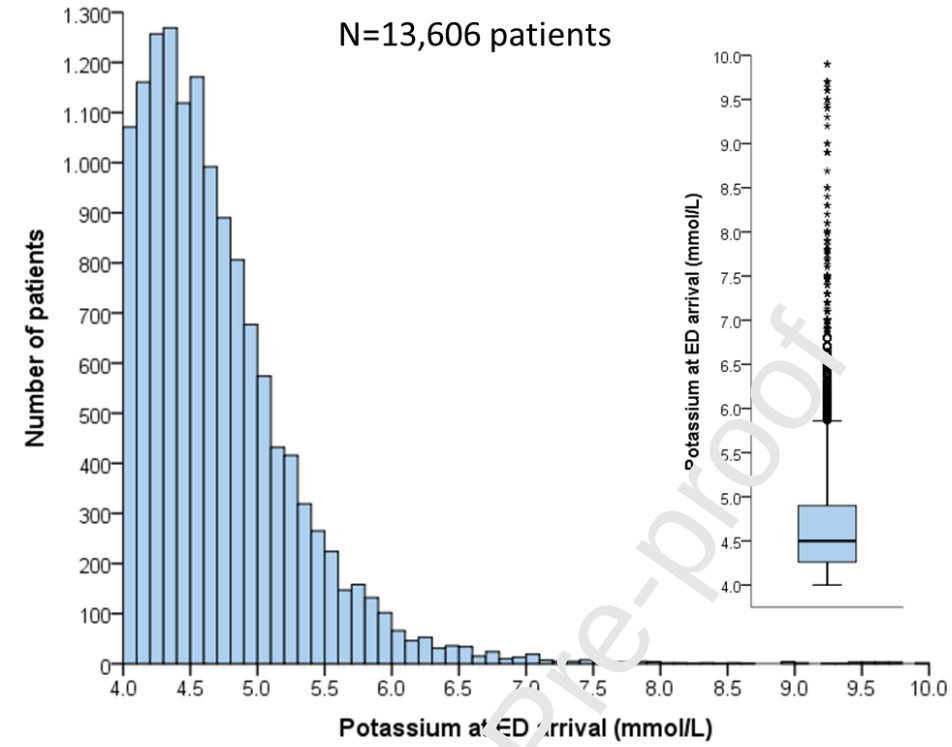
	Total N=13,606 n (%)
Demographic data	
Age (years) [median (RIC)]	83 (76-88)
-Age over 80 years	7,927 (58.3)
Female	7,354 (54.2)
Comorbidities	
Hypertension	11,309 (83.4)
Diabetes mellitus	5,916 (43.5)
Chronic kidney disease (creatinine >2 mg/mL)	3,962 (29.2)
Coronary artery disease	3,868 (28.5)
Heart valve disease	3,457 (25.5)
Chronic obstructive pulmonary disease	3,232 (23.8)
Active neoplasia	1,773 (14.1)
Cerebrovascular disease	1,656 (12.4)
Dementia	1,469 (11.7)
Peripheral artery disease	1,286 (9.5)
Liver cirrhosis	167 (1.2)
Baseline status	
Barthel Index (points) [median (RIC)]	90 (65-100)
-Barthel index <100 points	7,952 (64.4)
NYHA class	
I	3,011 (23.5)
II	6,578 (51.2)
III	3,056 (23.8)
IV	194 (1.5)
Chronic treatments	
Loop diuretics	8,735 (65.8)
Betablockers	5,881 (44.4)
Angiotensin-converter enzyme inhibitor	4,345 (32.8)
Antiotensin-II receptor blockers	3,270 (24.7)
Thiazide diuretics	1,714 (12.9)
Mineralcorticosterid-receptor antagonists	2,260 (17.1)

Figure 1: Flow chart for patient inclusion



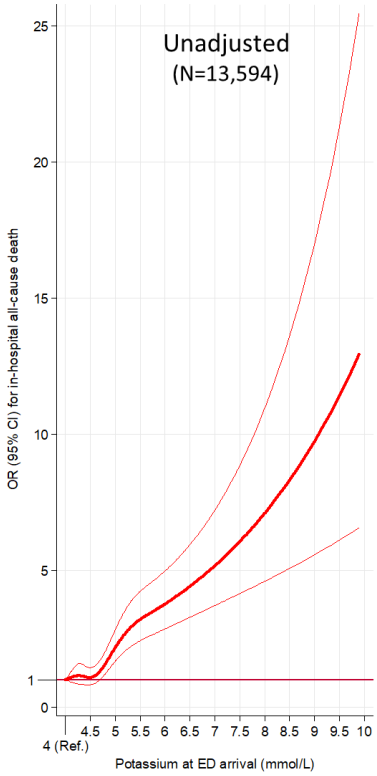
ED: emergency department

Figure 2: Patient distribution according to potassium concentration at emergency department arrival

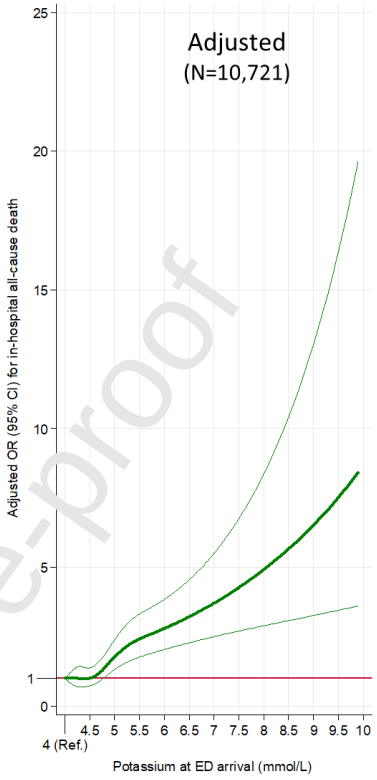


ED: emergency department

Figure 3: Unadjusted (left) and adjusted (right) restricted spline curves showing the relationship between potassium concentration at emergency department arrival and in-hospital all-cause (primary outcome).



K⁺	OR	LB	UB
4	1.00	(Reference)	
4.1	1.08	0.93	1.26
4.2	1.14	0.87	1.50
4.3	1.15	0.83	1.60
4.4	1.11	0.81	1.51
4.5	1.08	0.81	1.44
4.6	1.16	0.88	1.52
4.69	**1.30**	**1.00**	**1.70**
4.7	**1.32**	**1.02**	**1.72**
4.8	**1.57**	**1.22**	**2.03**
4.9	**1.88**	**1.45**	**2.42**
5	**2.18**	**1.67**	**2.83**
5.1	**2.45**	**1.87**	**3.21**
5.2	**2.70**	**2.05**	**3.55**
5.3	**2.90**	**2.20**	**3.83**
5.4	**3.07**	**2.33**	**4.06**
5.5	**3.21**	**2.43**	**4.24**
5.6	**3.33**	**2.53**	**4.40**
5.7	**3.44**	**2.61**	**4.53**
5.8	**3.55**	**2.70**	**4.68**
5.9	**3.67**	**2.78**	**4.83**
6	**3.78**	**2.87**	**4.99**
6.2	**4.03**	**3.04**	**5.35**
6.4	**4.29**	**3.21**	**5.74**
6.6	**4.57**	**3.38**	**6.18**
6.8	**4.87**	**3.55**	**6.67**
7	**5.18**	**3.72**	**7.22**
7.2	**5.52**	**3.90**	**7.82**
7.4	**5.88**	**4.07**	**8.49**
7.6	**6.27**	**4.25**	**9.24**
7.8	**6.67**	**4.43**	**10.**
8	**7.11**	**4.61**	**10.**
8.5	**8.32**	**5.**	**3.6**
9	**9.74**	**5.59**	**1.0**
9.5	**11.4**	**6.12**	**21.2**
9.9	**12.9**	**6.**	**25.4**



K⁺	OR	LB	UB
4	1.00	(Reference)	
4.1	1.00	0.84	1.19
4.2	1.00	0.73	1.35
4.3	0.99	0.69	1.42
4.4	0.98	0.69	1.39
4.5	1.00	0.73	1.37
4.6	1.08	0.79	1.46
4.7	1.21	0.90	1.62
4.78	**1.35**	**1.01**	**1.80**
4.8	**1.38**	**1.04**	**1.85**
4.9	**1.58**	**1.18**	**2.11**
5	**1.77**	**1.32**	**2.39**
5.1	**1.94**	**1.43**	**2.64**
5.2	**2.09**	**1.53**	**2.86**
5.3	**2.22**	**1.62**	**3.05**
5.4	**2.33**	**1.70**	**3.20**
5.5	**2.42**	**1.76**	**3.32**
5.6	**2.50**	**1.82**	**3.42**
5.7	**2.57**	**1.88**	**3.52**
5.8	**2.64**	**1.93**	**3.62**
5.9	**2.72**	**1.98**	**3.73**
6	**2.80**	**2.03**	**3.84**
6.2	**2.96**	**2.13**	**4.10**
6.4	**3.13**	**2.23**	**4.39**
6.6	**3.31**	**2.32**	**4.72**
7	**3.71**	**2.50**	**5.50**
7.2	**3.92**	**2.58**	**5.96**
7.4	**4.15**	**2.66**	**6.47**
7.6	**4.39**	**2.74**	**7.04**
7.8	**4.65**	**2.82**	**7.67**
8	**4.92**	**2.89**	**8.36**
8.5	**5.66**	**3.08**	**10.4**
9	**6.52**	**3.26**	**13.0**
9.5	**7.51**	**3.45**	**16.3**
9.9	**8.41**	**3.60**	**19.6**

Bold numbers in table denote statistical significance (p<0.05).

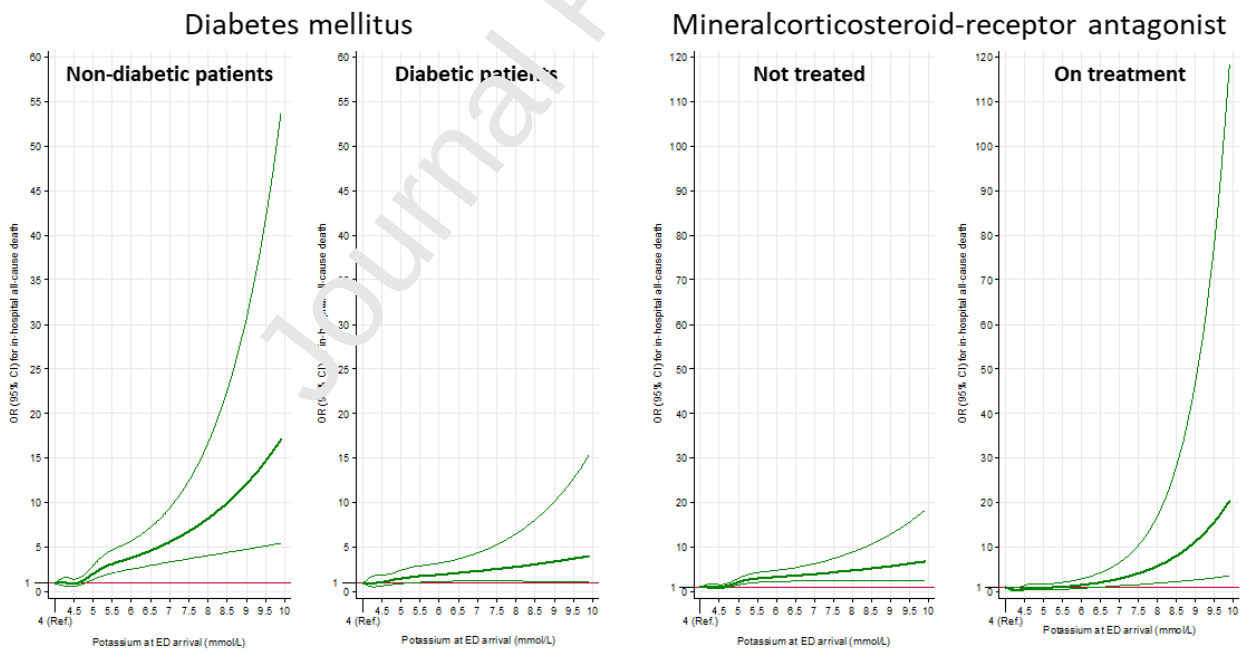
Adjustment was performed by age, sex, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, heart valve disease, chronic obstructive pulmonary disease, active neoplasia, cerebrovascular disease, dementia, peripheral artery disease, liver cirrhosis), baseline status (HYHA class and Barthel index) and chronic treatments (loop diuretics, betablockers, angiotensin-converting enzyme inhibitors, antiotensin-II receptor blockers, thiazide diuretics, mineralcorticosterid-receptor antagonists).

ED: emergency department; OR: odds ratio; CI: confidence interval; LB: lower bound for 95% confidence interval; UB: upper bound for 95% confidence interval.

Figure 4: Analysis of interaction in the adjusted model of association between potassium concentration and the primary outcome (in-hospital all-cause mortality) for all the variables included in the adjustment (left table) and magnitude of associations in the different subgroups of patients for those variables for which interaction was present (right table and bottom panels).

	P for interaction
Demographic data	
Age over 80 years	0.999
Female	0.242
Comorbidities	
Hypertension	0.411
Diabetes mellitus	**0.007**
Chronic kidney disease	0.564
Coronary artery disease	0.820
Heart valve disease	0.377
Chronic obstructive pulmonary disease	0.527
Active neoplasia	0.600
Cerebrovascular disease	0.629
Dementia	0.607
Peripheral artery disease	0.370
Liver cirrhosis	0.859
Baseline status	
Barthel Index below 100 points	0.999
NYHA class III-IV	0.189
Chronic treatments	
Loop diuretics	0.768
Betablockers	0.078
Angiotensin-converter enzyme inhibitor	0.427
Antiotensin-II receptor blockers	0.350
Thiazide diuretics	0.710
Mineralcorticosterid-receptor antagonists	**0.015**

Selected K^+ values for comparation (when significant interaction was present)	Factor absent OR (95% CI)	Factor present OR (95% CI)
Diabetes mellitus		
4.0	1 (Reference)	1 (Reference)
4.5	0.93 (0.62-1.40)	1.09 (0.65-1.83)
5.0	**2.02 (1.38-2.95)**	1.49 (0.91-2.41)
5.5	**3.13 (2.09-4.69)**	**1.75 (1.05-2.91)**
6.0	**3.82 (2.54-5.74)**	**1.92 (1.15-3.21)**
6.5	**[illegible]63 (2.95-7.24)**	**2.11 (1.21-3.68)**
7.0	**5.61 (3.34-9.42)**	**2.32 (1.23-4.37)**
8.0	**8.23 (4.05-16.7)**	**2.80 (1.21-6.51)**
9.[illegible]	**12.1 (4.76-30.7)**	**3.39 (1.13 (10.1)**
[illegible].9	**17.1 (5.44-53.7)**	**4.01 (1.05-15.3)**
Mineralcorticosteroid-receptor antagonist		
4.0	1 (Reference)	1 (Reference)
4.5	1.10 (0.76-1.59)	0.73 (0.38-1.41)
5.0	**2.13 (1.51-3.00)**	0.91 (0.49-1.67)
5.5	**3.00 (2.08-4.32)**	1.09 (0.56-2.10)
6.0	**3.31 (2.29-4.78)**	1.51 (0.79-2.90)
6.5	**3.62 (2.42-5.42)**	**2.11 (1.05-4.25)**
7.0	**3.97 (2.51-6.30)**	**2.95 (1.32-6.55)**
8.0	**4.78 (2.57-8.89)**	**5.74 (1.94-17.0)**
9.0	**5.74 (2.55-12.9)**	**11.2 (2.69-46.7)**
9.9	**6.78 (2.52-18.2)**	**20.5 (3.53-118)**

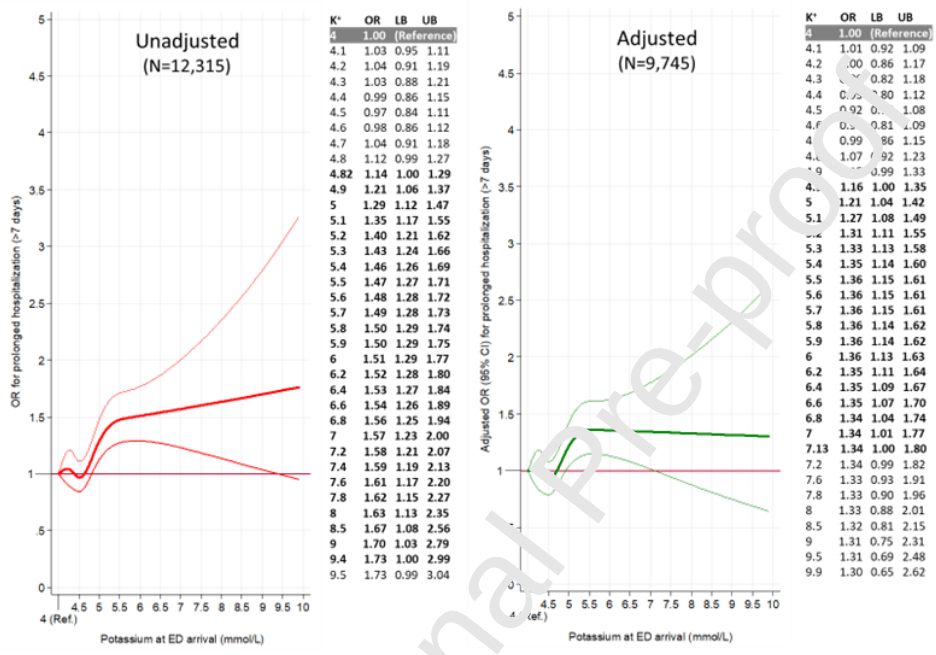


Bold numbers in table denote statistical significance (p<0.05).

Adjustment was performed by age, sex, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, heart valve disease, chronic obstructive pulmonary disease, active neoplasia, cerebrovascular disease, dementia, peripheral artery disease, liver cirrhosis), baseline status (HYHA class and Barthel index) and chronic treatments (loop diuretics, betablockers, angiotensin-converter enzyme inhibitors, antiotensin-II receptor blockers, thiazide diuretics, mineralcorticosterid-receptor antagonists).

ED: emergency department; OR: odds ratio; CI: confidence interval; LB: lower bound for 95% confidence interval; UB: upper bound for 95% confidence interval.

Figure 5: Unadjusted (left) and adjusted (right) restricted spline curves showing the relationship between potassium concentration at emergency department arrival and prolonged hospitalization (>7 days; upper panels) and 7-day post-discharge adverse event (bottom panels) (secondary outcomes).



K+	OR	LB	UB
4	1.00	(Reference)	
4.1	1.03	0.95	1.11
4.2	1.04	0.91	1.19
4.3	1.03	0.88	1.21
4.4	0.99	0.86	1.15
4.5	0.97	0.84	1.11
4.6	0.98	0.86	1.12
4.7	1.04	0.91	1.18
4.8	1.12	0.99	1.27
4.82	1.14	1.00	1.29
4.9	1.21	1.06	1.37
5	1.29	1.12	1.47
5.1	1.35	1.17	1.55
5.2	1.40	1.21	1.62
5.3	1.43	1.24	1.66
5.4	1.46	1.26	1.69
5.5	1.47	1.27	1.71
5.6	1.48	1.28	1.72
5.7	1.49	1.28	1.73
5.8	1.50	1.29	1.74
5.9	1.50	1.29	1.75
6	1.51	1.29	1.77
6.2	1.52	1.28	1.80
6.4	1.53	1.27	1.84
6.6	1.54	1.26	1.89
6.8	1.56	1.25	1.94
7	1.57	1.23	2.00
7.2	1.58	1.21	2.07
7.4	1.59	1.19	2.13
7.6	1.61	1.17	2.20
7.8	1.62	1.15	2.27
8	1.63	1.13	2.35
8.5	1.67	1.08	2.56
9	1.70	1.03	2.79
9.4	1.73	1.00	2.99
9.5	1.73	0.99	3.04

K+	OR	LB	UB
4	1.00	(Reference)	
4.1	1.01	0.92	1.09
4.2	1.00	0.86	1.17
4.3	[illegible]	0.82	1.18
4.4	[illegible]	0.80	1.12
4.5	0.92	[illegible]	1.08
[illegible]	[illegible]	0.81	1.09
[illegible]	0.99	0.86	1.15
[illegible]	1.07	0.92	1.23
[illegible]	[illegible]	0.99	1.33
[illegible]	1.16	1.00	1.35
5	1.21	1.04	1.42
5.1	1.27	1.08	1.49
[illegible]	1.31	1.11	1.55
5.3	1.33	1.13	1.58
5.4	1.35	1.14	1.60
5.5	1.36	1.15	1.61
5.6	1.36	1.15	1.61
5.7	1.36	1.15	1.61
5.8	1.36	1.14	1.62
5.9	1.36	1.14	1.62
6	1.36	1.13	1.63
6.2	1.35	1.11	1.64
6.4	1.35	1.09	1.67
6.6	1.35	1.07	1.70
6.8	1.34	1.04	1.74
7	1.34	1.01	1.77
7.13	1.34	1.00	1.80
7.2	1.34	0.99	1.82
7.6	1.33	0.93	1.91
7.8	1.33	0.90	1.96
8	1.33	0.88	2.01
8.5	1.32	0.81	2.15
9	1.31	0.75	2.31
9.5	1.31	0.69	2.48
9.9	1.30	0.65	2.62

K+	OR	LB	UB
4	[illegible]	[illegible]	[illegible]
4.1	1.02	[illegible]	1.16
4.2	1.04	[illegible]	1.30
4.3	[illegible]	[illegible]	1.37
[illegible]	1.04	[illegible]	1.35
4.5	[illegible]	0.82	1.32
4.6	[illegible]	0.82	1.31
[illegible]	1.04	0.84	1.30
4.8	1.05	0.84	1.31
[illegible]	1.06	0.85	1.32
[illegible]	1.06	0.84	1.35
5.1	1.07	0.84	1.37
5.2	1.07	0.83	1.38
5.3	1.07	0.83	1.39
5.4	1.07	0.83	1.39
5.5	1.07	0.83	1.39
5.6	1.07	0.83	1.39
5.7	1.07	0.83	1.39
5.8	1.07	0.82	1.39
5.9	1.07	0.82	1.40
6	1.07	0.81	1.41
6.2	1.06	0.79	1.43
6.4	1.06	0.77	1.47
6.6	1.06	0.74	1.52
6.8	1.06	0.71	1.57
7	1.05	0.68	1.63
7.2	1.05	0.65	1.69
7.4	1.05	0.62	1.76
7.5	1.05	0.61	1.80
7.8	1.04	0.57	1.91
8	1.04	0.54	2.00
8.5	1.03	0.48	2.23
9	1.03	0.42	2.49
9.5	1.02	0.37	2.79
9.9	1.02	0.34	3.06

K+	OR	LB	UB
4	1.00	(Reference)	
4.1	1.03	0.89	1.20
4.2	1.05	0.81	1.37
4.3	1.05	0.77	1.44
4.4	1.03	0.76	1.38
4.5	1.00	0.76	1.32
4.6	1.00	0.77	1.31
4.7	1.03	0.79	1.33
4.8	1.06	0.82	1.37
4.9	1.10	0.85	1.43
5	1.13	0.86	1.49
5.1	1.15	0.86	1.53
5.2	1.16	0.87	1.56
5.3	1.17	0.87	1.57
5.4	1.17	0.86	1.57
5.5	1.16	0.86	1.56
5.6	1.15	0.85	1.55
5.7	1.14	0.84	1.54
5.8	1.13	0.83	1.53
5.9	1.12	0.82	1.53
6	1.11	0.80	1.53
6.2	1.09	0.77	1.55
6.4	1.07	0.73	1.57
6.6	1.05	0.69	1.60
6.8	1.03	0.65	1.65
7	1.01	0.60	1.69
7.2	0.99	0.57	1.75
7.4	0.98	0.53	1.80
7.6	0.96	0.49	1.87
7.8	0.94	0.46	1.93
8	0.92	0.43	2.00
8.5	0.88	0.35	2.20
9	0.84	0.29	2.41
9.5	0.80	0.24	2.66
9.9	0.78	0.21	2.87

Bold numbers in table denote statistical significance (p<0.05).

Adjustment was performed by age, sex, comorbidities (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, heart valve disease, chronic obstructive pulmonary disease, active neoplasia, cerebrovascular disease, dementia, peripheral artery disease, liver cirrhosis), baseline status (HYHA class and Barthel index) and chronic treatments (loop diuretics, betablockers, angiotensin-converter enzyme inhibitors, antiotensin-II receptor blockers, thiazide diuretics, mineralcorticosterid-receptor antagonists).

ED: emergency department; OR: odds ratio; CI: confidence interval; LB: lower bound for 95% confidence interval; UB: upper bound for 95% confidence interval.

Supplemental Table (S1): Patient characteristics with missing values.

	Total **N=13,606** n (%)	**Missing values** n (%)
Demographic data		
Age (years) [median (RIC)]	83 (76-88)	17 (0.1)
-Age over 80 years	7,927 (58.3)	
Female	7,354 (54.2)	41 (0.3)
Comorbidities		
Hypertension	11,309 (83.4)	44 (0.3)
Diabetes mellitus	5,916 (43.5)	46 (0.3)
Chronic kidney disease (creatinine >2 mg/mL)	3,962 (29.2)	43 (0.3)
Coronary artery disease	3,668 (27.5)	47 (0.3)
Heart valve disease	3,457 (25.5)	46 (0.3)
Chronic obstructive pulmonary disease	3,232 (23.8)	40 (0.4)
Active neoplasia	1,773 (14.1)	1,066 (7.8)
Cerebrovascular disease	1,686 (12.4)	45 (0.3)
Dementia	1,469 (11.7)	1,064 (7.8)
Peripheral artery disease	1,286 (9.5)	48 (0.4)
Liver cirrhosis	167 (1.2)	1,069 (7.9)
Baseline status		
Barthel Index (points) [median (RIC)]	90 (65-100)	1,255 (9.2)
-Barthel index <100 points	7,952 (64.4)	
NYHA class		767 (5.6)
I	3,011 (23.5)	
II	6,578 (51.2)	
III	3,056 (23.8)	
IV	194 (1.5)	
Chronic treatments		
Loop diuretics	8,735 (65.8)	332 (2.4)
Betablockers	5,881 (44.4)	370 (2.7)

Angiotensin-converter enzyme inhibitor	4,345 (32.8)	353 (2.6)
Antiotensin-II receptor blockers	3,270 (24.7)	370 (2.7)
Thiazide diuretics	1,714 (12.9)	352 (2.6)
Mineralcorticosterid-receptor antagonists	2,260 (17.1)	352 (2.6)

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