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Electrolytes variability and clinical outcomes, in-hospital mortality and acute kidney injury

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CHAPTER 1

General Introduction

General Introduction

Serum electrolytes are essential for basic life functioning. They play an important role in maintaining electrical neutrality in cells, generating and conducting action potentials in the nerves and muscles, cooperating to enzymatic functions.

Electrolytes come from diet and serum concentrations are strictly regulated by the kidney, the main human organ deputed to control human hydro-electrolyte homeostasis.

These electrolytes can have an imbalance, leading to either high or low levels. Disorders of sodium (Na^+) and potassium (K^+) are the most common electrolytes derangements observed in hospitalized population. High or low electrolytes levels disrupt normal bodily functions and can lead to even life-threatening complications.

Medical literature has clearly demonstrated the association of Na^+ and K^+ disorders with poor prognosis of hospitalized patient. Recent scientific research reveals, however, that even little electrolyte changes might have a significant influence on patient survival. Furthermore, electrolytes fluctuations in a theoretical normal range should also warn medical attention.

Given that the kidney is the primary organ engaged in electrolyte and water balance, the link between renal dysfunction and electrolyte abnormalities is unsurprising. Even though these disorders are generally considered to be a consequence of renal damage or simple bystanders, recent scientific evidence are now suggesting that electrolytes imbalance might precede kidney injury.

The aim of my dissertation will focus on the studies conducted during the three years of my PhD program. Herein I am going to analyse the strong association between Na^+ and K^+ derangements and in-hospital clinical outcomes with particular attention on electrolytes variability or fluctuations even in the normal ranges and its relationship with in-hospital mortality and acute kidney injury.

Sodium and Potassium disorders: epidemiology and clinical significance

Electrolytes are essential for metabolic pathways, enzyme activity, acid-base balance, muscle function modulation and nervous-tissue contractions.

Kidney regulates electrolyte levels by several processes such as active transport in the proximal convoluted tubules, osmosis and passive diffusion, which are all reliant on water and pH balance. The Na-K–adenosine triphosphatase (ATPase) pump maintains and regulates Na^+ and K^+ levels at the cellular level. The renin-aldosterone system, as well as circulating vasopressin and natriuretic peptides in body fluids, regulate the distal convoluted tubules function.

Sodium disorders (1)

Changes in the relative ratio of Na^+ to body water are caused by abnormalities in water homeostasis, resulting in anomalies in blood Na^+ concentration. The two primary effectors in the defense of serum osmolality are water intake and circulating AVP; anomalies in one or both of these defensive systems underlie the majority of hyponatremia (HoNa) and hypernatremia cases. Disorders in Na^+ homeostasis, on the other hand, result in a deficit or excess of whole-body Na+-Cl– content, which is a critical predictor of extracellular fluid volume (ECFV) and circulatory integrity. Notably, volume status influences the posterior pituitary's production of AVP, with hypovolemia resulting in increased circulating levels of the hormone at each level of serum osmolality. Similarly, with "hypervolemic" causes of arterial underfilling, such as heart failure and cirrhosis, neurohumoral activation includes a rise in circulating AVP, resulting in water retention and HoNa. As a result, one of the most important concepts in Na^+ disorders is that the absolute plasma Na^+ concentration has no relation on a patient's volume status, which must be taken into account in the diagnostic and therapeutic process.

Potassium disorders (2)

Despite significant fluctuation in dietary K^+ consumption, homeostatic processes keep plasma K^+ concentrations between 3.0 and 5.0 mM. The kidney has a key role in K^+ homeostasis in a healthy individual at steady state, excreting ~90% of daily K^+ intake in the urine and 10% in the stool. However, approximately 98 percent of total body K^+ is intracellular, mostly in muscle, and this enormous intracellular pool buffers extracellular K^+, which is crucial for plasma K^+ concentration management. Changes in intracellular and extracellular K^+ exchange and distribution can result in severe hypo- or hyperkalemia.

The kidney is primarily responsible for fluctuations in whole-body K^+ concentration, since it reabsorbs filtered K^+ in hypokalemic, K^+-deficient conditions and secretes K^+ in hyperkalemic, K^+-replete situations. Although K^+ is transported throughout the nephron, K^+ secretion is dominated by

the principal cells of the connecting segment and cortical collecting duct (CD), whereas in K^+-deficient states, alpha-intercalated cells of the outer medullary CD play a role in renal tubular reabsorption of filtered K^+. A lumen-negative potential difference is generated in main cells by apical Na^+ entry via the amiloride-sensitive ENaC, which induces passive K^+ exit through apical K^+ channels. The secretory K^+ channel ROMK and the flow-sensitive "big potassium" (BK) or maxi-K K^+ channel facilitate distal tubular K^+ secretion. Increases in distal flow rate and/or genetic lack of ROMK are considered to stimulate K^+ secretion via the BK channel, whereas ROMK is expected to mediate the majority of constitutive K^+ secretion.

The bedside interpretation of K^+ abnormalities requires an understanding of the link between ENaC-dependent Na^+ entry and distal K^+ secretion. For example, in hypovolemic, prerenal conditions, reduced distal supply of Na^+ tends to impair the ability to excrete K^+, resulting in hyperkalemia (HerK); on the other hand, increased distal delivery of Na^+ and distal flow rate, which occurs after treatment with thiazide and loop diuretics, can enhance K^+ secretion and result in hypokalemia (HoK). Because of the importance of this Na^+ channel in creating a lumen-negative potential difference, medications that directly block ENaC can cause HerK. Aldosterone, in turn, has a significant impact on K^+ excretion, boosting the activity of ENaC channels and therefore magnifying the driving force for K^+ secretion across main cell luminal membranes. Both HoK and HerK can be caused by abnormalities in the renin-angiotensin-aldosterone system. K^+ excess and restriction, on the other hand, have opposite, aldosterone-independent effects on the density and activity of apical K^+ channels in the distal nephron, indicating that variables other than aldosterone affect the renal ability to release K^+. Furthermore, K^+ restriction and HoK induce aldosterone-independent distal reabsorption of filtered K^+ in intercalated cells within the outer medullary CD, stimulating apical H^+/K^+-ATPase activity. Changes in plasma K^+ concentration are not universal in illnesses linked with changes in aldosterone activity, possibly reflecting this physiology.

Clinical outcomes and electrolytes disorders

The association between electrolytes disorders and poor clinical outcomes have been widely discussed in medical literature.

Dysnatremia (hypo- or hypernatremia) can progress to a serious illness with substantial morbidity and mortality (3–5), regardless of the fact that it is usually asymptomatic. Brain shrinkage can occur as a result of severe hypernatremic circumstances, which can lead to cerebral bleeding, subarachnoid hemorrhage, and death (6).

One of the most dangerous disorders caused by electrolyte disruption is hyponatremic encephalopathy with brain damage. Chronic HoNa, on the other hand, is classified as a non-severe condition if it is mild to moderate.

In the hospital setting, both HoK and HerK have been strongly linked to a higher risk of death (2,7–9). There is a well-documented cardiac toxicity caused by K^+ imbalance, which justifies the increased risk in such individuals (2,7,10).

The kidney, as the primary organ involved in water metabolism and homeostasis, is frequently the cause of such problems. Kidney diseases and failure impair the regulatory functions, resulting in life-threatening changes in electrolyte and acid-base balances. HoNa is caused by inadequate of urine dilution combined with an excessive amount of water consumption. Hypernatremia (HerNa) is caused by abnormalities with urine concentration and insufficiently low water consumption (10,11). As a result, it's not unexpected that Na^+ and K^+ abnormalities are widespread in people with chronic renal disease (12,13). This is especially true in the case of acute kidney injury (AKI), which is characterized by a sudden loss of renal function (14–18) and the adaptative response is more hampered.

Electrolyte changes before AKI are frequently described as simple bystanders that accompany other clinical diseases (15,19). However, recently a direct and independent causative link with kidney damage has been proposed (20–22), but it is still poorly investigated in scientific literature.

If this viewpoint is accepted, electrolytes anomalies may be a valuable indicator for diagnosing kidney disease before it manifests, allowing for more timely medical intervention. As a result, identifying electrolyte abnormalities is critical in clinical practice.

It is, however, a little more difficult than that. Recently, a rising number of research have re-analysed and studied the influence of electrolytes imbalance on patient outcomes (21–23). It is now obvious that defining a precise cut-off point above or beyond which the risk of mortality or other clinical outcomes increases is challenging. The medical literature has extensively reported a J- or U-shaped association between serum electrolytes (e.g. Na^+ and K^+) and in-hospital mortality (24,25). Electrolytes variations, even within the notional "normal" range, have recently gotten a lot of attention because of their relationship to poor clinical outcomes (19,24,26).

Aim of the study and data source and data collection

The aim of my thesis focuses on the association between Na^+ and K^+ with particular attention on electrolytes variability or fluctuations and in-hospital clinical outcomes, in-hospital mortality and AKI.

In order to explore these issues a wide retrospective cohort of hospitalized population have been analysed.

We conducted a retrospective single-center observational study on patients admitted to the Fondazione Policlinico A. Gemelli IRCCS, a tertiary care academic medical hospital in Rome (Italy), between January 1, 2010, and December 31, 2014.

Data were extracted from the Hospital's central electronic database using a specific website interface. We gathered demographic information such as gender and age, clinical information, vital status at hospital discharge, main and secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD 9 CM) codes, and laboratory parameters retrospectively.

Outline of this thesis

The **first part** of this thesis discusses the association between electrolytes disorders and in-hospital mortality with particular attention on electrolytes variability.

In **chapter 2** Na^+ disorders are investigated for association with in-hospital mortality and the continuous relationship between Na^+ fluctuations and in-hospital death is analysed.

In **Chapter 3** we pay attention to K^+ disorders and variability with in-hospital mortality.

The **second part** of the thesis addresses the association between electrolytes disorder and variability with acute kidney injury.

Chapter 4 explore the possible relationship between Na^+ derangements and AKI.

Chapter 5 evaluate the same relationship considering K^+ disorder as predictor of AKI.

In **chapter 6**, the general discussion, the main findings of the previous chapters are recapitulated, interpreted and put into perspective. Finally, conclusions are drawn concerning the methods, their implications for clinical practice, and recommendations for further studies.

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PART 1

Sodium and Potassium variability associate with increased mortality in the hospitalized population

CHAPTER 2

Sodium Fluctuations and Mortality in a General Hospitalized Population

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Abstract

Background/Aims:

Aim of our study was to describe the association between natremia (Na) fluctuation and hospital mortality in a general population admitted to a tertiary medical center.

Methods:

We performed a retrospective observational cohort study on the patient population admitted to the Fondazione Policlinico A. Gemelli IRCCS Hospital between January 2010 and December 2014 with inclusion of adult patients with at least 2 Na values available and with a normonatremic condition at hospital admission. Patients were categorized according to all Na values recorded during hospital stay in the following groups: normonatremia, hyponatremia, hypernatremia, and mixed dysnatremia. The difference between the highest or the lowest Na value reached during hospital stay and the Na value read at hospital admission was used to identify the maximum Na fluctuation. Cox proportional hazards models were used to estimate hazard ratios (HRs) for in-hospital death in the groups with dysnatremias and across quartiles of Na fluctuation. Covariates assessed were age, sex, highest and lowest Na level, Charlson/Deyo score, cardiovascular diseases, cerebrovascular diseases, dementia, congestive heart failure, severe kidney disease, estimated glomerular filtration rate, and number of Na measurements during hospital stay.

Results:

46,634 admissions matched inclusion criteria. Incident dysnatremia was independently associated with in-hospital mortality (hyponatremia: HR 3.11, 95% CI 2.53, 3.84, $p < 0.001$; hypernatremia: HR 5.12, 95% CI 3.94, 6.65, $p < 0.001$; mixed-dysnatremia: HR 4.94, 95% CI 3.08, 7.92, $p < 0.001$). We found a higher risk of in-hospital death by linear increase of quartile of Na fluctuation (p trend < 0.001) irrespective of severity of dysnatremia (HR 2.34, 95% CI 1.55, 3.54, $p < 0.001$, for the highest quartile of Na fluctuation compared with the lowest).

Conclusions:

Incident dysnatremia is associated with higher hospital mortality. Fluctuation of Na during hospital stay is a prognostic marker for hospital death independent of dysnatremia severity.

Introduction

Dysnatremia is the most common electrolyte disorder in hospitalized patients; it encompasses hyponatremic and hypernatremic conditions. Hyponatremia is a pathological condition defined as a serum sodium < 135 mmol/L. Epidemiological studies report a prevalence in the general population between 1 and 10% (1,2) and between 15 and 20% in the hospital setting (3).

Hypernatremia is defined as a serum sodium > 145 mmol/L. It is generally related to water losses with increase of plasma osmolality. It is less frequent than hyponatremia (4) with a reported in-hospital prevalence of up to 7.7% (5).

Serum sodium is the main cation of extracellular fluid and plays a key role in serum osmolarity. Although generally asymptomatic, dysnatremia may develop to a severe condition with high morbidity and mortality (6–8). Severe hypernatremic conditions can lead to brain shrinkage potentially associated with cerebral bleeding, subarachnoid hemorrhage, and death (9). Hyponatremic encephalopathy with brain injury is one of the most serious diseases following electrolyte disturbance. By contrast, mild to moderate chronic hyponatremia is considered a non-severe disease (6). However, recent literature suggests that even mild hyponatremia and hypernatremia may have a considerable burden on patient outcomes, being associated with significantly higher mortality and length of hospital stay (10).

Although several studies evaluated the association between dysnatremia and in-hospital death, only a few reported on the association between incident in-hospital dysnatremia and mortality (11–15) and described the relation between sodium variations and patient outcomes (12,14,15).

The aim of our study was to report the incidence of dysnatremia and to analyze the association between development of dysnatremia, magnitude of sodium fluctuations, and in-hospital mortality in a general medical-surgical inpatient population admitted to a tertiary medical center.

Materials and Methods

Study Population

We performed a retrospective single-center observational study on the patient population admitted between January 1, 2010, and December 31, 2014, to the Fondazione Policlinico A. Gemelli IRCCS, a tertiary care academic medical center in Rome (Italy). Data extraction and analysis included only adult patients (≥18 years) admitted to the hospital during the period of interest with at least 2 sodium measurements available and with a normonatremic condition (sodium values between 135 and 145 mmol/L) at hospital admission. All patients admitted to the intensive care units (ICU) during hospital stay were excluded.

Data Source and Data Collection

Data were extracted from the Hospital's central electronic database using a specific website interface. We retrospectively collected demographic data including sex and age, clinical data, vital status at hospital discharge, primary and secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD 9 CM) codes at discharge, and laboratory parameters (serum sodium, serum glucose). If a patient had multiple hospital admissions, all of them were included in the analysis.

Definitions

Hyponatremia was defined as a sodium level < 135 mmol/L. Hypernatremia was defined as a sodium level > 145 mmol/L. Patients were categorized according to all sodium values recorded during hospital stay in the following dysnatremic groups: hyponatremia (lowest/highest sodium values during hospital stay < 135 and ≤145 mmol/L, respectively), hypernatremia (lowest/highest sodium values ≥135 and > 145 mmol/L), mixed dysnatremia (lowest/highest sodium values < 135 and > 145 mmol/L), normonatremia (lowest/highest sodium values ≥135 and ≤145 mmol/L). The difference between the highest or lowest sodium value reached during hospital stay and the sodium value at hospital admission was used to identify the sodium fluctuation.

Sodium levels were corrected for the dilutional effect associated with hyperglycemia using validated methods (16,17).

Outcomes and Covariates

The outcome of interest was in-hospital mortality. Our exposures of interest were the groups of dysnatremia and quartiles of sodium fluctuation. Covariates assessed to control confounding were age, sex, highest and lowest sodium level reached during hospital stay, cardiovascular diseases, cerebrovascular diseases, diabetes, severe kidney disease, dementia, congestive heart failure, estimated glomerular filtration rate (eGFR), malignancies, number of measurements, and Charlson/Deyo comorbidity index score (18). ICD 9 CM codes were used to identify all comorbid conditions (diabetes: ICD 9 CM 250.1–250.7; cardiovascular diseases: ICD 9 CM 390–459; cerebrovascular diseases: ICD 9 CM 430–438; dementia: ICD 9 CM 290; malignancies: ICD 9 CM 140–239; liver diseases: ICD 9 CM 571.2, 571.4–571.6, 572.2–572.8). Severe kidney disease was identified at hospital admission as an eGFR < 15 mL/min/1.73 m2. eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation (19).

Statistical Analysis

Continuous variables were described using means (SDs) or medians (interquartile ranges) and categorical variables as counts (percentages). Categorical variables were compared using the chi-square test. Continuous variables were compared using Student t test or Mann-Whitney test as appropriate. The normality of the data distribution was assessed by visually inspecting the histograms and Q-Q plots.

Cox proportional hazards models were used to estimate unadjusted and adjusted hazard ratios (HRs) and 95% CIs for in-hospital death among the groups of dysnatremias (with the normonatremic group used as the reference) and across quartiles of sodium fluctuation (expressed as percentage and absolute values; the lowest quartile was used as the reference). Time at risk was calculated from the date of hospital admission up to the date of in-hospital death or discharge. All hospitalizations were censored at 60 days of hospital stay.

We assessed nonlinear relationships as well as the potential effect of the velocity (rate) of sodium changes by calculating the rate of change in mmol/L per 24 h and performing an analysis of the sodium slope and in-hospital death in the dysnatremic groups using restricted cubic splines (R studio, "rms" package (20)). Four knots were used at 5th, 25th, 75th, and 95th percentiles of the sodium fluctuation rate distribution. The sodium slope was calculated from an ordinary least-square regression model using all available sodium measurements for each patient between the sodium value at hospital admission and the highest or lowest sodium value reached during hospital stay.

All analyses incorporated standard errors clustered by patient identity to account for within-patient correlations.

A p value < 0.05 was considered as statistically significant in all analyses.

All analyses were conducted using R version 3.4.4 (R Foundation for Statistical Computing, Vienna University of Economics and Business).

Results

Demographics

Between January 1, 2010, and December 31, 2014, 338,754 adult patients were admitted to the hospital. Overall, 46,634 admissions from 36,447 unique patients matched inclusion criteria (Fig. 1). There were 6,848 incident dysnatremic admissions (14.7%). The baseline characteristics of the cohort (referred to the first hospital admission for each patient) are shown in Table 1. As expected, compared with normonatremic patients, dysnatremic patients were older and had higher prevalence of comorbidities (mean Charlson/Deyo score comorbidity index: 0.6 [SD 1.2] vs. 0.3 [SD 0.9], $p < 0.001$). Specifically, we found a higher prevalence of cardiovascular diseases (41.6 vs. 33.4%, $p < 0.001$), cerebrovascular diseases (8.8 vs. 6.5%, $p < 0.001$), severe kidney diseases (3.4 vs. 1.3%, $p < 0.001$) in the dysnatremic

groups. The characteristics of the entire cohort stratified by quartiles of percentage sodium fluctuation are reported in Table 2.

Fig 1. Flawchart of the study

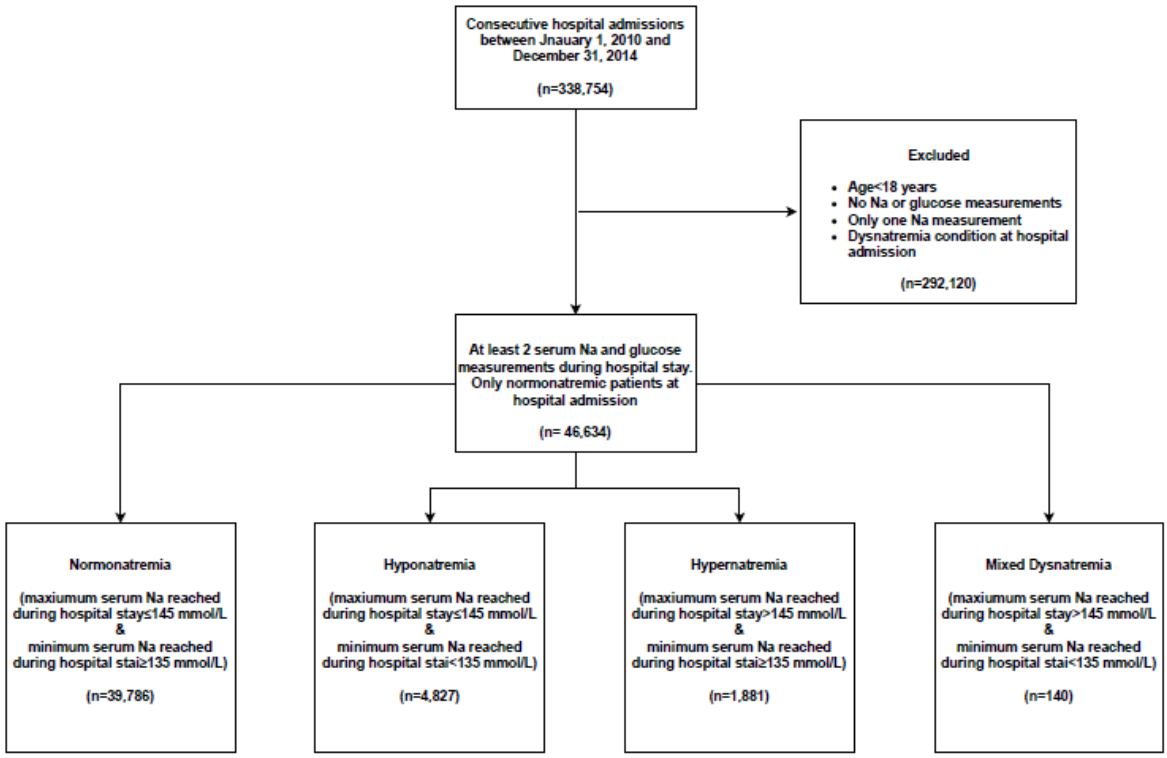


Table 1. Demographic and clinical characteristics of study cohort at first hospital admission by serum sodium status

	Normonatremic group	Dysnatremic group	*p* value
Number	31,425	5,022	
Age, years	59.8 (17.8)	67.0 (16.3)	<0.001
Gender, males	13,883 (44.2)	2,436 (48.5)	<0.001
Charlson score			<0.001
0	25,045 (79.7)	3,449 (68.7)	
1	4,073 (13.0)	925 (18.4)	
2	1,299 (4.1)	327 (6.5)	
>2	1,008 (3.2)	321 (6.4)	
Charlson score	0.3 (0.9)	0.6 (1.2)	<0.001
Diabetes	307 (1.0)	63 (1.3)	0.060
Cardiovascular disease	10,485 (33.4)	2,090 (41.6)	<0.001
Congestive heart failure	1,126 (3.6)	316 (6.3)	<0.001
Malignancies	10,898 (34.7)	2,096 (41.7)	<0.001
Cerebrovascular disease	2,037 (6.5)	440 (8.8)	<0.001
Liver disease	673 (2.1)	203 (4.0)	<0.001
Dementia	133 (0.4)	50 (1.0)	<0.001
Severe kidney disease	412 (1.3)	173 (3.4)	<0.001
eGFR	79.7 (27.2)	70.7 (29.6)	<0.001

Values are presented as mean (SD) or *n* (%).
eGFR, estimated glomerular filtration rate.

Table 2. Demographic and clinical characteristics of study cohort at first hospital admission by quartile of sodium fluctuation

	1st quartile (<0.7%)	2nd quartile (0.7–2.1%)	3rd quartile (2.1–2.9%)	4th quartile (>2.9%)
Number	9,841	9,667	8,420	8,519
Age, years	58.3 (17.9)	60.5 (17.7)	60.5 (17.8)	64.1 (17.2)
Gender, males	4,266 (43.3)	4,336 (44.9)	3,773 (44.8)	3,944 (46.3)
Charlson score				
0	8,015 (81.4)	7,620 (78.8)	6,599 (78.4)	6,289 (73.8)
1	1,252 (12.7)	1,324 (13.7)	1,145 (13.6)	1,295 (15.2)
2	321 (3.3)	391 (4.0)	388 (4.6)	501 (5.9)
>2	253 (2.6)	332 (3.4)	288 (3.4)	434 (5.1)
Charlson score	0.3 (0.8)	0.4 (0.9)	0.4 (0.9)	0.5 (1.0)
Diabetes	78 (0.8)	93 (1.0)	93 (1.1)	113 (1.3)
Cardiovascular disease	3,202 (32.5)	3,357 (34.7)	2,862 (34.0)	3,098 (36.4)
Congestive heart failure	261 (2.7)	369 (3.8)	335 (4.0)	421 (4.9)
Malignancies	3,164 (32.2)	3,353 (34.7)	3,071 (36.5)	3,508 (41.2)
Cerebrovascular disease	643 (6.5)	633 (6.5)	490 (5.8)	692 (8.1)
Liver disease	191 (1.9)	232 (2.4)	221 (2.6)	236 (2.8)
Dementia	29 (0.3)	44 (0.5)	34 (0.4)	62 (0.7)
Severe kidney disease	66 (0.7)	124 (1.3)	136 (1.6)	235 (2.8)
eGFR	82.1 (25.6)	78.9 (27.0)	78.5 (27.9)	73.8 (29.3)

Values are presented as mean (SD) or *n* (%).
eGFR, estimated glomerular filtration rate.

Outcomes

Incident Dysnatremia and In-Hospital Death

Incident dysnatremia was associated with increased risk of in-hospital death (Table 3): the incidence of in-hospital death among dysnatremic patients was 4.6% (subgroup analysis: incident hyponatremia 3.9%; incident hypernatremia 5.4%; mixed-dysantremia mortality of 14.2%) compared with 0.5% in patients who did not develop dysnatremia during hospital stay.

In multivariate analysis, incident dysnatremia was independently associated with in-hospital death (hyponatremia HR 3.11, 95% CI 2.53, 3.84, $p < 0.001$; hypernatremia: HR 5.12, 95% CI 3.94, 6.65, $p < 0.001$; mixed-dysnatremia: HR 4.94, 95% CI 3.08, 7.92, $p < 0.001$). Patients with hypernatremia showed increased risk for in-hospital death compared with hyponatremic patients (HR 1.64, 95% CI 1.27, 2.12, $p < 0.001$).

Table 3. Association between serum sodium status and in-hospital death

	Normonatremia	Hyponatremia	Hypernatremia	Mixed dysnatremia
Admissions, *n*	39,786	4,827	1,881	140
Patients, *n*	31,425	3,466	1,450	106
In-hospital death, *n* (%)	144 (0.5)	135 (3.9)	79 (5.4)	15 (14.2)
Univariate HR (95% CI) *p* value	1.00 Reference	3.93 (3.21, 4.80) <0.001	7.04 (5.48, 9.05) <0.001	8.73 (5.63, 13.54) <0.001
Multivariate HR (95% CI)* *p* value	1.00 Reference	3.11 (2.53, 3.84) <0.001	5.12 (3.94, 6.65) <0.001	4.94 (3.08, 7.92) <0.001
Multivariate HR (95% CI)* *p* value	0.32 (0.26, 0.40) <0.001	1.00 Reference	1.64 (1.27, 2.12) <0.001	1.59 (0.99, 2.54) 0.056
Multivariate HR (95% CI)* *p* value	0.20 (0.15, 0.25) <0.001	0.61 (0.47, 0.78) <0.001	1.00 Reference	0.96 (0.59, 1.58) 0.886
Multivariate HR (95% CI)* *p* value	0.20 (0.13, 0.32) <0.001	0.63 (0.39, 1.01) 0.056	1.04 (0.63, 1.69) 0.886	1.00 Reference

*Adjusted for baseline covariates (age, sex, Charlson/Deyo Score, diabetes, cardiovascular disease, congestive heart failure, malignancies, eGFR, severe kidney disease, cerebrovascular disease, dementia, liver diseases, number of sodium measurements).
HR, hazard ratio; eGFR, estimated glomerular filtration rate.

Sodium Fluctuation and Mortality

Tables 4 and 5 report the association between quartiles of sodium fluctuation and in-hospital death. There was a higher risk of in-hospital death among increasing quartiles of sodium fluctuation (p value for trend < 0.001).

Multivariate analysis revealed a HR of 2.34 (95% CI 1.55, 3.54, p < 0.001) for in-hospital death in the highest quartile of percentage sodium fluctuation compared with the lowest (Table 4).

Similar results were found when absolute values of sodium fluctuation were used (Table 5).

Figure 2 shows the association between the sodium slope and in-hospital death in incident hyponatremic and hypernatremic patients. Using restricted cubic splines, we found a nonlinear (p < 0.001) increase in the risk of in-hospital death with increasing sodium slope.

Table 4. Association between quartiles of sodium fluctuation (expressed as percentage) and in hospital death

	1st quartile (<0.7%)	2nd quartile (0.7–2.1%)	3rd quartile (2.1–2.9%)	4th quartile (>2.9%)	*p* value trend
Admissions, *n*	12,109	12,165	10,890	11,470	
Patients, *n*	9,841	9,667	8,420	8,519	
In-hospital death, *n* (%)	22 (0.2)	33 (0.3)	55 (0.7)	208 (2.4)	
Univariate HR (95% CI) *p* value	1.00 Reference	1.22 (0.77, 1.92) 0.396	1.88 (1.24, 2.83) 0.003	4.72 (3.28, 6.78) <0.001	<0.001
Multivariate HR (95% CI)* *p* value	1.00 Reference	1.03 (0.65, 1.63) 0.899	1.51 (0.99, 2.31) 0.057	2.34 (1.55, 3.54) <0.001	<0.001

* Adjusted for baseline covariates (age, sex, Charlson/Deyo Score, diabetes, cardiovascular disease, congestive heart failure, malignancies, eGFR, severe kidney disease, cerebrovascular disease, dementia, liver diseases, the lowest and the highest serum sodium levels reached during hospital stay, number of sodium measurements).
HR, hazard ratio; eGFR, estimated glomerular filtration rate.

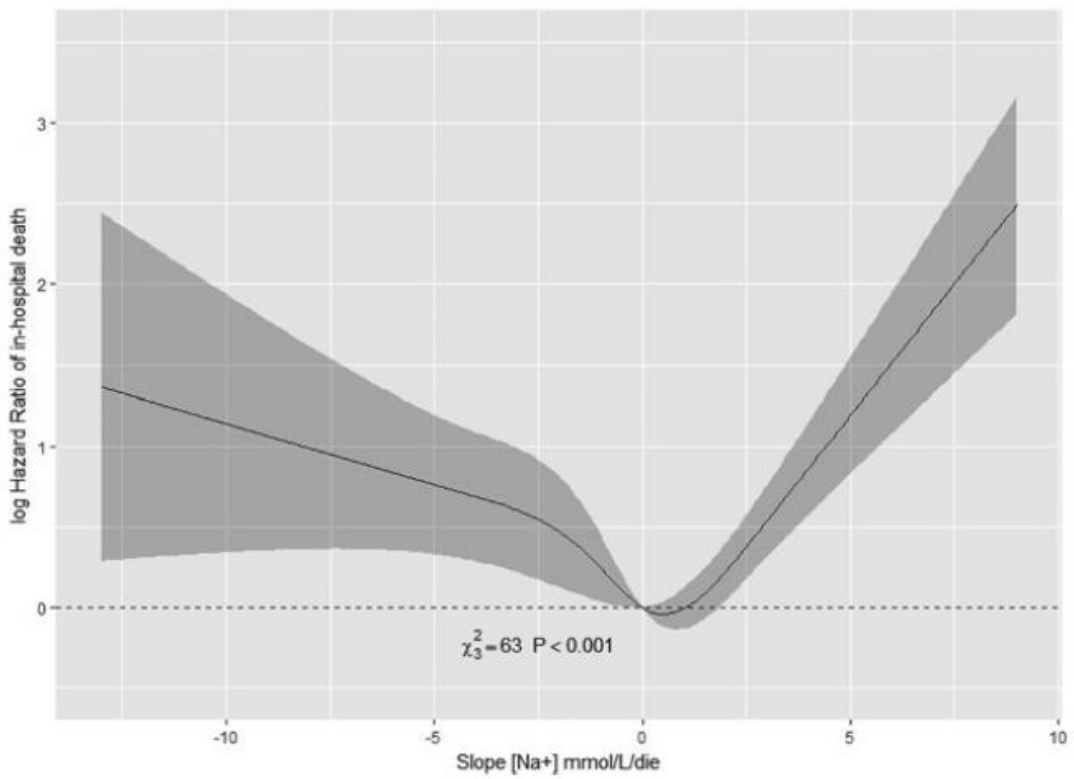
Table 5. Association between quartile of sodium fluctuation (expressed as absolute value) and in hospital death

	1st quartile ≤1 mmol/L	2nd quartile 1–3 mmol/L	3rd quartile 3–4 mmol/L	4th quartile >4 mmol/L	*p* value trend
Admissions, *n*	12,590	17,388	5,790	10,866	
Patients, *n*	10,205	13,727	4,443	8,072	
In-hospital death, *n* (%)	28 (0.3)	56 (0.4)	29 (0.7)	205 (2.5)	
HR crude (95% CI)	1.00	1.29 (0.88, 1.88)	1.34 (0.85, 2.10)	4.08 (2.93, 5.69)	<0.001
p value	Reference	0.189	0.207	<0.001	
HR adjusted (95% CI)*	1.00	1.08 (0.74, 1.59)	1.01 (0.64, 1.61)	1.93 (1.30, 2.85)	<0.001
p value	Reference	0.685	0.965	0.001	

* Adjusted for baseline covariates (age, sex, Charlson/Deyo Score, diabetes, cardiovascular disease, congestive heart failure, malignancies, eGFR, cerebrovascular disease, dementia, liver diseases, the lowest and the highest serum sodium levels reached during hospital stay, number of sodium measurements).

HR, hazard ratio; eGFR, estimated glomerular filtration rate.

Fig. 2. Association between sodium slope and in-hospital death.



Multivariate HRs (95% CI) of in-hospital death associated with sodium slopes using restricted cubic splines, adjusted for age, sex, Charlson/Deyo Score, diabetes, cardiovascular diseases, congestive heart failure, malignancies, eGFR, severe kidney disease, cerebrovascular disease, dementia, liver diseases, the lowest and the highest serum sodium level reached during hospital stay, number of sodium measurements. HR, hazard ratio.

Discussion/Conclusion

In this study, we describe the association between incident dysnatremia and in-hospital death and, to the best of our knowledge for the first time, the association between sodium fluctuation and in hospital death in a general medical-surgical non-ICU hospitalized population. Incident dysnatremia

is confirmed to be an independent risk factor for in-hospital death and sodium fluctuations are associated with increased in-hospital death independent of the severity of dysnatremia.

Dysnatremia is the most common electrolyte disorder. To date, a variety of studies evaluated its epidemiology in hospital patients reporting a quite varied incidence and prevalence especially because it is strongly influenced by the study population (ICU vs. non-ICU). The prevalence of hyponatremia in the hospital setting has been described to range between 12 and 17% (5,11,21–23) and 40% in the hospitalized population (24). Similarly, several studies demonstrated that hypernatremia appeared also to be common at hospital admission ranging from 0.5 to 7.7% (5,25–28). However, most of these studies focused on critically ill ICU patients or analyzed community-acquired dysnatremia observed at hospital admission. Conversely, few studies have investigated hospital-acquired dysnatremia and its incidence during hospital stay. The incidence of in-hospital hyponatremia and hypernatremia has been described ranging from 9.0 to 13.6% (11,12) and from 1.0 to 9.1% (11,12), respectively.

In order to describe the incidence of dysnatremia during hospital stay, we considered only normonatremic patients at hospital admission. Here we reported one of the largest retrospective studies focusing on hospital-acquired dysnatremia, with an incidence of hyponatremia and hypernatremia of 10.7 and 4.3%, respectively (Table 3).

Explanations for differences in dysnatremia epidemiology compared with previous works include study design (retrospective vs prospective), sample sizes, differences in study population, and in cutoff levels used to define dysnatremia.

Medical interest in dysnatremic conditions is justified by the burden of morbidity and mortality associated with its development. Adverse consequences following dysnatremic conditions have been widely reported in the scientific literature. The association between dysnatremia and mortality is well known in clinical practice and documented in medical literature. Waikar et al. (22) showed that 98,411 prospective patients with hyponatremia had higher in-hospital, 1-year, and 5-year mortality rates than patients without hyponatremia. Hu et al. (11) demonstrated that all kinds of dysnatremia were independently associated with in-hospital mortality, and mixed dysnatremia (especially “hypo- to hyper”) and hypernatremia (especially hospital-acquired and persistent hypernatremia), were strong predictors of mortality. Recent scientific literature suggests also a possible role of borderline or mild forms of dysnatremia on patient outcomes (5,12,13,22,29,30).

In our cohort, 4.6% of all patients who developed a dysnatremic condition died during hospital stay. In survival analysis, incident dysnatremia was associated with increased in-hospital mortality both in incident hyponatremic and hypernatremic patients. Worthy of notice, the hypernatremic groups had higher risk of death compared with the hyponatremic group.

Our study focused also on sodium fluctuations and mortality. According to data an increase of the blood sodium concentration > 2.9% from its baseline value is associated with in-hospital death independently of severity of dysnatremia. Furthermore, as expected, a fluctuation occurring too quickly was associated with increased risk of in-hospital death, regardless of sodium value (Fig. 2). Investigations into sodium fluctuation are still lacking. In particular, the link between sodium fluctuations and in-hospital death is poorly characterized. Until now, this issue has been investigated only in 3 other works (12,14,15). However, those studies were set in ICU in critically ill patients rather than general population patients. Here, focusing on a mixed medical-surgical non-ICU population, we provide increased generalizability to our results, underlining the importance that mild sodium fluctuations (> 2.9% or 4 mmol/L from baseline value) and incident dysnatremia carry on patient outcomes.

Similar to previous works, we found a significant association between severity of dysnatremia and mortality. However, while the link between the most severe forms of dysnatremia and mortality has a strong rationale, data on the risk associated with small sodium fluctuations are lacking and the mechanism leading to higher mortality are still unclear. According to our data, a sodium fluctuation just a bit over 4 mmol/L from baseline was significantly associated with higher in-hospital death. As recently elucidated by a consensus statement from the Italian Society of Endocrinology, Italian Society of Nephrology and the Italian Association of Medical Oncology electrolytes disorders (especially in hyponatremic status) are frequently associated with cardiovascular, liver, malignancies, renal diseases (as well as showed in our study) (31). It is possible that sodium fluctuation is a potential marker of underlying disease severity. In fact, in our data, we report a higher baseline prevalence of cerebrovascular, renal, and cardiovascular diseases in the highest quartile of sodium fluctuation, all conditions characterized by deranged osmolality control. A direct effect of dysnatremia and mild sodium fluctuations on mortality could also be hypothesized. Sodium is not only the main determinant of plasma osmolality (32) but it also plays a key role in several biochemical and electrical processes within the body (33). However, our study was not designed to elucidate a possible causal relationship between sodium fluctuations and in-hospital death. Because of the retrospective observational study design, here we can only document an association between exposures and outcomes and only speculate on potential mechanisms.

Our work has several limitations. First, it is a retrospective study conducted on a single hospital center; hence, generalizability of our results could be limited. However, we could include in our analysis admissions from all kinds of medical and surgical wards, which in part improves external validity of our findings. We have no information on causes of dysnatremia and treatments administered during hospital stay, so we could not correct our outcomes for different causes of

dysnatremia. Furthermore, we used administrative codes for identification of all comorbid conditions; however, to account for comorbidities, we used the Charlson/Deyo score, a validated method of categorizing comorbidities of patients based on the ICD diagnosis codes from administrative data. Regarding the strengths of our study, to date this is one of the largest retrospective works on the epidemiology of incident dysnatremia and in-hospital death and, to the best of our knowledge, our work describes for the first time the impact of sodium fluctuations on in-hospital death in a general hospitalized population.

What we would emphasize with our study is the importance that even mild variations in sodium levels have on patient outcomes. It is necessary to pay attention to both small and rapid sodium fluctuations, even when in a normonatremic range.

In summary: (i) incident dysnatremia is associated with increased in-hospital death; (ii) incident hypernatremia is associated with higher mortality than hyponatremia; (iii) sodium fluctuations during hospital stay is a potential predictor of in-hospital death independent of dysnatremia severity.

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CHAPTER 3

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 the role of serum potassium concentrations [K^+] variability on clinical outcomes is still poorly investigated. Aim of our study was to analyze the association between serum potassium concentrations ([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 January 1, 2010 and December 31, 2014 with inclusion of adult patients with [K^+] measurements ≥2. The outcome of interest was in-hospital mortality. The exposures of interest were [K^+] fluctuations and hypo-hyperkalemia and mixed dyskalemia 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 3rd (OR 1.45, 95% CI 1.13, 1.88, p=0.003) and 4th (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 normokaliemia (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.

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 hypo- and hyperkaliemia 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). Particularly, the kidney plays a key role in $[K^+]$ homeostasis. So, the association between kidney diseases and $[K^+]$ disorders (1,6) is not surprising.

Although several studies have analyzed 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 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 more than 1 million people in Rome, between January 1, 2010 and December 31, 2014.

We included only adult patients (≥18years), 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 ICD-9-CM (International Classification of Disease, 9th Revision, Clinical Modification) diagnosis codes at

hospital discharge, 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 below 2.3% (range 1.3 to 1.7%). Extreme [K^+] levels (<2 mEq/L and [K^+] >7.5 mEq/L), that could introduce distortion in the analyses, were removed.

Definitions

The coefficient of variation (CV) (12), defined as the ratio between the standard deviation 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: hypokalemia (HoK, any [K^+] value <3.0 mmol/L), hyperkalemia (HerK, any [K^+] value >5.0 mmol/L), normokalemia (NK, all [K^+] values ≥3.0 mmol/L and ≤5.0 mmol/L), mixed dyskalemia (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 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: 1) 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, V56.8); 2) any of the following procedure codes: 39.95 (hemodialysis), V45.1 (renal dialysis status), V56.0 (extracorporeal dialysis), or V56.1 (fitting and adjustment of extracorporeal dialysis catheter); 3) 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, MD).

Statistical analysis

Quantitative variables were described using mean and standard deviation (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 (95% 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, baseline eGFR.
A 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 different patient populations 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, 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-value < 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, had lower baseline eGFR and higher prevalence of comorbidities.

Table 1. Baseline characteristics of the study population stratified by quartile of [Kþ] 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.

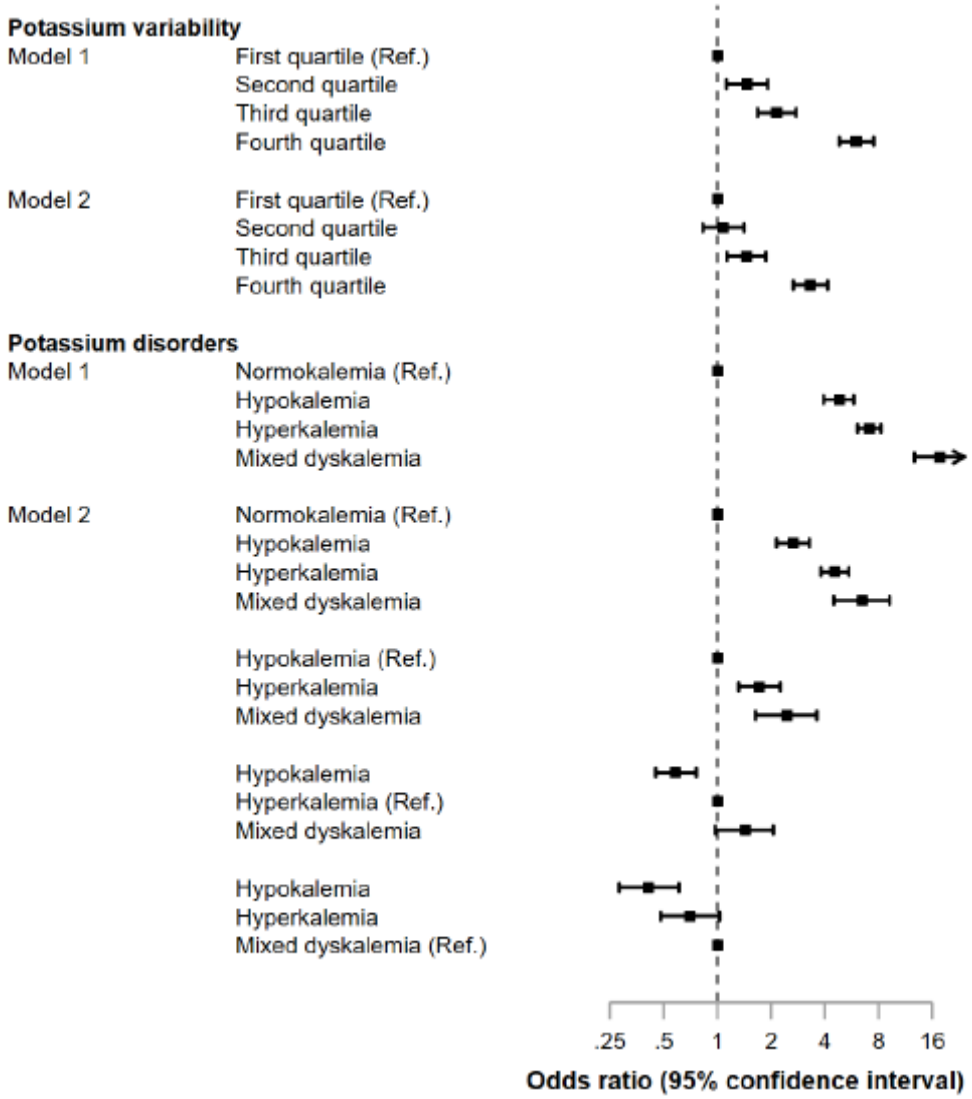
During a median follow-up of 8 days (IQR 8, range 0 to 456 days), 965 patients (1.5%) died. Results of the association between [K^+] variability and in-hospital death are reported in Table 2 and Figure 1. Logistic regression models suggested a higher risk for death across increasing quartiles of [K^+] 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.

Table 2. Association between [Kþ] 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.

Figure 1. Association between [Kþ] disorders/variability and in-hospital mortality



Results did not change after restricting the analyses to NK patients, i.e. those without any [K+] disorder during hospital stay (Supplementary Table 1).

In our study cohort, [K+] disorders were observed in 11.8% of the cohort (*n* = 7,600). Specifically, 3,047 (4.7%) patients had HoK, 4,228 (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 Table 2). The association did not change after stratifying by number of [K+] measurements (Supplementary Table 3; p-value for interaction = 0.834) and by observation time between [K+] measurements (Supplementary Table 4; p-value for interaction = 0.158). Restricted analysis after removal of 264 patients with ESKD confirmed our findings (Supplemetary Table 5).

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 Table

6). 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-value = 0.065).

Discussion

In this paper, 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 have been widely explored in the scientific literature. Both hypo- and hyperkaliemia conditions have been strongly associated with increased mortality risk in the hospital setting (4,5,7,8). Particularly, 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-analyzed and explored the role of electrolytes imbalance on patients' 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 hypo- or hyperkaliemia is especially useful in clinical practice 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 and 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. Using, unlike others published studies, 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), 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, independently of the presence of hypo- or hyperkaliemia.

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, with clear guidelines regarding the definition of potassium variability. Another important limitation of the present study is that the associations could not be finely controlled for patient medications or underlying diseases, which might have altered the results of the present study. Further research is need, in order to see whether specific health conditions show differential associations between potassium variability and clinical outcomes. As a result, the finding of elevated mortality in patients with potassium variability within the normal range should be interpreted with caution. However, this is the first study analyzing [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 Tables

Supplementary Table 1. Association between [K+] variability and in-hospital mortality (only patients with normokalemia during hospital stay)

	Events (n, %)	Model 1		Model 2	
		OR (95% CI)	p-value for trend	OR (95% CI)	p-value for trend
Q1 (CV ≤3.67)	74 (0.5)	1.00 (Reference)	p<0.001	1.00 (Reference)	p<0.001
Q2 (3.67<CV≤6.37)	100 (0.7)	1.35 (1.00, 1.84) p= 0.049		1.06 (0.78, 1.44) *p*=0.707	
Q3 (6.37<CV≤9.39)	128 (0.9)	1.73 (1.30, 2.32) p<0.001		1.21 (0.91, 1.63) *p*=0.193	
Q4 (CV >9.39)	224 (1.6)	3.07 (2.37, 4.02) p<0.001		2.01 (1.54, 2.65) *p*<0.001	

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

Supplementary Table 2. Baseline characteristics of the study population according to [K+] status

	Normokalemia n=56,907	Hypokalemia n=3,047	Hyperkalemia n=4,228	Mixed dyskalemia n=325
Age, years, mean (SD)	59.5 (18.1)	67.65 (15.95)	69.00 (15.17)	72.30 (14.12)
Males, n (%)	26,239 (46.1)	1,165 (38.2)	2,344 (55.4)	125 (38.5)
Charlson/Deyo score, n (%)				
- 0	45,122 (79.3)	2,093 (68.7)	2,661 (62.9)	191 (58.8)
- 1	8,358 (14.7)	662 (21.7)	796 (18.8)	76 (23.4)
- 2	1,930 (3.4)	182 (6.0)	445 (10.5)	30 (9.2)
- 3+	1,497 (2.6)	110 (3.6)	326 (7.7)	28 (8.6)
Comorbidities, n (%)				
- Cardiovascular	21,165 (37.2)	1,478 (48.5)	2,177 (51.5)	190 (58.5)
- Malignancies	17,522 (30.8)	1,029 (33.8)	1,352 (32.0)	94 (28.9)
- Gastrointestinal	8,554 (15.0)	562 (18.4)	789 (18.7)	55 (16.9)
- Genitourinary	6,299 (11.1)	452 (14.8)	976 (23.1)	86 (26.5)
- Endocrine/Metabolic	9,336 (16.4)	699 (22.9)	1,045 (24.7)	89 (27.4)
- Infectious	2,580 (4.5)	350 (11.5)	324 (7.7)	83 (25.5)
- Respiratory	6,819 (12.0)	718 (23.6)	866 (20.5)	127 (39.1)
eGFR, mean (SD), mL/min/1.73 m^2	81.0 (25.7)	74.0 (28.0)	56.28 (30.4)	59.3 (30.6)
[K+], mean (SD), mmol/L*	4.0 (0.4)	3.43 (0.60)	4.68 (0.72)	4.10 (1.0)
[K+] measurements, median (IQR)	3.0 (2.0)	6.0 (6.0)	5.0 (5.0)	12.0 (10.0)
[K+] CV, median (IQR)	6.4 (5.7)	14.1 (6.2)	12.9 (7.2)	21.6 (6.8)

* Value at hospital admission

Supplementary Table 3. Association between [K+] variability and in-hospital mortality stratified by number of [K+] measurements

Quartiles	Quartiles	[K+] measurements ≤3		[K+] measurements >3	
[K+] measurements≤3	[K+] measurements>3	OR (95% CI)	p-value for trend	OR (95% CI)	p-value for trend
Q1 (CV ≤3.14)	Q1 (CV ≤6.18)	1.00 (Reference)	p<0.001	1.00 (Reference)	p<0.001
Q2 (3.14<CV≤5.66)	Q2 (6.18<CV≤8.70)	0.98 (0.68, 1.41) p=0.923		1.23 (0.89, 1.71) p=0.216	
Q3 (5.66<CV≤9.22)	Q3 (8.70<CV≤11.94)	0.85 (0.59, 1.24) p=0.397		1.87 (1.39, 2.54) p<0.001	
Q4 (CV >9.22)	Q4 (CV >11.94)	2.44 (1.82, 3.33) p<0.001		3.55 (2.71, 4.72) p<0.001	

Multivariable models adjusted for age, sex, comorbidities, Charslon/Deyo score, [K+] value at hospital admission, eGFR baseline

Supplementary Table 4. Association between [K+] variability and in-hospital mortality stratified by [K+] observation time

Quartiles [K⁺] CV	Quartiles [K⁺] CV	Observation time ≤5 days		Observation time >5	
Observation time ≤5	Observation time >5	OR (95% CI)	p-value for trend	OR (95% CI)	p-value for trend
Q1 (CV ≤3.29)	Q1 (CV ≤5.39)	1.00 (Reference)		1.00 (Reference)	p<0.001
Q2 (3.29<CV≤5.66)	Q2 (5.39<CV≤8.14)	1.12 (0.78, 1.61) p=0.543		1.71 (1.17, 2.55) p=0.007	
Q3 (5.66<CV≤9.41)	Q3 (8.14<CV≤11.47)	1.12 (0.79, 1.60) p=0.525		2.53 (1.77, 3.71) p<0.001	
Q4 (CV >9.41)	Q4 (CV >11.47)	2.69 (2.00, 3.69) p<0.001		5.82 (4.18, 8.34) p<0.001	

Multivariable models adjusted for age, sex, comorbidities, Charslon/Deyo score, [K⁺] value at hospital admission, eGFR baseline. Observation time is calculated as the difference between the first and last [K⁺] measurement for each hospitalization.

Supplementary Table 5. Association between [K+] variability and in-hospital mortality after removal of patients with ESKD

	Events (n, %)	Model 1		Model 2	
		OR (95% CI)	p-value for trend	OR (95% CI)	p-value for trend
Q1 (CV ≤3.92)	92 (0.6)	1.00 (Reference)	p<0.001	1.00 (Reference)	p<0.001
Q2 (3.92<CV≤6.99)	132 (0.8)	1.44 (1.10, 1.89) p=0.007		1.08 (0.83, 1.42) p=0.573	
Q3 (6.99<CV≤10.50)	196 (1.2)	2.15 (1.68, 2.76) p<0.001		1.45 (1.13, 1.88) p=0.004	
Q4 (CV >10.50)	536 (3.3)	6.00 (4.83, 7.54) p<0.001		3.33 (2.67, 4.21) p<0.001	

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

Supplementary Table 6. Association between [K+] disorders and in-hospital mortality (pairwise comparisons)

	OR (95% CI)	OR (95% CI)	OR (95% CI)
Hypokalemia	1.00 (Reference)	0.57 (0.44, 0.74) p<0.001	0.40 (0.27, 0.60) p<0.001
Hyperkalemia	1.75 (1.34, 2.29) p<0.001	1.00 (Reference)	0.70 (0.48, 1.03) p=0.065
Mixed dyskalemia	2.50 (1.67, 3.70) p<0.001	1.43 (0.97, 2.07) p=0.065	1.00 (Reference)

Multivariable model adjusted for age, sex, comorbidities, Charslon/Deyo score, [K⁺] value at hospital admission, eGFR baseline

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PART 2

Sodium and Potassium disorders and variability predict acute kidney injury in the hospitalized population

CHAPTER 4

Serum sodium variability and acute kidney injury: a retrospective observational cohort study on a hospitalized population

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Abstract

Aim of our study was to analyze the association between serum sodium (Na) variability and acute kidney injury (AKI) development.

We performed a retrospective observational cohort study on the inpatient population admitted to Fondazione Policlinico Universitario A. Gemelli IRCCS between January 1, 2010 and December 31, 2014 with inclusion of adult patients with ≥2 Na and ≥2 serum creatinine measurements. We included only patients with ≥2 Na measurements before AKI development. The outcome of interest was AKI. The exposures of interest were hyponatremia, hypernatremia and Na fluctuations before AKI development. Na variability was evaluated using the coefficient of variation (*CV*). Multivariable Cox proportional hazards and logistic regression models were fitted to obtain hazard ratios (HRs), odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the exposures of interest and AKI.

Overall, 56,961 patients met our inclusion criteria. During 1,541 person-years of follow-up AKI occurred in 1,450 patients. In multivariable hazard models, patients with pre-existent dysnatremia and those who developed dysnatremia had a higher risk of AKI compared with patients with normonatremia. Logistic models suggested a higher risk for AKI in the 3rd (OR 1.41, 95% CI 1.18, 1.70, p<0.001) and 4th (OR 1.53, 95% CI 1.24, 1.91, p<0.001) highest quartiles of Na *CV* with a significant linear trend across quartiles (p-trend <0.001). This association was also independent from Na highest and lowest peak value.

Dysnatremia is a common condition and is positive associated with AKI development. Furthermore, high Na variability might be considered an independent early indicator for kidney injury development.

Introduction

Electrolyte disturbances are common disorders in the hospitalized population (1). Serum sodium (Na) imbalance is frequently observed in the hospital setting (2). Dysnatremia conditions (including hyponatremia [Na<135 mEq/L] and hypernatremia [Na>145 mEq/L] are reported in approximately 30-40% of all hospital admissions (3).

Medical and scientific interest on these conditions is justified by the significant burden of Na disorders on the patient's prognosis (4). Both hyponatremia and hypernatremia have been widely associated with increased morbidity and mortality. Furthermore, as suggested by recently published studies, even small fluctuations in serum Na levels have been associated with a significant increase of in-hospital mortality (5–8).

As the main organ involved in water metabolism and homeostasis, the kidney is generally the main culprit for such disorders. Defective urine dilution with disproportionally high water intake causes hyponatremia. On the other way around, disorders involving urine concentration with inadequately low water intake cause hypernatremia (9,10). Therefore, it is not surprising that kidney diseases, especially acute kidney injury (AKI), characterized by an abrupt reduction in renal function, are commonly associated with these pathological conditions (11–15).

On the other hand, as sparsely reported in medical literature, an inverse relationship between dysnatremia and AKI emerges, where Na imbalance precedes and predicts kidney damage. A plausible cross-talk on a biological and pathogenetic ground might justify such relationship (16–18), but it still remains poorly investigated (14,19).

The aim of our study is to analyze the association between dysnatremia, in the whole range of its manifestations (hyponatremia, hypernatremia and mild Na fluctuations in the normonatremic range), and AKI development using a large retrospective cohort of hospitalized patients.

Methods

Setting and study population

We performed a retrospective observational study on the hospitalized population admitted to Fondazione Policlinico Universitario A. Gemelli IRCCS, a tertiary level hospital serving more than 1 million people in Rome, between January 1, 2010 and December 31, 2014. We included only adult patients (aged 18 years or older) with at least two serum Na (with consensual serum glucose) and at least two serum creatinine measurements during hospital stay. For analysis and data calculation we included only patients with at least two Na measurements before AKI development. Patients with end-stage kidney disease (ESKD) were excluded. Study patients were included at the time of their

first hospital admission. If a patient was hospitalized multiple times during the study period, we considered only the first one.

Data collection

All data were extracted from the hospital electronic database. We exported the following demographic, clinical and laboratory data: age, sex, serum Na, glucose, creatinine, primary and secondary ICD-9-CM (International Classification of Disease, 9th Revision, Clinical Modification) diagnosis codes at hospital discharge.

Definitions

Acute kidney injury (AKI) was defined according to creatinine kinetics criteria (20).
In-hospital AKI was defined as AKI developed after ≥48h from hospital admission.
Patients were grouped according to all Na values recorded during hospital stay and preceding AKI development in the following dysnatremic groups: hyponatremia (Na value <135 mmol/L), hypernatremia (Na value>145 mmol/L), normonatremia (lowest/highest Na values ≥135 mmol/L and ≤145 mmol/L). In patients with mixed dysnatremia, only the first Na disorder (what happened first), hypo or hypernatremia, was considered.
All Na levels were corrected for the dilutional effect associated with hyperglycemia using a validated method (21).
Na variability (or fluctuations) was evaluated using the coefficient of variation (*CV*), defined as the ratio between the standard deviation and the mean of all Na values preceding AKI development.
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 (22) was calculated for each hospital admission using primary and secondary diagnosis ICD-9-CM codes at hospital discharge.
ESKD was identified using administrative data (ICD -9 CM codes using chronic ESKD criteria: 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, V56.8). Dialysis criteria were: any of the following procedure codes: 39.95 (hemodialysis), V45.1 (renal dialysis status), V56.0 (extracorporeal dialysis), or V56.1 (fitting and adjustment of extracorporeal dialysis catheter); the initiation of dialysis in a patient with no known history of prior dialysis (ICD-9p 39.95, 54.98)) or laboratory data (baseline estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2). The

baseline GFR was estimated for each hospital admission with the CKD-EPI formula (23) using the first creatinine value read at hospital admission.

Outcomes and covariates

The outcome of interest was in-hospital AKI development.

The exposures of interest were the dysnatremia groups and Na fluctuations (expressed as quartiles of *CV* and analyzed as categorical and numeric variable).

The covariates that were used for risk adjustment in multivariable regression analyses were: age, sex, Charlson/Deyo score, comorbidities, Na value at hospital admission, eGFR at hospital admission.

Survival time was defined as the time from in-hospital admission to primary outcome, loss to follow-up or censoring, whichever occurred first.

Statistical analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as means with standard deviations (SDs) (normal distribution) or medians with interquartile ranges (IQRs) (skewed distribution). Normality of distributions were evaluated by visual inspection of histogram and Q-Q plot.

To explore the association between dysnatremia and AKI, we used a cause-specific regression hazard model. In order to confirm our results, as sensitivity analysis, we performed subdistribution hazard models considering in-hospital death as competitive risk. Cumulative acute kidney outcome was obtained using the cumulative incidence function for competitive risk. Time at risk started when Na disorder (hypo- or hypernatremia) was first observed, in normonatremic patients at first Na measurement. All alive patients were censored at the time of hospital discharge. Unadjusted and multivariable adjusted hazard ratios (HRs) with 95% confidence interval (95% CI) were reported for all survival analyses.

A logistic regression model, unadjusted and adjusted for all covariates, was fitted to obtain the odds ratios (ORs) and 95% CI of the association between the quartiles of Na *CV* and in-hospital AKI. Three models were built: Model 1 represents unadjusted ORs; Model 2 was adjusted for age, sex, comorbidities, Na value at hospital admission, baseline eGFR; Model 3 was adjusted for Na lowest and highest peak value in addition to factors included in Model 2. The first CV quartile was used as reference. A p-value for trend was calculated by treating quartiles as continuous variables in each model.

In order to evaluate the modification effects of subgroups on the relationship between dysnatremia and AKI development, a preplanned subgroup analysis was performed. The study population was

stratified in the following subgroups: age (<60 or ≥60 years old), sex (men or women), comorbidities (cardiovascular diseases, malignancies, gastrointestinal diseases, genitourinary disorders, endocrine/metabolic disorders, infectious and respiratory diseases), baseline eGFR (<60 or ≥60 mL/min/1.73 m^2).

For analysis and data calculation we used R statistics (version 3.4.4, R Foundation for Statistical Computing Platform). A p-value < 0.05 was considered as statistically significant.

Ethical

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

Results

A total of 56,961 patients met our inclusion criteria. Table 1 presents the baseline characteristics of the study population. In total, 22,068 (38.7%) had cardiovascular diseases, 18,070 (31.7%) had malignancies, 9,120 (16.0%) had gastrointestinal diseases, 6,328 (11.1%) had genitourinary disorders, 10,070 (17.7%) had endocrine/metabolic disorders, 3,049 (5.4%) infectious diseases, 7,625 (13.4%) respiratory diseases, with a mean eGFR at hospital admission of 79.6 (SD 25.9) mL/min/1.73 m^2 and a median Na value at hospital admission of 140 mEq/L (IQR 138.0-142.0, range lowest-highest 101.0-175.0 mEq/L) (Table 1).

Table 1. Baseline characteristics of the study population

	All $n=56,961$	Normonatremia $n=44,178$	Hyponatremia $n=8803$	Hypernatremia $n=3980$	*p* value
Age, years, mean (SD)	60.9 (18.0)	59.3 (18.0)	65.7 (17.4)	67.8 (15.6)	<0.001
Males, *n* (%)	26,632 (46.8)	20,368 (46.1)	4411 (50.1)	1853 (46.6)	<0.001
Charlson/Deyo score, *n* (%)					<0.001
0	43,957 (77.2)	35,156 (79.6)	6138 (69.7)	2663 (66.9)	
1	9082 (15.9)	6477 (14.7)	1692 (19.2)	913 (22.9)	
2	2169 (3.8)	1456 (3.3)	470 (5.3)	243 (6.1)	
>2	1753 (3.1)	1089 (2.5)	503 (5.7)	161 (4.0)	
Comorbidities, *n* (%)					
Cardiovascular	22,068 (38.7)	16,263 (36.8)	3795 (43.1)	2010 (50.5)	<0.001
Malignancies	18,070 (31.7)	13,672 (30.9)	3166 (36.0)	1232 (31.0)	<0.001
Gastrointestinal	9120 (16.0)	6757 (15.3)	1874 (21.3)	489 (12.3)	<0.001
Genitourinary	6328 (11.1)	4593 (10.4)	1175 (13.3)	560 (14.1)	<0.001
Endocrine/metabolic	10,070 (17.7)	7520 (17.0)	1709 (19.4)	841 (21.1)	<0.001
Infectious	3049 (5.4)	1740 (3.9)	1008 (11.5)	301 (7.6)	<0.001
Respiratory	7625 (13.4)	4871 (11.0)	1781 (20.2)	973 (24.4)	<0.001
eGFR, mean (SD), mL/min/1.73 m^2*	79.6 (25.9)	81.4 (25.2)	75.0 (28.1)	70.7 (25.5)	<0.001
Na, median (IQR), mEq/L*	140.0 (138.0, 142.0)	140.0 (139.0, 142.0)	135.0 (132.0, 139.0)	144.0 (141.0, 146.0)	<0.001
Na CV, median (IQR)	1.3 (0.7,1.9)	1.0 (0.5, 1.5)	2.3 (1.7, 3.0)	2.1 (1.5, 2.9)	< 0.001

*Value at hospital admission

In the study population, 44,178 stayed in a normonatremic condition while in 12,783 (22.4%) a dysnatremic status occurred (hyponatremia in 8,803 [15.5%], hypernatremia in 3,980 [7.0%]). Dysnatremic patients aged older (59.3 years [SD 18.0], 65.7 years [SD 17.4], 67.8 years [SD 15.6], in normo-, hypo-, hypernatremics, respectively, $p<0.001$) with a higher prevalence in males (46.1%, 50.1%, 46.6%, in normo-, hypo- and hypernatremics, respectively, $p<0.001$). Hyponatremia, and hypernatremia showed a worse comorbidity index, with a higher prevalence in cardiovascular diseases (36.8%, 43.1%, 50.5% in normo-, hypo- and hypernatremics, respectively, $p<0.001$), malignancicies (30.9%, 36.0%, 31.0% in normo-, hypo- and hypernatremics, respectively, $p<0.001$), genitourinary disorders (10.4%, 13.3%, 14.1% in normo-, hypo- and hypernatremics, respectively, $p<0.001$), endocrine/metabolic disorders (17.0%, 19.4%, 21.1% in normo-, hypo- and hypernatremics, respectively, $p<0.001$), infectious diseases (3.9%, 11.5%, 7.6% in normo-, hypo- and hypernatremics, respectively, $p<0.001$), respiratory diseases (11.0%, 20.2%, 24.4% in normo-, hypo- and hypernatremics, respectively, $p<0.001$). Lower eGFR was observed in patients with Na disorders (81.4 ml/min [SD 25.2], 75.0 ml/min [SD 28.1], 70.7 ml/min [SD 25.5] in normo-, hypo- and hypernatremics, respectively, $p<0.001$).

Coefficient of Na variation (Na *CV*) was used to describe Na fluctuation in the study cohort. Patients with higher Na variability showed worse comorbidty index and higher prevalence in comorbidities. Older age and lower baseline eGFR was also observed in subjects with higher Na fluctuations (Table 2).

Table 2. Baseline characteristics of the study population stratified by quartile of Na coefficient of variation (CV)

	1st CV ≤ 0.71 *n* = 14,580	2nd 0.71 < CV ≤ 1.25 *n* = 14,037	3rd 1.25 < CV ≤ 1.94 *n* = 14,206	4th CV > 1.94 *n* = 14,138	*p* value
Age, years, mean (SD)	57.8 (18.3)	60.5 (17.9)	62.1 (17.3)	63.2 (18.0)	< 0.001
Men, *n* (%)	6587 (45.2)	6806 (48.5)	6925 (48.7)	6314 (44.7)	< 0.001
Charlson/Deyo score, *n* (%)					< 0.001
0	11,771 (80.7)	10,869 (77.4)	10,754 (75.7)	10,563 (74.7)	
1	2063 (14.1)	2232 (15.9)	2375 (16.7)	2412 (17.1)	
2	411 (2.8)	531 (3.8)	585 (4.1)	642 (4.5)	
> 2	335 (2.3)	405 (2.9)	492 (3.5)	521 (3.7)	
Comorbidities, *n* (%)					
Cardiovascular	5130 (35.2)	5424 (38.6)	5837 (41.1)	5677 (40.2)	< 0.001
Malignancies	4151 (28.5)	4440 (31.6)	4808 (33.8)	4671 (33.0)	< 0.001
Gastrointestinal	2307 (15.8)	2229 (15.9)	2342 (16.5)	2242 (15.9)	0.363
Genito/urinary	1408 (9.7)	1502 (10.7)	1617 (11.4)	1801 (12.7)	< 0.001
Endocrine/metabolic	2466 (16.9)	2441 (17.4)	2655 (18.7)	2508 (17.7)	0.001
Infectious	496 (3.4)	632 (4.5)	820 (5.8)	1101 (7.8)	< 0.001
Respiratory	1277 (8.8)	1654 (11.8)	2122 (14.9)	2572 (18.2)	< 0.001
eGFR, mean (SD), mL/min/1.73 m^2*	83.0 (25.0)	80.1 (25.5)	78.1 (25.8)	77.3 (27.1)	< 0.001
Na, median (IQR), mEq/L*	140.0 (139.0, 142.0)	140.0 (138.0, 142.0)	140.0 (138.0, 142.0)	139.0 (136.0, 142.0)	< 0.001
Na CV, median (IQR)	0.5 (0.0, 0.5)	1.0 (1.0, 1.1)	1.5 (1.5, 1.7)	2.5 (2.1, 3.1)	< 0.001

*Value at hospital admission

Sodium and AKI

Dysnatremia and AKI

During 1,541 years of follow-up the outcome occurred in 1,450 (2.5%, incidence rate 940.9 per 1000 person-yr).

A dysnatremic condition was associated with increased risk of AKI development (Table 3). Patients with dysnatremia or patients who developed dysnatremia had a higher risk of AKI occurrence with an HR, in multivariable adjusted model, of 1.87 (95% CI 1.61, 2.16, p<0.001), HR 1.67 (95% CI 1.41, 1.98, p<0.001), in hyponatremia and hypernatremia, respectively.

Table 3. Association of dysnatremia with AKI development

	Overall	Normonatremia	Hyponatremia	Hypernatremia
No. of patients	56,961	44,178	8803	3980
Person-years	1541	1167	269	106
Time to AKI, median (IQR), days	–	–	8.0 (10.0)	7.0 (8.0)
Kidney outcome				
AKI (*N*, %)	1450 (2.5)	864 (2.0)	381 (4.3)	205 (5.2)
AKI per 1000 person-year	940.9	740.4	1416.4	1934.0
Cause-specific hazard model				
HR (95% CI	–	1.00 (Reference)	1.98 (1.76, 2.24) $p<0.001$	2.69 (2.31, 3.13) $p<0.001$
HR (95% CI)*	–	1.00 (Reference)	1.87 (1.61, 2.16) $p<0.001$	1.67 (1.41, 1.98) $p<0.001$

*Adjusted for: age, sex, comorbidities, Na value at hospital admission, eGFR at baseline

Sodium variability and AKI

In Table 4 we investigated the association between Na variability and AKI. Unadjusted regression models suggested a higher risk for AKI development in the 2nd (OR 1.45, 95% CI 1.21, 1.73, p<0.001), 3rd (OR 2.08, 95% CI 1.77, 2.47, p<0.001) and 4th (OR 2.70, 95% CI 2.30, 3.18, p<0.001) quartile of Na *CV*. This association was also observed in the multivariable adjusted model (Model 2) with an OR of 1.25 (95% CI 1.04, 1.50, p= 0.017), an OR of 1.66 (95% CI 1.40, 1.97, p<0.001) and an OR of 2.12 (95% CI 1.79, 2.51, p<0.001) in the 2nd, 3rd and in the 4th quartile of Na *CV* respectively with a significant linear trend across all quartiles (p for trend <0.001). Of note, even after adjustment for Na lowest and highest peak value (Model 3) the significant and independent relationship was confirmed.

Table 4. Association between Na variability (CV) and AKI development

	No. of events (%)	Model 1		Model 2		Model 3	
		OR (95% CI)	*p* value for trend	OR (95% CI)	*p* value for trend	OR (95% CI)	*p* value for trend
Q1 CV ≤ 0.71	209 (1.4)	1.00 (Reference)	< 0.001	1.00 (Reference)	< 0.001	1.00 (Reference)	< 0.001
Q2 0.71 < CV ≤ 1.25	289 (2.1)	1.45 (121, 1.73) *p* < 0.001		1.25 (1.04, 1.50) *p* = 0.017		1.16 (0.97, 1.40) *p* = 0.115	
Q3 1.25 < CV ≤ 1.94	418 (2.9)	2.08 (1.77, 2.47) *p* < 0.001		1.66 (1.40, 1.97) *p* < 0.001		1.41 (1.18, 1.70) *p* < 0.001	
Q4 CV > 1.94	534 (3.8)	2.70 (2.30, 3.18) *p* < 0.001		2.12 (1.79, 2.51) *p* < 0.001		1.53 (1.24, 1.91) *p* < 0.001	

Model 1: Unadjusted model

Model 2: Multivariable adjusted logistic regression. Adjusted for age, sex, comorbidities, Na value at hospital admission, eGFR baseline

Model 3: Multivariable adjusted logistic regression. Adjusted for age, sex, comorbidities, Na value at hospital admission, eGFR baseline, Na lowest and highest peak value

Subgroup analysis

We evaluated the modification effects of subgroups on the relationship between dysnatremia and AKI development performing subgroup analysis (Table 5). A significant interaction was observed in dysnatremic patients older than 60 yrs, with cardiovascular and endocrine/metabolic disorders; there was also an effect modification only in hyponatremic patients male, with gastrointestinal diseases, genito/urinary disorders and eGFR<60 ml/min.

Table 5. Subgroup associations of dysnatremia with AKI development

	AKI (hyponatremia sample)		AKI (hypernatremia sample)	
	HR (95% CI)	*p* for interaction	HR (95% CI)	*p* for interaction
Age ≥ 60	4.32 (3.26, 5.71)	< 0.001	4.26 (2.80, 6.48)	0.003
Age < 60	1.53 (1.34, 1.76)		2.14 (1.81, 2.52)	
Male	2.58 (2.12, 3.14)	< 0.001	3.23 (2.53, 4.13)	0.075
Female	1.65 (1.41, 1.92)		2.43 (2.00, 2.95)	
Cardiovascular	3.35 (2.73, 4.10)	< 0.001	4.39 (3.36, 5.73)	< 0.001
No cardiovascular	1.42 (1.22, 1.66)		1.85 (1.53, 2.23)	
Malignancies	1.85 (1.60, 2.15)	0.069	2.73 (2.30, 3.26)	0.652
No malignancies	2.36 (1.91, 2.92)		2.52 (1.84, 3.45)	
Gastrointestinal	1.85 (1.61, 2.11)	0.005	2.68 (2.28, 3.15)	0.960
No gastrointestinal	2.93 (2.19, 3.91)		2.71 (1.97, 4.40)	
Genito/urinary	2.04 (1.78, 2.34)	0.031	2.75 (2.32, 3.27)	0.089
No genito/urinary	1.47 (1.13, 1.92)		2.00 (1.44, 2.77)	
Endocrine/metabolic	2.25 (1.96, 2.59)	< 0.001	3.10 (2.61, 3.70)	0.001
No endocrine/metabolic	1.34 (1.05, 1.71)		1.71 (1.25, 2.34)	
Infectious	2.08 (1.83, 2.37)	0.085	2.59 (2.20, 3.05)	0.314
No infectious	1.46 (1.00, 2.14)		3.29 (2.12, 5.11)	
Respiratory	2.21 (1.93, 2.54)	< 0.001	2.71 (2.24, 3.28)	0.100
No respiratory	1.23 (0.96, 1.59)		2.06 (1.58, 2.69)	
eGFR ≥ 60	1.37 (1.17, 1.61)	< 0.001	1.95 (1.61, 2.36)	0.123
eGFR < 60	2.28 (1.89, 2.73)		2.51 (1.94, 3.24)	

Sensitivity analysis

As sensitivity analysis a subdistribution hazard model between AKI development and dysnatremic groups was built (Supplemental Table 1) using death as competitive risk. The relationship between the outcome of interest and the exposures was confirmed, with a significant and independent increase risk of AKI development in dysnatremic groups (HR 1.84, 95% CI 1.58, 2.16, $p<0.001$, HR 1.62, 95% CI 1.35, 1.95, $p<0.001$, respectively in hyponatremia and hypernatremia condition).

Discussion

Our study demonstrates a strong and independent association between Na disturbances and Na variability with the risk of AKI development. Dysnatremia, hyponatremia or hypernatremia are significantly associated with acute kidney injury and higher Na variability (CV) predicts AKI development during hospital stay.

AKI is a complex clinical syndrome characterized by a sudden reduction in renal function and defined as an increase (absolute or relative) of creatinine levels or a reduction in urinary output (24). The high burden on in-hospital patient prognosis (25,26) justifies the medical and scientific interest in

this clinical syndrome. Since the kidney is the main organ engaged in fluid and electrolyte homeostasis, it is not surprising that renal dysfunctions are frequently associated with water imbalance and so alterations in serum electrolyte levels. In particular, hypo and hypernatremia conditions, often observed in the hospitalized population (1), have been related to kidney injury (11–15).

A growing body of recent evidences highlight the relationship between disorders of metabolism and electrolyte homeostasis and strong outcomes (27,8,28). Several studies have described the association between Na balance and kidney function (11–13) however, a few of them have considered dysnatremia as predictor of AKI (14,19) and none has investigated Na variability as a marker in kidney injury development.

During 1,541 person-years of follow-up, AKI was observed in 1,450 (2.5 %) patients (incidence rate 940.9 per 1,000 person-yr); 588 (40.4%) of them showed a dysnatremia condition (at hospital admission or during hospital stay) before AKI development. As clearly demonstrated by our results, Na disturbances were strongly and independently associated with in-hospital AKI. Of note, higher Na fluctuations were linearly related to an increased risk of AKI independently of Na peak value.

Many pathological conditions may share dysnatremia and AKI such as volume overload or depletion, heart and liver diseases, infectious diseases and partly explain our findings. In fact, under specific conditions, such as cardiovascular diseases, cardio-renal syndrome, gastrointestinal diseases or malignancies, hyponatremia has been associated with AKI development (11–13). According to our findings, older patients, with cardiovascular diseases and endocrine/metabolic disorders with dysnatremia were especially associated with increased risk of AKI.

However, an independent relationship between Na disturbances and Na variability emerges from our study. Recently Lee et al, focusing only on an hyponatremic hospitalized population, described an independent correlation between dysnatremia and AKI development, where pre-existing hyponatremia increased the risk of AKI by 30% (19).

Using our retrospective cohort we decided to go further these findings. Not only pre-existing hyponatremia condition was associated with kidney injury, but also hypernatremia demonstrated as a potential independent predictor of AKI. Interestingly, higher Na variability was often observed before kidney damage. From this point of view, since serum creatinine is such a poor sensitive marker of kidney damage, higher Na fluctuations may anticipate worsening of renal function.

An appropriate question should be whether dysnatremia is a simple bystander or contributing factor of AKI. Dysnatremia and kidney injury may be two different manifestations of a common underlying disease or reflect the severity of the illness and comorbidities of the patient. Volume depletion that generally accompanies hypernatremia is frequently recognized as a common cause of AKI

development. On the other hand, Na dilution (or true Na depletion due to diuretics) can be observed in systemic disorders (i.e. heart, liver failure) causing AKI, characterized by increased extracellular volume.

However, according to our results, although we could not exclude residual confounding due to the retrospective nature of the study, a direct pathogenic relationship between Na imbalance and kidney injury might be hypothesized. Concerning this, it is interesting to note the median time between dysnatremia and the onset of AKI (7-8 days), as reported on Table 3. An interesting finding in our study, Na variability and kidney injury were associated independently from Na peak value (highest or lowest), in accordance with what has been shown by other Authors (8,27), suggesting a potentially more damaging role of Na rapid variations rather than Na absolute value. Evidence suggests that osmotic stress can cause cellular damage, even if we do not know the exact mechanism at kidney level. The direct effect of serum sodium concentration and variation on extracellular tonicity is well known. Serum sodium fluctuations induce water shift in and out of the cells threatening their survival (29–31). A wide variety of experimental models have demonstrated that osmo-stress can evoke multiple apoptotic pathways, inhibit anti-apoptotic gene expression, induce multiple cytokines and reactive oxygen species generation (32–34). Even if we do not know the exact mechanism of osmotic damage at kidney level, it would be consistent with the reported evidence; however, it has yet to be elucidated in detail. Further studies, with a prospective design, are required in order to carefully explore and confirm such causal association.

Several study limitations have to be reported such as a retrospective and monocentric design, the use of ICD-9-CM codes to identify comorbid conditions, unavailability of information on chronic or acute therapy administered during hospital stay. However, the use of Charlson/Deyo comorbidity index score to account for patient comorbidity (a validated index of diseases severity based on ICD-9-CM codes), a wide general in-hospital cohort and a creatinine-based definition of in-hospital AKI give strength to our results.

To our knowledge this is the first study that has widely analyzed the association between Na disorders and kidney injury demonstrating that: i) dysnatremia is a common condition that involves AKI patients; and ii) high Na variability might be considered a good biological marker that anticipates kidney injury development.

Supplementary Tables

Supplementary Table 1. Association of dysnatremia with AKI development

Subdistribution hazard model

	Normonatremia	Hyponatremia	Hypernatremia
No. of patients	44,178	8,803	3,980
In-hospital outcome			
Death	195 (0.4)	304 (3.5)	194 (4.9)
AKI	864 (2.0)	381 (4.3)	205 (5.2)
Subdistribution hazard model			
HR (95% CI)	1.00 (Reference)	1.95 (1.73, 2.21)	2.62 (2.25, 3.05)
		p<0.001	p<0.001
HR (95% CI)*	1.00 (Reference)	1.84 (1.58, 2.16)	1.62 (1.35, 1.95)
		p<0.001	p<0.001

*Adjusted for: Age, Sex, Comorbidities, Na value at hospital admission, eGFR baseline

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CHAPTER 5

Serum potassium disorders predict subsequent kidney injury: a retrospective observational cohort study of hospitalized patients

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Abstract

Introduction

Electrolytes disorders are common findings in kidney diseases and might represent a useful biomarker preceding kidney injury. Serum potassium [K^+] imbalance is still poorly investigated for association with acute kidney injury (AKI) and most evidence come from intensive care units (ICU). The aim of our study was to comprehensively investigate this association 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 January 1, 2010 and December 31, 2014 with inclusion of adult patients with at least 2 [K^+] and 3 serum creatinine (sCr) measurements who did not develop AKI during an initial 10-day window. The outcome of interest was in-hospital AKI. The exposures of interest were [K^+] fluctuations and hypo (HoK) and hyperkalemia (HerK). [K^+] variability was evaluated using the coefficient of variation (CV). Cox proportional hazards regression models were used to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between the exposures of interest and development of AKI.

Results

21,830 hospital admissions from 18,836 patients were included in our study. During a median follow-up of 5 (interquartile range [IQR] 7) days, AKI was observed in 555 hospital admissions (2.9%); median time for AKI development was 5 (IQR 7) days. Higher [K^+] variability was independently associated with increased risk of AKI with a statistically significant linear trend across groups (p-value = 0.012). A significantly higher incidence of AKI was documented in patients with HerK compared with normokalemia. No statistically significant difference was observed between HoK and HerK (p-value = 0.92).

Conclusion

[K^+] abnormalities including fluctuations even within the normal range are associated with development of AKI.

Introduction

Acute kidney injury (AKI) is a severe pathological condition often observed in the hospitalized population (1,2). The reported incidence is quite variable, ranging from 7% to 57% (3,4). Higher morbidity and mortality associated with such a severe disease justify medical and scientific interest (5). AKI is strongly associated with increased short-term (more than fourfold increased likelihood of death in some reports (5)) and long-term mortality (mortality risk ranging from 40% to 60% (6)), higher risk of incident chronic kidney disease (CKD) or progression of pre-existing CKD (7) as well as increased hospital resource utilization with a significant burden on the healthcare systems (8).
Since the kidney is the main organ involved in the homeostasis of water and electrolytes, it is not surprising that electrolyte disturbances have been frequently observed in AKI patients (9,10). However, the few studies focusing on the electrolyte imbalances preceding kidney injury (11–14) reported a significant association between electrolyte disorders and AKI (11,12,14). The electrolyte alterations associated with AKI were often described as simple bystanders that accompany other pathological conditions (9,10), although a direct and independent causal association with kidney injury might be hypothesized (11,12,14). Embracing this point of view, electrolyte disorders might represent a useful biomarker preceding overt kidney damage and potentially improving timely medical intervention.
Serum potassium [K^+] disorders preceding AKI are still poorly investigated in the medical literature. To date, no works have comprehensively explored the relationship between [K^+] imbalance and kidney injury or have explored its direct association with kidney damage.
In order to provide new insights on such topic, we performed an observational study on a large cohort of hospitalized patients aimed at investigating the relationship between [K^+] disorders (including [K^+] variability, hyperkalemia and hypokalemia) and AKI.

Materials and Methods

Setting and study population

We performed a retrospective observational cohort study on the inpatient population admitted to the Fondazione Policlinico Universitario Agostino Gemelli IRCCS between January 01 2010 and December 31 2014. We included only adult patients (≥18 years) with at least 2 [K^+] and 3 serum creatinine (sCr) measurements during the study period (Figure 1). At least 2 [K^+] and 2 sCr measurements during a 10-day window starting at in-hospital admission were considered necessary in order to explore the relationship between [K^+] variability and AKI (Figure 2). All patients developing AKI during the 10-day window were excluded, as well as patients with end-stage kidney disease (ESKD).

Figure 1. Flowchart of the study

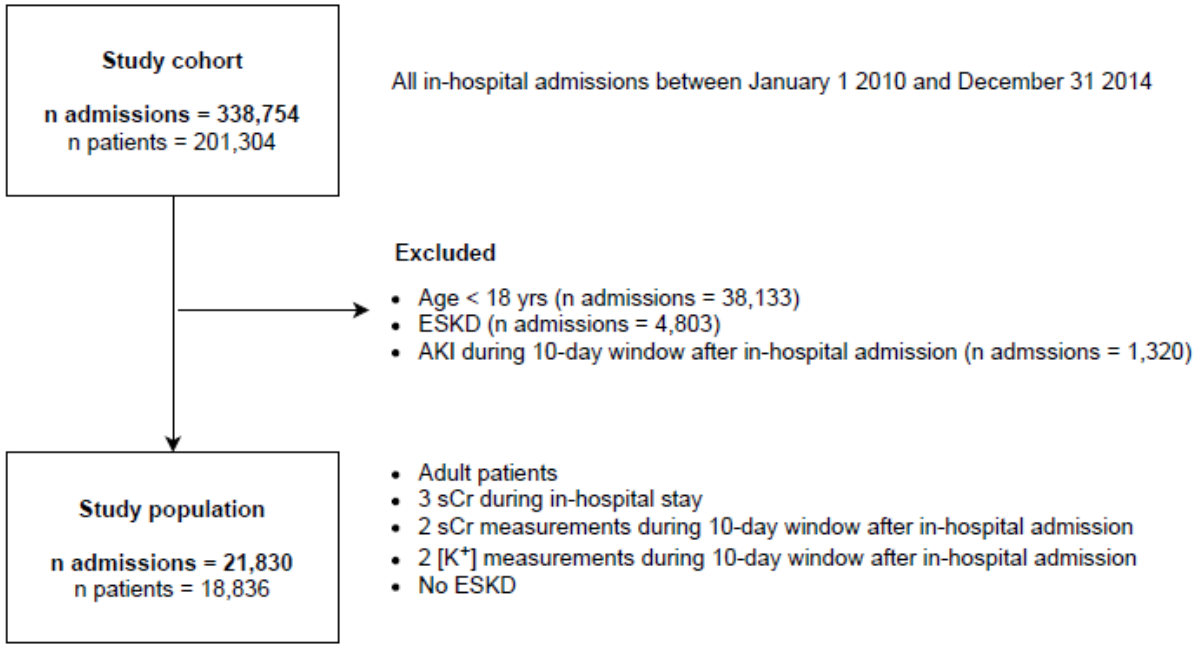
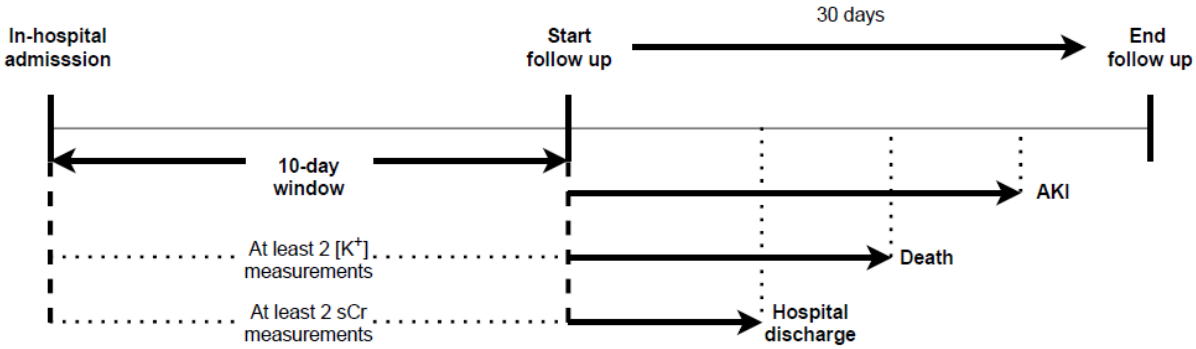


Figure 2. Study design



Data collection

Demographic, clinical and laboratory data were collected for each patient: age, sex, [K^+], sCr, primary and secondary ICD-9-CM (International Classification of Disease, 9th Revision, Clinical Modification) diagnostic codes at hospital discharge, 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 below 2.3% [range 1.3 to 1.7%]). Extreme [K^+] levels (<2.0 mmol/L and >7.5 mmol/L), that could introduce distortion in the analyses and reflect untrue values (e.g., due to haemolysis), were removed.

Definitions

The coefficient of variation (CV) was used as the measure of [K^+] variability. Creatinine kinetics (CrK) criteria were used for AKI definition (15). The presence of AKI was assessed using absolute increases of sCr concentration during hospitalization. To do this, we calculated the difference between each sCr and the previous measured value during hospitalization. According to CrK criteria, we defined AKI as an absolute increase in sCr of ≥0.3 mg/dL over 24-h or ≥0.5 mg/dL over 48-h observed after the initial 10 days (15).

Patients were categorized according to all [K^+] values recorded during hospital stay in the following groups: hypokalemia (HoK, any [K^+] value <3.0 mmol/L), hyperkalemia (HerK, any [K^+] value >5.0 mmol/L), normokalemia (NK, all [K^+] values ≥3.0 mmol/L and ≤5.0 mmol/L). Patients with a mixed [K^+] disorder (lowest [K^+] value <3.0 mmol/L and highest [K^+] >5.0 mmol/L) were classified as HoK or HerK, whichever occurred first.

Comorbid conditions (cardiovascular diseases, malignancies, gastrointestinal diseases, genitourinary disorders, endocrine/metabolic disorders, infectious and respiratory diseases) were identified using ICD-9-CM codes.

ESKD was identified using ICD-9-CM diagnostic and procedural codes or laboratory data (baseline estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2) (14).

Outcomes and exposures

In-hospital AKI was the main outcome of interest. [K^+] variability, expressed as quartiles of [K^+] CV and analyzed as both categorical and numerical variable, was the main exposure of interest. HoK and HerK were also evaluated for association with the outcome of interest.

Statistical analysis

Quantitative variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were described using frequencies and percentages. Normality of distribution for continuous variables was evaluated by inspecting Q-Q plots and histograms.

The association between [K^+] variability and [K^+] disorders with AKI was explored using a Cox regression hazard model. To account for multiple in-hospital admissions from the same patient, we used a Cox proportional hazards mixed effect "frailty" regression model, which incorporates a random intercept per patient. Survival time was defined as the time from the end of the 10-day window after in-hospital admission to development of AKI, end of hospital stay (hospital discharge

or death), or end of-follow-up (30 days after the start of time at risk). All alive patients were censored at the time of hospital discharge or at the end of follow-up (Figure 2). Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported for all survival analyses. The covariates included in multivariable regression analyses were: age, sex, comorbidities, [K^+] value at hospital admission, eGFR value at hospital admission.

To determine whether CKD modifies the relationship between [K^+] disorders (HoK and HerK) and AKI, an interaction term for baseline eGFR, higher or lower than 60 mL/min/1.73 m^2, was entered into the model.

To confirm our results, as sensitivity analysis, a subanalysis was performed only in NK patients. 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, interaction analyses between subgroups (defined according to median values of those variables and reported as dichotomous variables) and [K^+] variability were performed.

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

Results

Overall, 21,830 hospital admissions from 18,836 patients were included in our study (Figure 1). Descriptive measurements of the study population are reported in Table 1.

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

	Q1 CV ≤4.62 (*n* = 4,775)	Q2 4.62 < CV ≤7.44 (*n* = 4,713)	Q3 7.44 < CV ≤10.88 (*n* = 4,728)	Q4 CV >10.88 (*n* = 4,620)
Age, mean (SD), years	61.9 (17.5)	63.2 (16.8)	64.5 (16.5)	66.7 (16.0)
Males, *n* (%)	2,461 (51.5)	2,596 (55.1)	2,469 (52.2)	2,094 (45.3)
Comorbidities, *n* (%)				
Cardiovascular	1,999 (41.9)	2,152 (45.7)	2,205 (46.6)	2,205 (47.7)
Malignancies	1,654 (34.6)	1,846 (39.2)	1,752 (37.1)	1,691 (36.6)
Gastrointestinal	714 (15.0)	775 (16.4)	812 (17.2)	902 (19.5)
Genitourinary	494 (10.3)	538 (11.4)	571 (12.1)	670 (14.5)
Endocrine/Metabolic	914 (19.1)	940 (19.9)	970 (20.5)	1,000 (21.6)
Infectious	395 (8.3)	417 (8.8)	424 (9.0)	536 (11.6)
Respiratory	871 (18.2)	969 (20.6)	952 (20.1)	1,085 (23.5)
eGFR, mL/min/1.73 m^2, mean (SD)	79.1 (25.6)	76.8 (26.3)	75.9 (26.5)	74.2 (26.9)
[K^+], mean (SD), mmol/L	4.0 (0.4)	4.0 (0.4)	4.0 (0.5)	3.9 (0.7)
[K^+] measurements, median (IQR)	3 (2)	4 (2)	4 (2)	4 (3)
Observation time, days, median (IQR)	7 (3)	8 (3)	8 (3)	8 (3)
[K^+] CV, median (IQR)	3.0 (2.0)	6.0 (1.4)	9.0 (1.7)	13.9 (4.5)

CV, coefficient of variation; SD, standard deviation.

Patients with higher [K+] variability were older with more comorbidities. In particular, we observed a higher prevalence in cardiovascular, genitourinary, gastrointestinal and respiratory diseases. As expected, patients in the highest quartile of [K+] variability showed lower baseline eGFR.

During a median follow-up of 5 (IQR 7) days, AKI was observed in 555 hospital admissions (2.9%), median time for AKI development 5 (IQR 7) days.

Table 2 reports the association between [K+] variability and AKI. Higher [K+] variability was independently associated with increased risk of kidney injury with a statistically significant linear trend across groups (p-value = 0.012); patients in the fourth quartile of [K+] variability had a 43% higher risk (95% CI 10, 85%) compared with the first quartile.

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

CV quartile	Events, *n* (%)	Person-time, years	Events per 1,000 person-years	Model 1		Model 2	
				HR (95% CI)	*p* value for trend	HR (95% CI)	*p* value for trend
Q1	100 (1.8)	101.3	987	1.00 (reference)		1.00 (reference)	
Q2	147 (2.7)	100.9	1,457	1.48 (1.14, 1.91) $p = 0.003$	$p = 0.001$	1.36 (1.05, 1.76) $p = 0.019$	0.012
Q3	151 (2.8)	98.6	1,531	1.56 (1.21, 2.01) $p < 0.001$		1.40 (1.08, 1.80) $p = 0.011$	
Q4	157 (2.9)	102.4	1,533	1.56 (1.21, 2.01) $p < 0.001$		1.43 (1.10, 1.85) $p = 0.007$	

Model 1: univariable model. Model 2: multivariable model adjusted for age, sex, comorbidities, [K+] value at hospital admission, eGFR, and value at hospital admission. CI, confidence interval; CV, coefficient of variation; HR, hazard ratio.

Results were materially unchanged in analyses restricted to NK patients (Supplementary Table 1). No significant interaction was observed for the number of [K+] measurements and observation time (p-values for interaction 0.44 and 0.46, respectively) on the association between [K+] variability and AKI.

The prevalence of [K+] disorders was not different compared to what already reported in the literature (16). In our study population, HerK and HoK were observed in 1,573 (7.2%) and 1,475 (6.8%) hospital admissions, respectively. A significantly higher incidence of AKI was documented in patients with HerK compared with NK (Table 3). However, there was no statistically significant difference between HoK and HerK (p-value = 0.92).

No statistically significant interactions by baseline eGFR were observed (p-values for interaction 0.93 and 0.15 for HerK and HoK, respectively).

Table 3. Association between [K+] disorders and AKI

Disorder	Events, *n* (%)	Person-time, years	Events per 1,000 person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 2 HR (95% CI)
NK	429 (2.3)	341.0	1,258	1.00 (reference)	1.00 (reference)	0.75 (0.55, 1.04) $p = 0.086$
HoK	51 (3.5)	31.8	1,604	1.27 (0.95, 1.71) $p = 0.11$	1.33 (0.96, 1.83) $p = 0.086$	1.00 (reference)
HerK	75 (4.8)	30.4	2,467	1.98 (1.54, 2.54) $p < 0.001$	1.36 (1.02, 1.82) $p = 0.039$	1.02 (0.65, 1.60) $p = 0.92$

Model 1: univariable model. Model 2: multivariable model adjusted for age, sex, comorbidities, [K+] value at hospital admission, eGFR, and value at hospital admission. CI, confidence interval; HR, hazard ratio.

Discussion

Our study demonstrates a relationship between [K^+] disorders and subsequent AKI. Based on these findings, [K^+] disorders are not only a consequence of kidney impairment but can also be considered a risk factor for the development of overt kidney injury.

Analysing a large cohort of hospitalized patients, we demonstrated a significant association between higher [K^+] variability and abnormalities and kidney injury (also confirmed in NK patients).

Serum potassium [K^+] imbalance is still poorly investigated for association with AKI and most evidence come from ICU. A recent paper from Chen et al documented a significant association between [K^+] disorders and AKI in a cohort of ICU patients (17). To our knowledge, our study is the first to assess the relationship between [K^+] disorders and AKI in a general hospitalized population.

Most of the previous studies have focused on electrolyte disorders following kidney injury. Recent scientific evidence have raised new interest on electrolyte derangements and their relationship with patient outcomes (11–14,18,19). Since the kidney is the main organ involved in the balance of water and electrolytes, its relationship with such disorders is not surprising.

Whether [K^+] disturbances are contributors to AKI or rather simple epiphenomena is not clear and was never discussed in previous studies. The direct mechanism underlying the association between [K^+] imbalance and AKI is not easy to hypothesize. Several kidney abnormalities have been related to hypokalemic status. Lower [K^+] concentrations are known to induce renal structural changes, consisting of renal hypertrophy, cystic changes and tubulointerstitial injury and fibrosis (20,21). It is plausible that pre-existing status of chronic kidney impairment, still unrevealed by sCr concentration, due to long-standing [K^+] depletion, may predispose to AKI development. Another possible explanation of our findings lies on the relationship between [K^+] and acid-base disorders and so between HerK and metabolic acidosis (22). It might be that HerK condition or positive [K^+] fluctuations could reflect an initial or overt acid-base disorder. Accumulating evidence identifies the significant association between acidosis and kidney damage (23–26). From a biological perspective, metabolic acidosis may reduce renal blood flow (24) and increase the release of inflammatory mediators (25), resulting in kidney injury.

However, it is worth noting that even subclinical AKI (27), yet undocumented by the rise in sCr, could justify electrolyte abnormalities. As sparsely reported in the scientific literature, electrolyte derangements may also accompany or precede kidney damage (11,12,14), serving as useful serological marker of renal impairment. Previous studies have already revealed the relationship between AKI and specific electrolyte disorders including hypernatremia, hyponatremia, hyperchloremia, hypomagnesemia (11–14,28). Recently, Chen et al established and validated a new risk scoring system involving several serum electrolyte disorders with a good performance on AKI

prediction (12). Since sCr is a suboptimal marker of kidney injury and kidney research still struggles seeking the "optimal" biomarker (29,30), electrolyte imbalance could play an important role on this issue improving AKI diagnosis and timely medical intervention. Embracing this concept, [K^+] disorders could represent a marker of patient instability, of the severity of the underlying diseases (9,10) as well as the need for greater use of medications that increase the risk of kidney injury. From this perspective, monitoring [K^+] variability and disorders might represent a useful serological marker that accompanies or anticipates kidney injury.

With our paper, we propose a new point of view. Surely, [K^+] disorders commonly follow AKI, but they may also precede overt kidney injury. Higher [K^+] variability, which may suggest possible subsequent renal impairment, should warrant medical attention in order to pursue an early diagnosis of kidney damage and consequently establish timely therapy.

Our study has several strengths. It is the first to comprehensively analyse the relationship between [K^+] disorders and subsequent AKI development in a general cohort of hospitalized patients. Furthermore, the large sample size, the robustness of results to sensitivity analyses and a creatinine-based model for AKI definition provide strength to our findings. Moreover, using a 10-day window since in-hospital admission with stable creatinine gave us the opportunity to exclude AKI during the first days, thus reducing the risk of reverse causation by attributing an AKI event already in development at admission to our exposure of interest. Finally, the inclusion of patients from medical and surgical wards as well as intensive and non-intensive care units provide more generalizability to our results. However, our study also has limitations, including the retrospective design, the lack of information on medications used during hospital stay, the use of ICD-9-CM codes for comorbidities definition.

In conclusion, potassium abnormalities including fluctuations even within the normal range are associated with development of AKI. Future longitudinal studies with prospective design are needed to provide more insights in such interesting topic.

Supplementary Tables

Supplementary Table 1. Association between [K+] variability and in-hospital AKI (only patients with normokalemia)

CV quartile	Events (n, %)	Person-time, years	Events per 1,000 person-years	Model 1		Model 2	
				HR (95% CI)	p-value for trend	HR (95% CI)	p-value for trend
Q1	78 (1.7)	87.2	895	1.00 (Reference)	p = 0.030	1.00 (Reference)	p = 0.060
Q2	126 (2.7)	86.0	1,465	1.64 (1.24, 2.18) p <0.001		1.50 (1.13, 2.00) p = 0.005	
Q3	115 (2.4)	84.3	1,364	1.53 (1.15, 2.05) p = 0.004		1.41 (1.05, 1.89) p = 0.022	
Q4	110 (2.3)	83.5	1,317	1.47 (1.10, 1.97) p = 0.009		1.41 (1.05, 1.89) p = 0.023	

Model 1: univariable model. Model 2: multivariable model adjusted for age, sex, comorbidities, [K+] value at hospital admission, eGFR value at hospital admission.

CI, confidence interval; CV, coefficient of variation; HR, hazard ratio

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CHAPTER 6

General Discussion

General discussion

Electrolytes disorders are common findings in the hospitalized population and associate with poor prognosis. Sodium (Na^+) and potassium (K^+) are the main cations of extracellular and intracellular space, respectively. Unbalance in their serum concentrations are the most common electrolytes derangements observed in the hospital setting. Even though the association between Na^+ and K^+ disorders are widely described in scientific literature, to date still a few studies focused on electrolytes variability and clinical outcomes.

The first part of this thesis discusses the association between electrolytes disorders and in-hospital mortality with particular attention on electrolytes variability. The second part addresses the association between electrolytes disorder and variability with acute kidney injury (AKI).

In this last chapter, the main findings of this thesis will be highlighted and discussed from a broader scientific and clinical perspective. Moreover, methodological considerations and implications for clinical practice will be discussed. Finally, new directions for future research will be formulated.

Electrolytes variability and in-hospital mortality

The first part of the thesis investigates the association between electrolytes variability and in-hospital death.

Analysing a wide cohort of hospitalized patients, we demonstrated that even mild disorders or higher variability in electrolytes concentration should get the physician's attention. We observed that, independently from the magnitude of Na^+ or K^+ alteration, higher variability significantly increases in-hospital mortality (**Chapter 2-3**) (1,2).

Evidence on the association between mild electrolytes variability and in-hospital outcomes are still poorly characterized. To date, only a few studies have analysed this issue, focusing most times on intensive care unit (ICU) population (3–7).

Using a wide unselected cohort of hospitalized patients, we confirmed what was previously reported and gave more generalizability to them.

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 continuous relationship (J- or U-shaped) between serum electrolytes (e.g. Na^+ an K^+) and in-hospital mortality has been widely described (8,9). However, while the link between the most severe forms of dysnatremia or dyskalemia and mortality have a strong rationale, data on the risk associated with small electrolytes fluctuations are lacking and the mechanisms leading to higher mortality are still unclear.

Even though a direct causal relationship cannot be demonstrated due to the observational and retrospective nature of the study design, a possible direct association between higher electrolytes variability and in hospital mortality can be hypothesized.

Osmo-stress, due to higher Na^+ variability, in a variety of experimental models has also been shown to interfere with cargo transport function of centriolar satellites, activate multiple apoptotic pathways, suppress anti-apoptotic gene expression and induce the generation of multiple cytokines and reactive oxygen species (10,11). However, the exact mortality influence of osmo-stress and its related effects has yet to be fully elucidated.

Likewise, K^+ variability inducing rapid changes in cell membrane resting conditions could justify an increase in cellular instability and consequently increased risk of arrhythmogenic deaths.

Furthermore, it must be noted that, on the other hand, higher electrolytes variability could represent a marker of patient instability and thus the severity of the underlying diseases or the need for greater use of medications warranting the associate burden on patient survival.

Electrolytes variability and acute kidney injury

The second part of the thesis focuses on the association between electrolytes disorders and AKI.

The association between electrolytes disorders and kidney disease is widely reported in medical literature (12–14). Since the kidney is the main organ engaged in water and electrolytes homeostasis this relationship is not surprising.

Dysnatremia and dyskalemia conditions are frequently encountered in the case of renal function impairment (12). This is even more true in the case of AKI, characterized by an abrupt reduction in kidney function (13–17).

However, even though the association between renal function and electrolytes disorders is widely reported in scientific literature and well characterized, to date, only a few studies explored the inverse relationship (17–19).

In our studies we clearly describe this inverse association, where Na^+ and K^+ disorders precede AKI. Furthermore, higher variability in serum electrolytes concentration significantly predict kidney injury (**Chapter 4-5**) (20,21). This is even more interesting considering the independence from other confounders.

From this point of view, Na^+ and K^+ disorders emerge as useful biomarkers in the AKI prediction.

The described association between electrolytes disorder before AKI development has not univocal interpretation. A plausible cross-talk on a biological and pathogenetic ground might justify such relationship, but it still remains poorly investigated.

An appropriate question should be whether electrolytes disorders are a simple bystander or contributing factor of AKI. Dysnatremia and kidney injury may be two different manifestations of a common underlying disease or reflect the severity of the illness and comorbidities of the patient. Volume depletion that generally accompanies hypernatremia is frequently recognized as a common cause of AKI development. On the other hand, Na^+ dilution (or true Na^+ depletion due to diuretics) can be observed in systemic disorders (i.e., heart, liver failure) causing AKI, characterized by increased extracellular volume. The same may be true of K^+ disorders which could be simple epiphenomena of kidney injury.

On the other way round, we cannot rule out a direct causal association. Osmo-stress associated with Na^+ change can cause cellular damage inducing water shift in and out of the cells threating their survival (22–24). Even if we do not know the exact mechanism of osmotic damage at kidney level, it would be consistent with the reported evidence. Similarly, several kidney abnormalities have been related to dyskalemic status. Lower K^+ concentrations are known to induce renal structural changes, consisting of renal hypertrophy, cystic changes, and tubulointerstitial injury and fibrosis (25,26). Higher K^+ concentration might associate acidotic disorders and so reduce renal blood flow (27) and increase the release of inflammatory mediators (28), resulting in kidney injury.

Clinical implications

Our results suggest the importance for all physicians engaged in clinical encounters to pay attention not only when Na^+ or K^+ disorders arise, but also when higher electrolytes variability is observed. Particular attention should be placed on electrolytes fluctuations, even within the theoretical "normal" range, given the significant association with strong clinical outcomes, in-hospital mortality and AKI.

To date, the "optimal" range for Na^+ and K^+ is still unknown. Currently, a range between 135-145 mmol/L and 3.0-5.0 mmol/L, respectively, is considered safe. Whether a cut-off point should be more precise is still unclear.

Surely, a precise definition of hypo- or hypernatremia and hypo- or hyperkaliemia is especially useful in clinical practice 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.

Methodological consideration: Limitations and Strengths of the studies

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 Na^+ and K^+ measurements per patient might not have been adequate to establish variability in all included cases. 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.

As regards the association of electrolytes disorders preceding AKI, it is worth noting that even subclinical kidney injury, yet undocumented by the rise in serum creatinine (Scr), could justify such anomalies.

On the other hand, ours are the first studies analysing electrolytes variability with a comprehensive approach in an unselected hospitalized population, improving the generalizability of our findings. Furthermore, to the best of our knowledge, our studies are the first that clearly demonstrate the association between Na^+ and K^+ disorders and kidney injury using a validated creatinine-based definition of AKI (29).

Future research

Prospective studies are necessary to confirm our findings, with clear guidelines regarding the definition of electrolytes variability. Further research is needed in order to see whether specific health conditions show differential associations between electrolytes variability and clinical outcomes. As a result, the finding of elevated mortality in patients with higher electrolytes variability within the normal range should be interpreted with caution.

Experimental research on animal models, should confirm the direct toxicity of electrolytes variability on human tissue and renal structures.

Furthermore, the surge of genetic epidemiology in the last years and the explosion of new genetic and molecular techniques (e.g GWAS studies, PWAS studies, mendelian randomization approach) could give the opportunity to demonstrate the independent association of electrolytes disorders with kidney injury.

Conclusions

We showed a previously unrecognized role of Na^+ and K^+ fluctuation in short-term strong clinical outcomes, in-hospital mortality and AKI, in a large cohort of unselected hospitalized adults. We also provide affirmatory data showing an increased risk of AKI in patients with borderline hypo- or hypernatremia and hypo- or hyperkalemia, irrespective of their comorbidities and diagnoses.

Although the retrospective design precluded any capacity to draw a causal relation, the observation of a significant increase in mortality risk and AKI across the study analyses in the general hospitalized population suggests potential deleterious effects of serum Na^+ and K^+ variations, even in the theoretical "normal" range.

Prospective controlled trials are required to establish causality.

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