Nephrol Dial Transplant (2022) 37: 522–530
doi: 10.1093/ndt/gfab003
Advance Access publication 28 January 2021

ORIGINAL ARTICLE

Long-term mortality and trajectory of potassium measurements following an episode of acute severe hyperkalaemia

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ABSTRACT

Background. Hyperkalaemia is a common condition in patients with comorbidities such as chronic kidney disease (CKD) or congestive heart failure (HF). Moreover, severe hyperkalaemia is a potentially life-threatening condition that is associated with a higher risk of adverse clinical events such as ventricular arrhythmias and sudden cardiac death. Currently, data regarding the prognostic implications of chronic hyperkalaemia are available; however, information about the long-term clinical consequences after an episode of severe hyperkalaemia remains scarce. The objective of this study was to evaluate the association between the trajectory of potassium measurements in patients with acute hyperkalaemia and long-term all-cause mortality.

Methods. This is a retrospective observational study that included patients with acute severe hyperkalaemia [potassium (K) >6 mEq/L] without haemolysis in the emergency room of Dr Peset University Hospital in Valencia, Spain searching the lab database from January 2016 to March 2017. The multivariable-adjusted association of serum potassium with mortality was assessed by using comprehensive state-of-the-art regression methods that can accommodate time-dependent exposure modelling.

Results. We found 172 episodes of acute hyperkalaemia in 160 patients in the emergency room. The mean ± standard deviation age of the sample was 77 ± 12 years and 60.5% were males. The most frequent comorbidities were CKD (71.2%), HF (35%) and diabetes mellitus (56.9%). Only 11.9% of the patients were on chronic dialysis. A quarter of the patients did not have previous CKD, making hyperkalaemia an unpredictable life-threatening complication. During the acute episode, mean potassium and estimated glomerular filtration rate (eGFR) were 6.6 ± 0.6 (range 6.1–9.2) mEq/L and 23 ± 16 (range 2–84) mL/min/1.73 m^2, respectively. After a median (interquartile range) follow-up of 17.3 (2.2–23.7) months, 68 patients died (42.5%). Recurrences of hyperkalaemia (K >5.5 mEq/L) were detected in 39.5% of the patients who were monitored during follow-up. We found that previous potassium levels during an acute severe hyperkalaemia episode were not predictors of mortality. Conversely, the post-discharge longitudinal trajectories of potassium were able to predict all-cause mortality (overall P = 0.0015). The effect of transitioning from hyperkalaemia to normokalaemia (K >5.5 mEq/L to K ≤5.5 mEq/L) after the acute episode was significant, and inversely associated with the risk of mortality.

Conclusions. Potassium levels prior to a severe hyperkalaemic event do not predict mortality. Conversely, following an episode of acute severe hyperkalaemia, serial kinetics of potassium trajectories predict the risk of death. Further evidence is needed to confirm these findings and clarify the optimal long-term management of these patients.

Keywords: hyperkalaemia, longitudinal studies, mortality, post-discharge, potassium

INTRODUCTION

Severe hyperkalaemia is a potentially life-threatening condition that is associated with a higher risk of adverse clinical events such as ventricular arrhythmias and sudden cardiac death [1]. Hyperkalaemia is common in patients with comorbidities such as chronic kidney disease (CKD), cardiovascular diseases, diabetes or liver diseases [2, 3]. Prior studies reported a prevalence of hyperkalaemia in ∼3.2% of all patients in data from institutional database companies [4]. However, its prevalence is up to

KEY LEARNING POINTS

What is already known about this subject?

- severe hyperkalaemia is a potentially life-threatening condition associated with a higher risk of short-term adverse clinical events such as ventricular arrhythmias and sudden cardiac death. Information about the long-term clinical consequences after an episode of severe hyperkalaemia remains scarce; and
- we conducted a retrospective observational study that evaluated the long-term the trajectory of potassium and risk of mortality in patients with acute severe hyperkalaemia (K >6 mEq/L).

What this study adds?

- severe hyperkalaemia may occur in patients who did not have chronic kidney disease (25% of our patients);
- after developing severe hyperkalaemia, recurrent hyperkalaemia is a frequent finding, especially during the first 6 months after the discharge;
- following an acute severe hyperkalaemia episode, potassium trajectories predict the risk of death; and
- during the post-discharge follow-up, transitioning from normal to higher potassium levels or persisting high values was associated with higher risk of death.

What impact this may have on practice or policy?

- this study strengthens the importance of close clinical and potassium monitoring after an episode of acute hyperkalaemia; and
- it reinforces the fact that new and well-tolerated treatments after discharge from a hyperkalaemia-related hospitalization should be strongly considered.

20% in patients with CKD or congestive heart failure (HF) who are also usually treated with drugs that increase the risk of hyperkalaemia such as renin–angiotensin–aldosterone system inhibitors (RAASis) [5–7]. In a study that evaluated the hyperkalaemia-related costs, the hospitalization rate was higher in CKD patients with hyperkalaemia than in those CKD patients who did not have this condition [8]. Moreover, recent evidence shows that hyperkalaemia-related hospitalizations were associated with significant economic and readmission burdens during the 1-year post-discharge period [9].

Although data regarding the prognostic implications of chronic hyperkalaemia are available, information about the long-term clinical consequences after an episode of severe hyperkalaemia remains scarce. This is especially true regarding whether the trajectory of potassium before and following the acute episode is associated with further clinical events.

In this study, we aimed to evaluate the association between trajectories of potassium measurements after an episode of acute hyperkalaemia and the risk of long-term all-cause mortality. This endpoint was assessed using the state-of-the-art techniques of longitudinal analysis.

MATERIALS AND METHODS

This is a retrospective study based on the detection of severe hyperkalaemia in the emergency room of Dr Peset University Hospital in Valencia, Spain. This health department covers 277 280 citizens. We performed a search of the lab database from January 2016 to March 2017, including laboratory data within the emergency room, detecting 1444 episodes of hyperkalaemia ≥5.5 mEq/L during this period.

Eligibility criteria

Inclusion criteria. Patients attended in the emergency room in which severe and well-documented hyperkalaemia [serum potassium (sK) >6 mEq/L] were registered.

Exclusion criteria. Patients with haemolysis (very mild, mild or severe) were excluded, to avoid interferences in the determination of serum potassium.

Study population

After excluding 193 episodes with mild or moderate haemolysis, we found 172 episodes of severe hyperkalaemia occurring in 160 patients admitted to the emergency room for any cause. This means that 11.4 episodes/month were detected in the emergency room in an area of 277 280 inhabitants. A flowchart of the patients in the study is shown in Supplementary data, Figure S1. The study was approved by the local hospital ethics committee and the regulatory authorities (Spanish Medicine Agency—AEMPS). We recorded, using pre-established electronic questionnaires, information related to demography, medical history, vital signs, 12-lead electrocardiogram, biomarkers and pharmacologic therapies. We retrospectively evaluated the all previously mentioned electronic medical and laboratory records.

Potassium measurements. For potassium trajectory analysis, we evaluated six time points during the follow-up period. At each time point, we registered the following data: clinical data, treatments, serum creatinine, serum sodium, estimated glomerular filtration rate (eGFR) and serum potassium. Overall, we registered serum potassium at the emergency room, during

hospitalizations and after discharge. The timing of these time points were: potassium before severe hyperkalaemia episode, potassium at the time of severe hyperkalaemia, potassium at the time of discharge, potassium 30 days after discharge, potassium between 30 and 90 days after discharge and potassium later than 90 days after discharge (mEq/L). As a result of haemolysis being an exclusion criterion, only non-haemolysed specimens were used. Thus, we use the sample interference index to generate a semi-quantitative index value and a qualitative estimate of the presence of haemolysis in serum [10]. Finally, the serum contains a certain amount of haemoglobin derived from haemolysis, which was measured in each sample to reflect the approximate concentration of the interferer (Supplementary data).

In these six points, a total of 786 serum potassium measurements in 172 episodes from 160 patients were analysed. Serum potassium concentrations were measured using the ARCHITECT c Systems Integrated Chip Technology assay.

The mean follow-up was 14.5 months [median 17.3 months; interquartile range (IQR) 2.2–23.7, range 0–28.9]. At the time of hospital discharge, 142 patients had a potassium measurement. During follow-up, the first potassium measurement was performed in 142 patients [mean ± standard deviation (SD) 34–54 days]. The second measurement during follow-up was made in 96 patients (mean ± SD 69–85 days) and the last measurement was made in 105 patients (mean ± SD 93–99 days) (Figure 1).

Statistical analysis

Continuous variables are presented as mean ± SD or median (IQR), as appropriate. Categorical variables are expressed as percentages. The association between baseline characteristics, including potassium levels, and risk of death was assessed by multivariate Cox regression analysis.

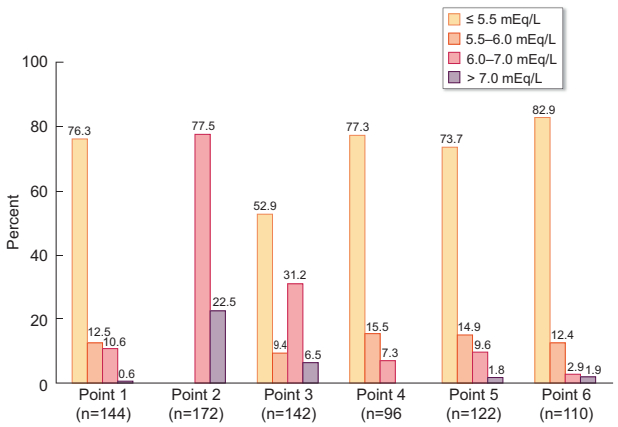


FIGURE 1: Serum potassium by categories in the six time points analysed in the study. Point 1: potassium before severe hyperkalaemia episode, Point 2: potassium at the time of severe hyperkalaemia, Point 3: potassium at the time of discharge, Point 4: potassium 30 days after discharge, Point 5: potassium between 30 and 90 days after discharge and Point 6: potassium later than 90 days after discharge (mEq/L).

Longitudinal analysis. After detecting no independent relationship between serum potassium levels analysed at each sample point and survival with classical Cox analysis (Supplementary data, Table S1), then we re-assessed the multivariable-adjusted association of serum potassium with mortality by using comprehensive state-of-the-art regression methods that can accommodate time-dependent exposure modelling. Multilevel survival analysis was used to combine the longitudinal (repeated measures) and survival (time-to-event endpoint) aspects of the data.

For longitudinal analysis, we initially evaluated the association of serum potassium levels at each sample point with mortality using Cox proportional hazards model of death. For the multivariate model building, we first included potassium levels and those variables related to mortality and morbidity according to the current literature (age, diabetes mellitus, etc.), as well as the predictors significantly associated with death in the univariate analysis. The variables included in the full-adjusted multivariate analysis were age, eGFR, serum levels of sodium and potassium, previous nephrology assessment and chronic treatment (including RAASi and calcium antagonists) before the episode of hyperkalaemia, diastolic blood pressure, presence of dehydration (including thirst, dry mucous membranes, sunken-appearing eyes, decreased skin turgor, increased capillary refill time and hypotension), ventricular tachycardia, different treatments of acute hyperkalaemia with resins and need for hospitalization, analytical follow-up and chronic treatment with resins and RAASi after hyperkalaemia episode.

After detecting no independent relationship between serum potassium levels analysed at each sample point and survival with classical Cox analysis, we re-assessed the multivariable-adjusted association of serum potassium with mortality by using comprehensive state-of-the-art regression methods that can accommodate time-dependent exposure modelling. Multilevel survival analysis was used to combine the longitudinal (repeated measures) and survival (time-to-event endpoint) aspects of the data. We fit a two-level model with patient identification as a random effect and the log (follow-up time) as a random coefficient. For the survival portion of the model, we used a Weibull distribution.

We selected explanatory variables for the multivariable regression model, with subject matter knowledge as the main criterion. Starting with this initial (oversaturated) model, backward elimination was applied to exclude variables with $P \geq 0.1$. For our continuous exposure (i.e. $K_{cumulative}$), we determined its appropriate functional form by using the multivariable fractional polynomial method. A 4 degree of freedom (4-df) fractional polynomial of (–2–1) was the best transformation suggested, which relates the continuum of $K_{cumulative}$ to the risk of mortality through a U-shaped curve with higher risk observed at both ends. Any decision about the use of random intercept, random coefficient and the polynomial that best describes the functional form for $K_{cumulative}$ was based on likelihood ratio test comparisons.

Multistage analysis. A multistage Markov model depicted the predicted probabilities of death at follow-up associated with being in a state of K ≤5.5 mEq/L versus K >5.5 mEq/L. Using the Multistage Markov model with continuous time, we determined the instantaneous transition hazards, and their respective 95% confidence intervals (CIs), among K-2 categories [11].

We set a two-sided $P < 0.05$ as the threshold for significance. Within Stata version 14.2 [Stata Statistical Software, Release 14 (2015); Stata Corp LP], the principal longitudinal analysis was performed with 'mestreg', a module that allows multilevel modelling to be combined with a parametric study of survival–time outcomes. For the estimation of the dynamic discrimination index and the Multistage Markov model longitudinal transitions analysis, we used the JM13 and msm 14 R-packages, respectively [R Development Core Team (2017): R: A language and environment for statistical computing, R Foundation for Statistical Computing, https://www.T-project.org].

RESULTS

Baseline characteristic of the patients

During median (IQR) follow-up period 17.3 (2.2–23.7, range 0–28.9) months, 172 episodes of acute hyperkalaemia (sK >6 mEq/L) were identified in 160 patients in the emergency room.

The baseline characteristics of the patients are summarized in Table 1. The mean ± SD age was 77 ± 12 years. About half of the patients (47%) were >80 years, 59% had non-dialysis CKD states (eGFR <60 mL/min/1.73 m^2) and 27.3% did not have renal dysfunction. In those patients with CKD, the aetiology was nephroangiosclerosis (28%), diabetic kidney disease (25%), interstitial disease (7%), glomerulonephritis (8%), polycystic kidney disease (3%) and other/unknown aetiology (29%). The mean ± SD of potassium in the emergency room was 6.6 ± 0.6 (IQR 6.2–6.9, range 6.1–9.2), with most of them with potassium levels between 6 and 7 mEq/L (76.7%). About one-quarter of episodes (23.3%) showed life-threatening hyperkalaemia (sK >7 mEq/L). The mean ± SD of potassium in the last measurement before the acute episode was 4.8 ± 0.8 mEq/L (IQR 4.2–5.4). A total of 125 patients (72.7%) were hospitalized.

Most of the patients showed one to four comorbidities (84.3%), and 7.5% had more than four comorbidities. The electronic record allows us to access electrocardiography (EKG) reports in 158 episodes (91.8%). We found EKG alterations in 107 (67.7%) episodes (Table 1); of these, 44.9% present at least one EKG alteration, mainly peaked T waves. Moreover, the 7, 8.9, 2.5, 1.9 and 2.5% showed 2, 3, 4, 5 or 6 EKG alterations, respectively. Thirty-six percent were on chronic treatment with RAASi, 28.5% received mineral receptor antagonists (MRAs) and 53.4% both treatments (Table 1). Only seven patients (4.1%) were receiving potassium-binding resins before the episode of acute hyperkalaemia (three of them were on haemodialysis treatment). Treatment with RAASi, loop-diuretics and potassium-sparing diuretics were more frequent in patients with better renal function. Table 1 shows the treatments received in the emergency department. Only 10.5% of patients

Table 1. Clinical characteristics, laboratory data and acute treatments in the patients of the study

Characteristics	Value
Sex (%)	96 (60.0)
Male	64 (40.0)
Female	
Age (mean ± SD), years	77 ± 12
Age by group (%), years	28 (17.5)
<65	24 (15.0)
65–74	32 (20.0)
75–80	76 (47.5)
>80	
Laboratory parameters, mean ± SD (range)	6.6 ± 0.6 (6.1–9.2)
Potassium, mEq/L	135 ± 6 (110–159)
Sodium, mEq/L	3.8 ± 3.3 (0.7–21)
Creatinine, mg/dL	23 ± 16 (2–84)
GFR, mL/min/1.73 m^2	20.9 ± 6 (6–34)
Bicarbonate, mEq/L	
Potassium at severe hyperkalaemia episode, %	124 (77.5)
6–7 mEq/L	36 (22.5)
>7 mEq/L	
Dehydration status, %	42 (26.3)
Diabetes mellitus, %	91 (56.9)
CKD stage, %	46 (28.7)
No CKD (eGFR ≥60 mL/min/1.73 m^2)	56 (35.0)
CKD Stage 3 (eGFR 30–59 mL/min/1.73 m^2)	29 (18.1)
CKD Stage 4 (eGFR 15–29 mL/min/1.73 m^2)	10 (6.3)
Non-dialysis CKD Stage 5 (eGFR <15 mL/min/1.73 m^2)	19 (11.9)
CKD Stage 5 on dialysis	
Systolic blood pressure at the hyperkalaemia, mean ± SD, mmHg	139 ± 36
Diastolic blood pressure at the hyperkalaemia, mean ± SD, mmHg	70 ± 16
Comorbidities, %	
Diabetes mellitus	91 (56.9)
Hypertension	91 (56.9)
Congestive HF	56 (35)
Coronary heart disease	58 (36.3)
Cerebrovascular disease	20 (12.5)
Peripheral vascular disease	29 (18.1)
Chronic liver disease	14 (8.8)
EKG changes pertinent to hyperkalaemia (%)	67.7
Peaked T waves	71 (41.3)
Shortened QT interval	20 (11.6)
Loss of P wave	22 (12.8)
Prolonged PR interval	18 (10.5)
Atrioventricular/bundle branch block	50 (29.1)
Prolonged QRS complex	8 (4.7)
Ventricular tachycardia	1 (0.6)
Treatments before acute hyperkalaemia episode, %	
Loop diuretics	80 (50)
RAAS blockade (ACEi or ARB II)	68 (42.5)
Beta blockers	59 (36.9)
MRAs	45 (28.1)
ARB II	38 (23.8)
ACEis	35 (21.9)
RAAS blockade + MRA	20 (12.5)
RAAS blockade or MRA	93 (58.1)
Thiazides	22 (13.8)
Oral binding resins	6 (3.8)
Non-steroidal anti-inflammatory drugs	4 (2.5)
Treatments for hyperkalaemia received in the emergency room, %	
Dextrose fluid + insulin	43

Continued

Table 1. Continued

Characteristics	Value
Loop diuretics IV	28.5
Inhaled salbutamol	26.7
Calcium polystyrene sulphonate oral	25
Sodium bicarbonate IV	25
Calcium gluconate IV	16.32
Haemodialysis	10.5
Calcium polystyrene sulphonate enema	8.1
Modifications in the treatments at hospital discharge, %)	
Dose reduction in ACEi/ARB II	7.6
Dose reduction in MRA	2.9
Discontinuation of ACEi/ARB II	19.8
Discontinuation of diuretics	12.1
Discontinuation of MRA	16.9
Adding oral binding resins	12.8
Adding bicarbonate	9.9
Education on low potassium diet	16.3

ACEi, angiotensin-converting enzyme inhibitor; ARB II, angiotensin II receptor blocker; ARB II, angiotensin II receptor blocker; QRS, electrocardiographic waves (Q wave, R wave and S wave).

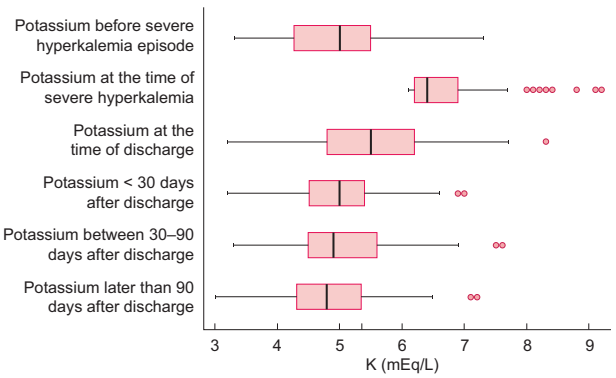


FIGURE 2: Observed trajectory of serum potassium along with the visits. Values are expressed as median (25–75 percentiles). Adjacent lines represent upper and lower adjacent values.

received dialysis as a treatment. Among them, 61% were patients with CKD Stage 5 already on dialysis.

The modifications in the treatments at hospital discharge are shown in Table 1, the most frequent being the discontinuation of RAASi or MRA (19.8 and 16.9%, respectively).

Potassium kinetics during the follow-up

Figure 1 shows the categories of serum potassium in the six time points analysed in the study. The rates of patients with hyperkalaemia were higher in the emergency room and decreased throughout successive visits.

Of the 786 potassium measurements in the study at the different six points, 451 (57.3%) were <5.5 mEq/L, 80 (10.2%) between 5.5 and 6 mEq/L, 206 (26.2%) between 6 and 7 mEq/L and 50 (6.4%) >7 mEq/L.

Recurrences of hyperkalaemia (K >5.5 mEq/L) were detected in 39.5% of the patients who were monitored during follow-up. In 16%, only one recurrence was detected, 13.6% had two recurrences and 9.9% had three recurrences during follow-up. Recurrences occurred in 22.8% within the first month after

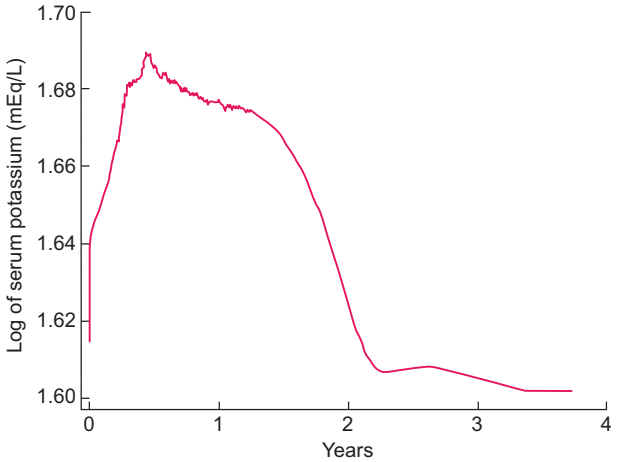


FIGURE 3: Trajectory of potassium measurements (transformed by its logarithm) along the entire follow-up period. The adjusted association with time (years) was highly significant (overall P-value for the trajectory <0.0001). The values were lower in the initial visit and corresponded to a patient's evaluation before the admission for hyperkalaemia. The zenith of potassium was found during the acute episode in the emergency room. Afterwards, we found a progressive and significant decrease in the potassium levels during follow-up.

discharge, in 26.3% between 30 and 90 days after discharge and in 17.2% later than 90 days after discharge. Figure 2 shows the observed trajectory of serum potassium along the visits, detecting a high number of measurements of hyperkalaemia after discharge making recurrence of hyperkalaemia as a frequent problem.

Figure 3 shows the trajectory of potassium measurements (transformed by its logarithm) along the entire follow-up period. The adjusted association with time (years) was highly significant (overall P-value for the trajectory <0.0001). The values were lower in the initial visit corresponded to a patient evaluation before the admission for hyperkalaemia (coinciding with the peak around 1 year). The zenith of potassium was found during the acute episode in the emergency room. Afterwards, we found a progressive and significant decrease in the potassium levels during follow-up.

Potassium serum levels and risk of mortality

After a median (IQR) follow-up of 17.3 (2.2–23.7) months, 68 patients had died (42.5%). Most of them died due to cardiovascular events (47.2%) or infection (23.5%). Other causes of mortality found were: liver-gastrointestinal (11.8%), malignancies (16.2) and other (1.5%). The mean survival was 18 ± 16 months [95% confidence interval (CI) 16–20 months]. Survival at 3, 6, 12, 18 and 24 months was 73, 66, 63, 60 and 55%, respectively.

Baseline characteristics and risk of mortality. The variables included in the multivariate analysis for survival were the predictors significantly associated with death in the univariate analysis: age, eGFR, serum levels of potassium and sodium, previous nephrology assessment and chronic treatment (including RAAS blockers and calcium antagonists) before the episode of hyperkalaemia, diastolic blood pressure, presence of

Table 2. Multivariate analysis of factors associated with high mortality

Factor	HR (95% CI)	P-value
Age, years	1.031 (1.001–1.061)	0.04
Serum sodium, mEq/L	0.921 (0.880–0.964)	<0.001
RAASi (previous treatment)	0.329 (0.174–0.621)	0.001
Ventricular tachycardia	11.955 (1.055–135.496)	0.045
Analytical follow-up after discharge	0.247 (0.133–0.458)	<0.001

dehydration, ventricular tachycardia, treatment of acute hyperkalaemia with resins and need for hospitalization and analytical follow-up and chronic treatment with resins and RAAS blockers after hyperkalaemia episode.

Multivariate Cox proportional hazards model of death showed that age, low serum sodium levels, absence of RAASi treatment before the episode of acute hyperkalaemia, the presence of ventricular tachycardia and lack of routine laboratory follow-up after discharge were independent factors related to increased mortality risk (Table 2). For each year of age the risk of mortality increases by 3%, RAASi treatment is associated with a 67% reduction in mortality risk, the presence of ventricular tachycardia was associated with a 12-fold increase in mortality risk, the performance of analytics at follow-up is associated with a 75% reduction in the risk of mortality and each decrease of 1 mEq/L in serum sodium levels was related to an increase in the risk of death by 0.08%.

Need for hospitalization during the acute phase of acute hyperkalaemia was borderline associated with higher risk of death [hazard ratio (HR) = 2.87; 95% CI 0.994–8.296; P = 0.051], whereas the potassium levels during the acute phase was not related with the risk of death (HR = 1.25; 95% CI 0.74–2.11; P = 0.394). Similarly, gender, eGFR at the time of acute hyperkalaemia, presence of other comorbidities (HF, ischaemic heart disease, peripheral vascular disease and liver disease), previous chronic treatments (except RAASi), treatment of acute hyperkalaemia and treatments after the episode of hyperkalaemia did not predict mortality.

Longitudinal potassium and risk of mortality. Figure 4 shows the cumulative and independent effect of all potassium measurements on all-cause mortality using joint modelling of survival and longitudinal data. In this analysis, the potassium trajectories were significantly associated (overall P-value for the trajectory = 0.0015) with an increased risk of all-cause mortality in a J-shape pattern. The nadir of risk was found within the range of normokalaemia, and a progressively increased risk was found at higher values (Figure 4).

The effect of transitioning from hyperkalaemia to normokalaemia (K >5.5 mEq/L to K ≤5.5 mEq/L) after the acute episode was significant and strongly associated with the risk of mortality. Multistage Markov model showed that patients with K >5.5 mEq/L since the admission for hyperkalaemia displayed a 7.73-fold (4.03–14.84; P < 0.0001) increased risk compared with those in the category of K ≤5.5 mEq/L. The table within Figure 4 shows the predicted probability of death (estimate, 95% CI) according to the time elapsed (years) since the admission for hyperkalaemia [at 3 months ($t = 0.25$), 6 months ($t = 0.5$), 1 year ($t = 1$), 2 years ($t = 2$) and 3 years ($t = 3$)], comparing the transition from K ≤5.5 mEq/L to K >5 mEq/L. The higher excess of risk from transitioning from K ≤5.5 mEq/L to K >5 mEq/L was found when occurred during the first 6-month of follow-up (Figure 5).

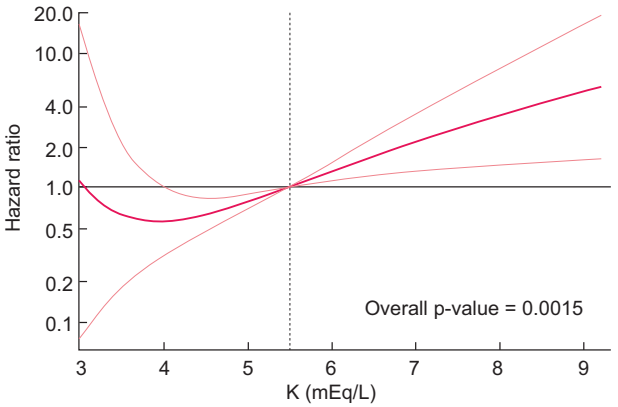


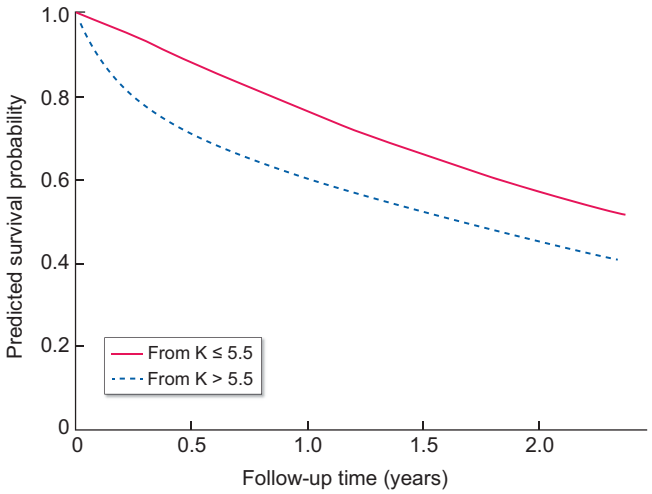
FIGURE 4: Cumulative and independent effect of all potassium measurements on all-cause mortality. Expressed as HR (per 1-U increase) and using a cut-point of 5.5 mEq/L as reference. Note: model adjusted by age, gender, creatinine, MRA use, RAAS blockade, use of calcium channel blockers, use of non-steroidal anti-inflammatory drugs and prior history of hypertension and diabetes.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the long-term prognostic implications of the kinetics of potassium after an episode of acute hyperkalaemia. The main findings of the study showed that previous potassium and potassium levels during the episode of acute severe hyperkalaemia were not predictors of mortality. Conversely, the post-discharge longitudinal trajectories of potassium were able to predict all-cause mortality. The risk-gradient trajectory was independently associated with mortality in a nonlinear shape.

Our analysis revealed that transitioning from normal to higher potassium levels during the post-discharge follow-up was strongly associated with the risk of mortality, indicating a higher risk when moving from lower to higher values. Indeed, patients who persisted with hyperkalaemia or transitioned from normokalaemia to hyperkalaemia exhibited a dramatic increase in mortality risk.

Previous studies have consistently shown in different clinical scenarios, including CKD, HF and diabetes mellitus, that potassium levels are associated with a higher risk of mortality in a U-shaped pattern [12, 13]. Prior studies have assessed the clinical determinants and prognosis in patients with severe hyperkalaemia in emergency departments [14–16]. Pfortmüller *et al.* performed a retrospective evaluation of 29 250 potassium determinations over a 24-month period, detecting hyperkalaemia (limit of normokalaemia not defined) in 2585 (8.8%) patients [17]. They reported that 88 patients (0.3%) had severe hyperkalaemia (>5.9 mEq/L). The analysis in our database detected 1444 cases of hyperkalaemia in all determinations (K ≥5 mEq/L); 1.1% of them with sK >6 mEq/L, which is three times higher than those shown by the authors cited above. Likewise, other



Time point			Death
t = 0.25	K ≤ 5.5	0.05587	(0.04299–0.07606)
t = 0.25	K >5.5	0.20468	(0.14936–0.27909)
t = 0.5	K ≤ 5.5	0.11884	(0.09376–0.15818)
t = 0.5	K >5.5	0.29135	(0.22823–0.37513)
t = 1	K ≤ 5.5	0.23731	(0.19024–0.30866)
t = 1	K >5.5	0.39553	(0.32458–0.47482)
t = 2	K ≤ 5.5	0.42986	(0.35984–0.52273)
t = 2	K >5.5	0.54856	(0.47233–0.64217)
t = 3	K ≤ 5.5	0.57383	(0.48758–0.68224)
t = 3	K >5.5	0.66256	(0.58033–0.75293)

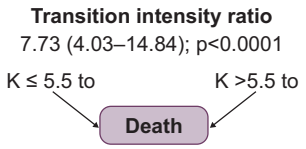


FIGURE 5: Multistate Markov model depicting the predicted probabilities of death at follow-up associated with being in a state of K ≤5.5 mEq/L versus K >5.5 mEq/L (all-cause mortality). The table within the figure shows the predicted probability of death (estimate, 95% CI) according to the time elapsed (years) since the admission for hyperkalaemia.

investigations reported similar results [15, 16]. They also detected a high prevalence of CKD, as well as increased use of RAAS blockers. Moreover, they describe high mortality rates associated with potassium levels in the emergency room in a 'U-shaped' mortality curve [15]. In our study, we confirm the prognostic value of serial assessment of potassium in a non-well and life-threatening condition such as acute severe hyperkalaemia. Conversely to other studies, and expected, only higher levels of potassium were associated with higher risk of complications.

The present findings provide novel insights into the natural history and current management of patients with acute hyperkalaemia. First, there is a typical clinical profile of patients with acute severe hyperkalaemia. This profile included patients with a high number of comorbidities such as CKD, diabetes mellitus, HF or coronary heart disease, all of which affected more than a third of the patients. However, and surprisingly, a quarter of our patients did not have CKD, making hyperkalaemia an unpredictable life-threatening complication (most of the cases due to the use of RAASi or the appearance of hydrosaline depletion). Secondly, it should also be noticed that up to one-third of patients were discharged from the emergency room with serum potassium not completely corrected to normokalaemia levels or without evidence of it. This issue deserves further evaluation but seems to reflect an improper management. Thirdly, this study shows that recurrent hyperkalaemia is a frequent finding, especially during the first 6 months after the discharge. Mild hyperkalaemia (sK = 5.6–6 mEq/L) was detected in between 12.5% and 15.5%, and severe hyperkalaemia (sK >6 mEq/L) was detected in between 4.8% and 10.4% of the patients in the same period. Since hyperkalaemia-related hospitalizations are associated with significantly higher readmission rates and higher costs [9], future studies are warranted to evaluate predictors of hyperkalaemia recurrence and hyperkalaemia-related readmissions. Fourthly, higher values of potassium during the longitudinal trajectory were importantly associated with a higher risk of death.

Concerning the EKG abnormalities and despite the limitations of the study, we can add that a previous study that included 188 episodes of severe hyperkalaemia (sK ≥6.5 mEq/L) using a very robust methodology for EKG abnormalities, showed that 71% of the episodes had at least one EKG abnormality suggestive of hyperkalaemia, with the two most common findings being QRS (electrocardiographic waves (Q wave, R wave and S wave)) prolongation (43%) and peaked T waves (30%) [18]. These data are similar to those shown in our study.

The management of an acute episode of hyperkalaemia is well-established. However, the evidence endorsing the frequency of monitoring and the optimal medical treatment avoiding the recurrences and the occurrence of adverse clinical outcomes remains not well defined. Recently, new approaches have been made in a summary from the Kidney Disease: Improving Global Outcomes conference about the handling of acute hyperkalaemia in the emergency department, reinforcing the idea that frequent re-evaluation of serum potassium concentrations is essential in order to follow the treatment success and screen for a rebound rise of serum potassium after an episode of severe hyperkalaemia and during the follow-up [19].

Classically, most of the approaches have focused on diet restriction and down-titrating or discontinuing RAASi [20]. However, these approaches have shown limited efficacy. First, down titrating or withdrawing RAASi may also have an important deleterious effect in the prognostic of patients with CKD and chronic heart disease (CHD) [20, 21]. In our study, 7.6 and 2.9% of patients received reduced doses of renin–angiotensin system inhibitor (RASi) and MRA after discharge, respectively. In 19.8 and 16.9%, the RASi and MRA doses were discontinued, respectively. Both actions result in a worse prognosis for the patients. Secondly, traditional dietary recommendations to renal patients limit the intake of fruits and vegetables because of their high potassium content.

In addition, several studies have demonstrated that a diet high in potassium may benefit kidney and cardiovascular outcomes. In an analysis of 13 917 participants in the National

Health and Nutrition Examination Survey, the participants in the lowest quartile of potassium intake, as assessed by 24-h dietary recall, had 44% increased odds of CKD [22]. A *post hoc* analysis of the ONTARGET and TRANSCEND trials showed that urinary potassium, but not sodium, excretion predicted clinically important renal outcomes [23–25]. The association between higher potassium intake and improved renal outcomes may be mediated by an increased in renal kallikrein–kinin system promoting vasodilation, reduction of vascular resistance and changes in blood pressure, as well as other physiological mechanisms such as the antioxidant and anti-inflammatory properties of a diet high in fruits and vegetables [26]. Thus, this evidence does not support the use of potassium-restricted diet for the prevention of hyperkalaemic events [27].

Classical potassium binding resins (sodium/calcium polystyrene sulphonate) have been related to poor tolerance, adherence and a high rate of side effects in patients with CKD [28]. On the other hand, we can find no convincing evidence that sodium polystyrene sulphonate increases faecal potassium losses in experimental animals or humans. It would be wise to exhaust other alternatives for chronic management of hyperkalaemia [29–31]. Accordingly, all of this may explain the limited use of sodium/calcium polysterene sulphonate in the treatment of acute and chronic hyperkalaemia. It is likely that this problem will be solved in the near future with the introduction of new potassium binders [29–31].

Along this line, two recent alternative potassium-binding agents—patiromer calcium sorbitex and sodium zirconium cyclosilicate (SZC) [32]—have shown to be effective and safe in treating hyperkalaemia and have been approved by US Food and Drug Administration and the European Medicines Agency for this indication. Patiromer is a calcium-based, non-absorbed cation binding polymer that binds potassium in the gastrointestinal (GI) tract in exchange for calcium. Its benefit has been demonstrated in the OPAL-HK trial, that included CKD on a stable dose of RAASi with persistent hyperkalaemia (5.1–6.5 mEq/L) [33]. Long-term efficacy of patiromer in RAASi-treated CKD patients was demonstrated in the AMETHYST-DN trial [34], which included Type 2 diabetics with hypertension, albuminuria, CKD and hyperkalaemia (sK >5.0 mEq/L). In patients treated with MRA, patiromer achieves a significantly higher percentage of patients remaining on spironolactone when compared with placebo [30].

SZC is a selective inorganic cation exchanger designed to selectively bind to potassium throughout the GI tract in exchange for Na and H, thereby increasing faecal potassium excretion. Its efficacy treating hyperkalaemia, including in patients with CKD, has been demonstrated in Phase 3 clinical trials. In the HARMONIZE trial [29], 258 ambulatory patients with persistent hyperkalaemia (sK ≥5.1 mEq/L), were treated with SZC in an open-label fashion and thereafter a randomized phase trial. In the open-label phase, normokalaemia was achieved in 84 and 98% at 24 and 48 h, respectively, with median time to normalize of 2.2 h. In the randomized phase of the trial, 46% of placebo patients maintained normokalaemia compared with 80–94% across the three doses of SZC. Additional evidence of efficacy in patients with moderate hyperkalaemia (K = 5.0–6.5 mEq/L) was demonstrated in a separate Phase 3 trial among 753 patients, including 75% with eGFR <60 mL/min/1.73 m^2 with significant benefit potassium levels in the short-term [35]. A subsequent 12-month long-term single-arm study demonstrate that SCZ maintains normokalaemia without substantial RAASi changes during the period of the study [36]. SCZ has also been shown to be safe and effective for treating hyperkalaemia in haemodialysis patients [14, 15].

Very recently, the ENERGIZE trial performed in 70 patients (hyperkalaemia sK >5.8 mEq/L) from the emergency department that were randomized to SZC or placebo have demonstrated that SZC with insulin and glucose may provide an incremental benefit in the emergency treatment of hyperkalaemia over insulin and glucose alone [37]. These new treatments for hyperkalaemia appear to be effective and well tolerated. However, it remains to be defined whether they are associated with improved outcomes, especially mortality.

In agreement with the current findings, we recommend a close clinical and potassium monitoring after an episode of acute hyperkalaemia. In addition, timely, appropriate and well-tolerated treatments after discharge from a hyperkalaemia-related hospitalization should be strongly considered. This may help to reduce the hospitalizations, economic burden and risk of mortality. Further studies are warranted for predicting the factors associated with the risk of recurrence of severe hyperkalaemia and its clinical implications.

Despite providing novel aspects of acute severe hyperkalaemia not yet studied, our study has several limitations. Due to the retrospective character of this investigation, there is missing relevant clinical information that could not be evaluated. Another aspect is that this is a single-centre study and may not be representative of all centres. However, this problem is compensated thanks to the exhaustive data record that the electronic medical record supposes. In addition, the strict criteria for considering absence of haemolysis is a strength of the study (patients with any degree of haemolysis were excluded). Similarly, the same occurs in other studies [14, 15], although they did not reflect whether it included minimal haemolysis of the blood samples.

In conclusion, potassium levels prior to a severe hyperkalaemic event do not predict mortality. Conversely, following an episode of acute severe hyperkalaemia, serial kinetic of potassium trajectories predict the risk of death. Further evidence is needed to confirm these findings and clarify the optimal long-term management of these patients.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

This is an investigator-initiated study, sponsored by the Institute of Clinical Research of Valencia and Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana. The study was supported by an unrestricted grant from AstraZeneca (ESR-17-13221).

CONFLICT OF INTEREST STATEMENT

The authors report no financial relationships or conflicts of interest regarding the content of this investigation.

REFERENCES

1. Acker CG, Johnson JP, Palevsky PM *et al.* Hyperkalemia in hospitalized patients: causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med* 1998; 158: 917–924
2. Hoskote SS, Joshi SR, Ghosh AK. Disorders of potassium homeostasis: pathophysiology and management. *J Assoc Physicians India* 2008; 56: 685–693
3. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004; 43: 155–161
4. Desai NR, Reed P, Alvarez PJ *et al.* The economic implications of hyperkalemia in a medicaid managed care population. *Am Health Drug Benefits* 2019; 12: 352–361
5. Cooper LB, Benson L, Mentz RJ *et al.* Association between potassium level and outcomes in heart failure with reduced ejection fraction: a cohort study from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2020; 22: 1390–1398
6. Lunney M, Ruospo M, Natale P *et al.* Pharmacological interventions for heart failure in people with chronic kidney disease. *Cochrane Database Syst Rev* 2020; 2: CD012466
7. Qiao Y, Shin JI, Chen TK *et al.* Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med* 2020; 180: 718
8. Fitch K, Woolley JM, Engel T *et al.* The clinical and economic burden of hyperkalemia on medicare and commercial payers. *Am Health Drug Benefits* 2017; 10: 202–209
9. Betts KA, Woolley JM, Mu F *et al.* Post-discharge healthcare costs and readmission in patients with hyperkalemia-related hospitalizations. *Kidney Int Rep* 2020; 5: 1280–1290
10. Sonntag O. Haemolysis as an interference factor in clinical chemistry. *J Clin Chem Clin Biochem* 1986; 2: 127–139
11. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Soft* 2011; 38: 1–28
12. Núñez J, Bayés-Genís A, Zannad F *et al.* Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation* 2018; 137: 1320–1330
13. Collins AJ, Pitt B, Reaven N *et al.* Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 2017; 46: 213–221
14. An JN, Lee JP, Jeon HJ *et al.* Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care* 2012; 16: R225
15. Singer AJ, Thode HC, Peacock WF. A retrospective study of emergency department potassium disturbances: severity, treatment, and outcomes. *Clin Exp Emerg Med* 2017; 4: 73–79
16. Aggarwal S, Topaloglu H, Kumar S. Trends in emergency room visits due to hyperkalemia in the United States. *Value Health* 2015; 18: A386
17. Pfortmüller CA, Leichtle AB, Fiedler GM *et al.* Hyperkalemia in the emergency department: etiology, symptoms and outcome of a life threatening electrolyte disorder. *Eur J Int Med* 2013; 24: e59–e60
18. Durfey N, Lehnhof B, Bergeson A *et al.* Severe hyperkalemia: can the electrocardiogram risk stratify for short-term adverse events? *West J Emerg Med* 2017; 18: 963–971
19. Lindner G, Burdmann EA, Clase CM *et al.* Acute hyperkalemia in the emergency department: a summary from a Kidney Disease: Improving Global Outcomes conference. *Eur J Emerg Med* 2020; 27: 329–337
20. Epstein M, Lifschitz MD. The unappreciated role of extrarenal and gut sensors in modulating renal potassium handling: implications for diagnosis of dyskalemias and interpreting clinical trials. *Kidney Int Rep* 2016; 1: 43–56
21. Sharma S, McFann K, Chonchol M *et al.* Association between dietary sodium and potassium intake with chronic kidney disease in US adults: a cross-sectional study. *Am J Nephrol* 2013; 37: 526–533
22. Smyth A, Dunkler D, Gao P *et al.* The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. *Kidney Int* 2014; 86: 1205–1212
23. Lin HB, Young DB, Smith MJ. Stimulation of renin release by hyperkalemia in the nonfiltering kidney. *Am J Physiol Renal Physiol* 1991; 260: F170–F176
24. Jablonski KL, Kendrick JB. Renal outcomes and dietary potassium: the overshadowed electrolyte? *Kidney Int* 2014; 86: 1077–1078
25. Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. *J Hum Hypertens* 2003; 17: 471–480
26. Cases A, Cigarrán-Guldrís S, Mas S *et al.* Vegetable-based diets for chronic kidney disease? It is time to reconsider. *Nutrients* 2019; 11: 1263
27. Sterns RH, Rojas M, Bernstein P *et al.* Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective. *J Am Soc Nephrol* 2010; 21: 733–735
28. Laureati P, Xu Y, Trevisan M *et al.* Initiation of sodium polystyrene sulphonate and the risk of gastrointestinal adverse events in advanced chronic kidney disease: a nationwide study. *Nephrol Dial Transplant* 2020; 35: 1518–1526
29. Packham DK, Rasmussen HS, Lavin PT *et al.* Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015; 372: 222–231
30. Kosiborod M, Rasmussen HS, Lavin P *et al.* Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA* 2014; 312: 2223–2233
31. Weir MR, Bakris GL, Bushinsky DA *et al.* Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; 372: 211–221
32. Pitt B, Bakris GL, Bushinsky DA *et al.* Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail* 2015; 17: 1057–1065
33. Bakris GL, Pitt B, Weir MR *et al.* Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease. *JAMA* 2015; 314: 151
34. Agarwal R, Rossignol P, Romero A *et al.* Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019; 394: 1540–1550
35. Spinowitz BS, Fishbane S, Pergola PE *et al.* Sodium zirconium cyclosilicate among individuals with hyperkalemia. *Clin J Am Soc Nephrol* 2019; 14: 798–809
36. Fishbane S, Ford M, Fukagawa M *et al.* A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol* 2019; 30: 1723–1733
37. Peacock WF, Rafique Z, Vishnevskiy K *et al.* Emergency potassium normalization treatment including sodium zirconium cyclosilicate: a phase II, randomized, double-blind, placebo-controlled study (ENERGIZE). *Acad Emerg Med* 2020; 27: 475–486

Received: 23.7.2020; Editorial decision: 16.12.2020