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ORIGINAL ARTICLE

Serum potassium variability is associated with increased mortality in a large cohort of hospitalized patients

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ABSTRACT

Background. Few studies have examined that the role of serum potassium concentration [K^+] variability on clinical outcomes is still poorly investigated. The aim of our study was to analyse the association between serum ([K^+]) disorders, with focus on [K^+] variability and mortality in a large, unselected cohort of hospitalized patients.

Methods. We performed a retrospective observational cohort study on the inpatient population admitted to Fondazione Policlinico Universitario A. Gemelli IRCCS between 1 January 2010 and 31 December 2014 with inclusion of adult patients with ≥2 [K^+] measurements. The outcome of interest was in-hospital mortality. The exposures of interest were [K^+] fluctuations, hypohyperkalaemia and mixed dyskalaemia during hospital stay. [K^+] variability was evaluated using the coefficient of variation (CV). Logistic regression models were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the exposures of interest and in-hospital death.

Results. Overall, 64 507 patients met our inclusion criteria. During a median follow-up of 8 days, 965 patients (1.5%) died. Multivariable adjusted logistic models suggested a higher risk for death in patients in the third (OR = 1.45, 95% CI 1.13–1.88; P = 0.003) and fourth (OR = 3.30, 95% CI 2.64–4.16; P < 0.001) highest quartiles of [K^+] CV compared with those in the lowest quartile with a significant linear trend across quartiles (P-trend <0.001). Results did not change after restricting the analyses to patients with normokalaemia (NK). All [K^+] disorders were independently associated with an increased risk of in-hospital death compared with NK.

Conclusions. High [K^+] variability is an independent risk factor of in-hospital mortality, even within the normal [K^+] range.

Keywords: cohort studies, electrolyte disorders, hypokalaemia, hyperkalaemia, mortality

INTRODUCTION

Potassium is the most important cation of intracellular space [1]. Serum potassium concentrations ([K^+]) are tightly regulated to allow fluctuations in a 'normal' range [2]. The Na^+/K^+-ATPase pump is the main protein involved in keeping the potassium gradient between intracellular and extracellular space. Disorders in such a balance can modify the electrophysiological properties of the resting membrane potential with deleterious effects on the human body and its physiological processes [3].

Both hypokalaemia (HoK) and hyperkalaemia (HerK) have been associated with lethal arrhythmias and cardiac dysfunction with a significant increase in mortality risk in hospitalized populations [4]. Different diseases and medications are known to induce alterations in [K^+] levels [5]. In particular, the kidney plays a key role in [K^+] homoeostasis, therefore the association between kidney diseases and [K^+] disorders [1, 6] is not surprising.

Although several studies have analysed the relationship between [K^+] disorders and mortality in the hospital setting [4, 5, 7–11], there are few data investigating the association between [K^+] fluctuations or variability and clinical outcomes [9–11]. Moreover, most studies have been focusing on a specific hospital population [intensive care unit (ICU) patients or patients with heart disease].

To provide new insights and more generalizability in such an important topic, in our study, we aimed to comprehensively investigate the association between [K^+] disorders, including [K^+] variability and mortality, in a large unselected cohort of hospitalized patients.

MATERIALS AND METHODS

Study population

We performed a retrospective observational study on the inpatient population admitted to Fondazione Policlinico Universitario A. Gemelli IRCCS, a tertiary level hospital serving 1 million people in Rome, between 1 January 2010 and 31 December 2014.

KEY LEARNING POINTS

What is already known about this subject?

- the relationship between serum potassium concentration ($[K^+]$) disorders and clinical outcomes has been widely explored in the scientific literature; and
- recently, an increasing number of studies have re-analysed and explored the role of electrolytes imbalance on patients' outcomes with increasing attention placed on electrolytes fluctuations.

What this study adds?

- in this observational retrospective cohort study, we demonstrated a strong relationship between $[K^+]$ variability and in-hospital mortality; and
- for the first time, we demonstrated how $[K^+]$ variability is an important predictor of in-hospital death, even in the normal range, independently of the presence of hypo- or hyperkalaemia.

What impact this may have on practice or policy?

- although a precise definition of hypo- or hyperkalaemia is especially useful in clinical practice identifying patients with increased hospital risk, at the same time, it is important to underline that physicians should also pay attention to excessive electrolytes variability during hospital stay.

We included only adult patients (≥18 years), with at least two $[K^+]$ measurements over two different days during hospital stay and at least one serum creatinine (sCr) determination at hospital entry. For patients with multiple hospital admissions, we considered only the first as the index hospitalization.

The ethics committee of Fondazione Policlinico Universitario A. Gemelli IRCCS approved the research protocol (Prot. number 34327/18 ID 2210).

Data collection

Data were obtained from the hospital digital medical records. For each patient, we collected the following demographic, clinical and laboratory data: age, sex, $[K^+]$, sCr, primary and secondary International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes at hospital discharge and vital status at hospital discharge. The same flame photometer was used for $[K^+]$ measurements during the whole study period [normal $[K^+]$ laboratory range 3.0–5.0 mmol/L; analytical coefficient of variation (CV) <2.3% (range 1.3–1.7%)]. Extreme $[K^+]$ levels (<2 mmol/L and $[K^+]$ >7.5 mmol/L), that could introduce distortion in the analyses, were removed.

Definitions

The CV [12], defined as the ratio between the standard deviation (SD) and the mean of all $[K^+]$ values preceding hospital discharge or death, was used as the measure of $[K^+]$ variability. Patients were categorized according to all $[K^+]$ values recorded during hospital stay in the following groups: HoK (any $[K^+]$ value <3.0 mmol/L), HerK (any $[K^+]$ value >5.0 mmol/L), normokalaemia (NK; all $[K^+]$ values ≥3.0 mmol/L and ≤5.0 mmol/L) and mixed dyskalaemia (MD; lowest $[K^+]$ value <3.0 mmol/L and highest $[K^+]$ >5.0 mmol/L).

The first sCr measurement during hospital stay was considered as baseline. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation [13]. Mortality data were obtained by checking vital status at hospital discharge.

Comorbid conditions (cardiovascular diseases, malignancies, gastrointestinal diseases, genitourinary disorders, endocrine/metabolic disorders, infectious and respiratory diseases) were identified using ICD-9-CM codes. The Charlson/Deyo comorbidity index score [14] was calculated for each hospital admission using primary and secondary diagnosis ICD-9-CM codes at hospital discharge.

End-stage kidney disease (ESKD) was identified according to: (i) ICD-9-CM codes using procedure codes for arteriovenous fistula creation or revision (39.27, 39.42, 39.43 and 39.93), history of ESKD requiring either kidney transplant (identified through discharge diagnosis ICD-9 V42.0) or maintenance dialysis (ICD-9 V45.1, V45.11, V45.12, V56, V56.0 and V56.8); (ii) any of the following procedure codes: 39.95 (haemodialysis), V45.1 (renal dialysis status), V56.0 (extracorporeal dialysis) or V56.1 (fitting and adjustment of extracorporeal dialysis catheter); (iii) the initiation of dialysis in a patient with no known history of prior dialysis (ICD-9p 39.95–54.98).

Outcome and exposures

The main outcome was in-hospital mortality. Exposures of interest were $[K^+]$ variability and $[K^+]$ disorders (HoK, HerK and MD).

Statistical analysis

Quantitative variables were described using mean and SD if normally distributed or median and interquartile range (IQR) for skewed distributions. Categorical variables were described using frequencies and percentages. Normality of variable distributions was assessed with the Shapiro–Wilk test and by visual inspection of Q–Q plots and histograms.

Logistic regression models, unadjusted and adjusted for all covariates, were fitted to obtain odds ratios (ORs) and 95% confidence intervals (CIs) of the association between the quartiles of [K^+] CV and in-hospital mortality. Two models were built: Model 1 estimated unadjusted ORs; Model 2 estimated ORs adjusted for age, sex, Charlson/Deyo score, comorbidities, [K^+] value at hospital admission and baseline eGFR.

P-value for trend was calculated by treating quartiles as continuous variables in each model. A sensitivity analysis restricted to patients who did not show any [K^+] disorder at baseline was performed.

In order to evaluate the effect of number of [K^+] measurements and differences in observation time between the first and last [K^+] measurement on the association between [K^+] variability and the outcome of interest, analyses were stratified according to median values of those variables and interaction analyses between subgroups (reported as dichotomous variables) and [K^+] variability were performed. Furthermore, since ESKD patients on dialysis are a different patient population that have significant abrupt change in [K^+] before and after dialysis, a sensitivity analysis restricted on patients without ESKD was performed.

Subsequently, the relationship between [K^+] disorders (HoK, HerK and MD) and in-hospital mortality was evaluated with similar logistic regression models with the same covariates.

For analysis and data calculation, we used the R software (version 3.4.4, R Foundation for Statistical Computing Platform). A two-tailed $P < 0.05$ was considered as statistically significant.

RESULTS

Overall, 64 507 patients were included in the final analysis. Baseline characteristics according to quartiles of [K^+] variability are shown in Table 1. Patients with higher [K^+] variability were older, and had lower baseline eGFR and higher prevalence of comorbidities.

During a median (IQR) follow-up of 8 (0–456) days, 965 patients (1.5%) died. Results of the association between [K^+] variability and in-hospital death are reported in Table 2 and Figure 1. Logistic regression models suggested that a higher risk for death across increasing quartiles of [K^+] variability (P-value for trend <0.001). After full adjustment, patients in the highest quartile of [K^+] variability had an OR for death of 3.30 (95% CI 2.64–4.16) compared with those in the lowest quartile.

Results did not change after restricting the analyses to NK patients, i.e. those without any [K^+] disorder during hospital stay (Supplementary data, Table S1).

In our study cohort, [K^+] disorders were observed in 11.8% of the cohort ($n = 7600$). Specifically, 3047 (4.7%) patients had HoK, 4228 (6.6%) had HerK and 325 (0.5%) had MD. As expected, higher comorbidity index scores were observed in patients with any [K^+] disorder compared with NK (Supplementary data, Table S2). The association did not change after stratifying by number of [K^+] measurements (Supplementary data, Table S3; P-value for interaction = 0.834) and by observation time between [K^+] measurements (Supplementary data, Table S4; P-value for interaction = 0.158). Restricted analysis after removal of 264 patients with ESKD confirmed our findings (Supplementary data, Table S5).

All [K^+] disorders were independently associated with an increased risk of in-hospital death compared with NK (Table 3). Compared with HoK, HerK and MD were associated with higher odds of death (OR = 1.75, 95% CI 1.34–2.29 and OR = 2.50, 95% CI 1.67–3.70, respectively; Supplementary data, Table S6). The MD category also showed a nominally higher risk of in-hospital death compared with HerK (OR = 1.43, 95% CI 0.97–2.07, P = 0.065).

Table 1. Baseline characteristics of the study population stratified by quartile of [K^+] variability

	Q1 CV ≤3.92, $n = 16\,129$	Q2 3.92 < CV ≤ 7.00, $n = 16\,169$	Q3 7.00 < CV ≤ 10.50, $n = 16\,085$	Q4 CV >10.50, $n = 16\,124$
Age, mean (SD), years	56.8 (18.3)	60.1 (18.0)	61.4 (17.8)	63.9 (17.4)
Males, *n* (%)	7206 (44.7)	7898 (48.8)	7758 (48.2)	7011 (43.5)
Charlson/Deyo score, *n* (%)				
0	13 383 (83.0)	12 590 (77.9)	12 271 (76.3)	11 823 (73.3)
1	1971 (12.2)	2479 (15.3)	2611 (16.2)	2831 (17.6)
2	426 (2.6)	635 (3.9)	676 (4.2)	850 (5.3)
3+	349 (2.2)	465 (2.9)	527 (3.3)	620 (3.8)
Comorbidities, *n* (%)				
Cardiovascular	5257 (32.6)	6239 (38.6)	6533 (40.6)	6981 (43.3)
Malignancies	4534 (28.1)	5132 (31.7)	5178 (32.2)	5153 (32.0)
Gastrointestinal	2309 (14.3)	2429 (15.0)	2525 (15.7)	2697 (16.7)
Genitourinary	1664 (10.3)	1816 (11.2)	2008 (12.5)	2325 (14.4)
Endocrine/metabolic	2385 (14.8)	2745 (17.0)	2836 (17.6)	3203 (19.9)
Infectious	504 (3.1)	748 (4.6)	876 (5.4)	1209 (7.5)
Respiratory	1339 (8.3)	2043 (12.6)	2256 (14.0)	2892 (17.9)
eGFR, mean (SD), mL/min/1.73 m^2	83.7 (25.5)	79.5 (26.5)	78.1 (26.8)	74.42 (28.15)
[K^+], mean (SD) (range: min–max),[a] mmol/L	4.0 (0.3) (2.3–7.0)	4.0 (0.4) (2.20–7.00)	4.0 (0.5) (2.00–6.60)	4.0 (0.7) (2.00–7.50)
[K^+] measurements, median (IQR)	2.0 (1.0)	3.0 (2.0)	3.0 (3.0)	4.0 (4.0)
Observation time, median (IQR),[b] days	3.0 (4.0)	5.0 (6.0)	6.0 (9.0)	7.0 (10.0)
[K^+] CV, median (IQR)	1.9 (1.7)	5.5 (1.4)	8.6 (1.7)	13.5 (4.5)

[a]Value at hospital admission;
[b]time difference between the last and first [K^+] measurements for each hospitalization.

Table 2. Association between [K^+] variability and in-hospital mortality

Quartile	Events, *n* (%)	Model 1		Model 2	
		OR (95% CI)	P-value for trend	OR (95% CI)	P-value for trend
Q1 (CV ≤3.92)	93 (0.6)	1.00 (Reference)	P < 0.001	1.00 (Reference)	P < 0.001
Q2 (3.92 < CV ≤ 7.00)	134 (0.8)	1.44 (1.11, 1.88); P = 0.007	–	1.08 (0.83, 1.41); P = 0.584	–
Q3 (7.00 < CV ≤ 10.50)	198 (1.2)	2.15 (1.68, 2.76); P < 0.001	–	1.45 (1.13, 1.88); P = 0.003	–
Q4 (CV >10.50)	537 (3.3)	5.94 (4.79, 7.46); P < 0.001	–	3.30 (2.64, 4.16); P < 0.001	–

Model 1: univariable model. Model 2: multivariable model adjusted for age, sex, comorbidities, Charlson/Deyo score, [K^+] value at hospital admission and eGFR baseline.

Table 3. Association between [K^+] disorders and in-hospital mortality

	Events, *n* (%)	Model 1, OR (95% CI)	Model 2, OR (95% CI)
NK	526 (0.9)	1.00 (Reference)	1.00 (Reference)
HoK	128 (4.2)	4.70 (3.85–5.70); P < 0.001	2.60 (2.09–3.21); P < 0.001
HerK	262 (6.2)	7.08 (6.08–8.23); P < 0.001	4.55 (3.79–5.45); P < 0.001
MD	46 (14.2)	17.67 (12.64–24.18); P < 0.001	6.49 (4.48–9.24); P < 0.001

Model 1: univariable model. Model 2: multivariable model adjusted for age, sex, co-morbidities, Charlson/Deyo score, [K^+] value at hospital admission and eGFR baseline.

DISCUSSION

In this article, we demonstrated a strong relationship between [K^+] variability and in-hospital mortality. Higher [K^+] fluctuations, mainly but not exclusively found in mixed disorders, are associated with poorer patient prognosis.

The relationship between [K^+] disorders and clinical outcomes has been widely explored in the scientific literature. Both HoK and HerK conditions have been strongly associated with increased mortality risk in the hospital setting [4, 5, 7, 8]. In particular, there is a well-described cardiac toxicity due to [K^+] imbalance, justifying the excess risk in those patients [4–6].

Recently, an increasing number of studies have re-analysed and explored the role of electrolytes imbalance on patient outcomes [15–17]. It is now clear that it is difficult to define a specific cut-off, above or below which the risk of death or other clinical outcomes increases. A J- or U-shaped relationship between serum electrolytes (e.g. sodium and potassium) and in-hospital mortality has been widely described in medical literature [18, 19]. However, to date, increasing attention is also placed on electrolytes fluctuations, even within the theoretical 'normal' range [16, 20, 21].

To date, the 'optimal' range for [K^+] is still unknown. Currently, a range between 3.0 and 5.0 mmol/L is considered safe [3, 22, 23]. Whether a cut-off point should be more precise is still unclear.

Surely, a precise definition of HoK or HerK is especially useful in clinical practice for identifying patients with increased hospital risk. However, at the same time, it is important to underline that physicians should also pay attention to—and avoid as much as possible—excessive electrolytes variability during hospital stay.

Surprisingly, to date, only a few studies have explored the association between [K^+] variability and in-hospital mortality. Hessels *et al.* [10] and Engelhardt *et al.* [9] demonstrated an increased risk of death in ICU patients with higher [K^+] variability. Similar findings were observed by Shiyovich *et al.* [11] in patients with heart disease.

Our results are consistent with previous findings. Unlike others published studies, we used the CV, a more appropriate measure of variability compared with the SD as it takes into account the average values of the variable of interest [12], and we demonstrated that higher [K^+] variability was associated with increased in-hospital mortality. This is particularly true in patients with [K^+] mixed disorders: to the best of our knowledge, this condition has never been investigated in the scientific literature. Notably, for the first time, we demonstrated how [K^+] variability is an important predictor of in-hospital death, even in the normal range, independent of the presence of HoK or HerK.

Although a direct causal relationship cannot be demonstrated due to the observational and retrospective nature of the study design, a possible direct association between higher [K^+] variability and in hospital mortality can be hypothesized. In fact, rapid changes in cell membrane resting conditions could justify an increase in cellular instability and consequently increased risk of arrhythmogenic deaths. On the other hand, higher [K^+] variability could represent a marker of patient instability and thus the severity of the underlying diseases or the need for greater use of medications. Unfortunately, we did not have information on the medications used during the hospital stay, but we included the Charlson/Deyo score in our analyses and the association between [K^+] variability and death remained statistically significant, corroborating the hypothesis of a direct link between the former and the latter.

Our study has several limitations: the retrospective and monocentric design, the use of ICD-9-CM codes for comorbidity definitions and the unavailability of medications administered during hospital stay. Statistical adjustment for the Charlson/Deyo score might not completely correct for the missing information regarding the medications used during hospital stay; this is a common limitation of observational studies. Furthermore, due to the retrospective and observational nature of this study, the number of [K^+] measurements per patient might not have been adequate to establish variability in all included cases. Unfortunately, to our knowledge, no direct specifications have been reported in the relevant published literature. Prospective studies are necessary to confirm our findings,

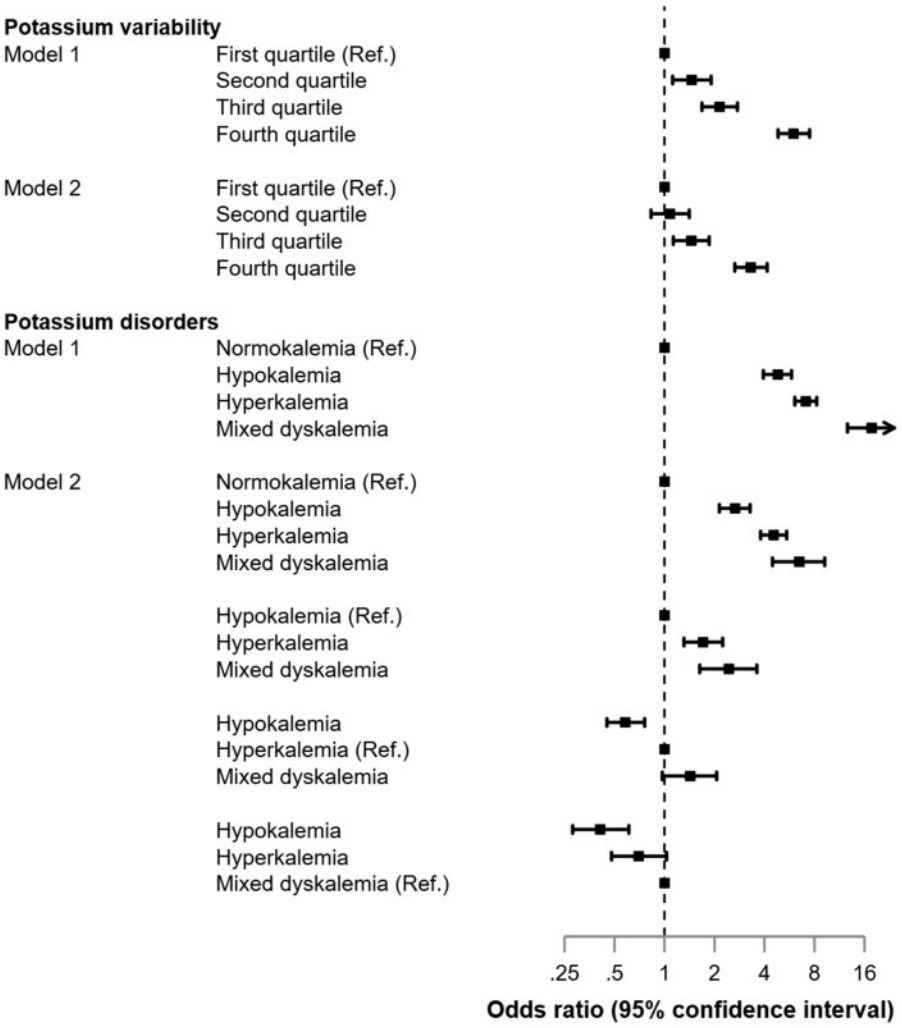

FIGURE 1: Association between [K^+] disorders/variability and in-hospital mortality.

with clear guidelines regarding the definition of [K^+] variability. Another important limitation of this study is that the associations could not be finely controlled for patient medications or underlying diseases, which might have altered the results of this study. Further research is needed in order to see whether specific health conditions show differential associations between [K^+] variability and clinical outcomes. As a result, the finding of elevated mortality in patients with [K^+] variability within the normal range should be interpreted with caution. However, this is the first study analysing [K^+] variability with a comprehensive approach in an unselected hospitalized population, improving the generalizability of previous findings. [K^+] variability was investigated using an adequate statistical measure and the analyses were controlled for potential confounders such as [K^+] values and renal function at baseline. Finally, sensitivity analyses provided further validity to our findings.

In conclusion, [K^+] variability and [K^+] disorders are associated with increased risk of death.

Future longitudinal studies with more detailed phenotyping (e.g. with information on urinary potassium excretion), investigating potential mechanisms of the associations reported and with information on medication use, should be carried out with the purpose to evaluate and define the causal association between [K^+] variability and clinical outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

G.L., P.M.F. and G.G. contributed to the research idea and study design. G.L. contributed to data acquisition. G.G., P.M.F. and G.L. contributed to data analysis/interpretation.

P.M.F. and G.L. contributed to statistical analysis. G.L. drafted the article. G.G. and P.M.F. contributed to supervision. Each author contributed important intellectual content during manuscript drafting for the overall work.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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