Serum Potassium and Adverse Outcomes Across the Range of Kidney Function: A CKD Prognosis Consortium Meta-Analysis

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ABSTRACT

Aims: Both hypo- and hyperkalemia can have immediate deleterious physiologic effects; less is known about long-term risks. The objective was to determine the risks of all-cause mortality, cardiovascular mortality and end-stage renal disease associated with potassium levels across the range of kidney function and evaluate for consistency across cohorts in a global consortium.

Methods & Results: We performed an individual-level data meta-analysis of 27 international cohorts (10 general population, 7 high cardiovascular risk, and 10 CKD) in the CKD Prognosis Consortium. We used Cox regression followed by random-effects meta-analysis to assess the relationship between baseline potassium and adverse outcomes, adjusted for demographic and clinical characteristics, overall and across strata of eGFR and albuminuria. We included 1,217,986 participants followed for a mean of 6.9 years. Average age was 55±16 years, average eGFR was 83±23 ml/min/1.73 m^2, and 17% had moderate- to severely-increased albuminuria. Mean baseline potassium was 4.2±0.4 mmol/L. The risk of serum potassium of >5.5 mmol/L was related to lower eGFR and higher albuminuria. The risk-relationship between potassium levels and adverse outcomes was U-shaped with the lowest risk at serum potassium 4-4.5 mmol/L. Compared to a reference of 4.2 mmol/L, the adjusted hazard ratio for all-cause mortality was 1.22 (95% CI: 1.15-1.29) at 5.5 mmol/L and 1.49 (95% CI: 1.26-1.76) at 3.0 mmol/L. Risks were similar by eGFR, albuminuria, renin-angiotensin-aldosterone system inhibitor use, and across cohorts.

Conclusions: Outpatient potassium levels both above and below the normal range are consistently associated with adverse outcomes, with similar risk relationships across eGFR and albuminuria.

INTRODUCTION

Abnormal serum potassium levels represent one of the most important electrolyte disturbances in clinical practice. Potassium plays a crucial role in normal cell membrane electrophysiology, with both hyperkalemia and hypokalemia resulting in electrophysiologic perturbations, most importantly in the cardiac system. Abnormalities in myocardial resting membrane potential, cardiac depolarization, and myocardial excitability can result in conduction system abnormalities, including malignant arrhythmias.[1-3]

The kidneys play a central role in potassium homeostasis, with chronic kidney disease (CKD) being an especially prominent risk factor for hyperkalemia.[4,5] Other risk factors for hyperkalemia commonly occur in combination with CKD, including clinical conditions such as acute kidney injury, cardiovascular disease (CVD), and diabetes mellitus (DM), and various medication classes which affect physiologic processes involved in potassium regulation, such as inhibitors of the renin-angiotensin aldosterone system (RAASi).[6] There is wide variation in the estimates of hyperkalemia incidence and prevalence reported in studies of CKD patients, ranging from as low as 7.7% to as high as 73%.[7-10] Although patients in the general population are reported to have lower risk of hyperkalemia than patients with CKD, with prevalence values ranging from 2.6% to 3.5% in Canadian and US studies, many of these studies are limited by small sample size or select populations.[4,10,11] There are less data on hypokalemia in general. The increasing worldwide prevalence of CKD and associated conditions compels a careful assessment of the prevalence and long-term risks associated with abnormal potassium levels in diverse international populations.[12,13]

Hyperkalemia and hypokalemia have been consistently associated with higher short-term all-cause mortality in observational studies.[8,14-18] Some, but not all, have suggested that risks

associated with hyperkalemia are greater in individuals with normal kidney function than in those with CKD.[10] Notwithstanding the putative role of cardiac arrhythmias in the mortality associated with hypo- and hyperkalemia,[19] few studies have examined the long-term association of abnormal potassium levels with CVD-associated mortality. Furthermore, the effects of abnormal serum potassium levels on outcomes in other organ systems, such as the kidneys, remain less well studied. In order to better guide clinical practice and future clinical trials, we performed a meta-analysis of the prevalence of abnormal potassium levels, risk factors of abnormal potassium levels, and long-term associations between potassium levels, all-cause mortality, CVD-associated mortality, and end stage renal disease (ESRD) in 27 large and diverse international cohorts. For the latter aim, we also evaluated whether risks varied by level of kidney function and other clinically relevant characteristics.

METHODS

Participating cohorts

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) has been described previously; additional information is available in Appendices 1-2.[20-24] Briefly, CKD-PC incorporates cohorts with at least 1,000 participants (at least 500 participants for those cohorts predominantly enrolling persons with CKD [CKD cohorts]), data on serum creatinine and albuminuria, and 50 or more events of the outcome of interest (mortality or kidney outcomes). The present study included 27 cohorts: 10 general population cohorts, 7 high-risk cohorts in terms of cardiovascular risk, and 10 CKD cohorts. Meta-analyses were restricted to participants aged ≥18 years old with an available value of potassium at baseline. This study was approved by

the institutional review board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland, USA).

Procedures

Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI creatinine equation.[25] In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry (IDMS), values were multiplied by 0.95 before eGFR calculation.[26] We defined diabetes as fasting glucose ≥7.0 mmol/L (126 mg/dL), non-fasting glucose ≥11.1 mmol/L (200 mg/dL), hemoglobin A1c ≥6.5%, use of glucose lowering drugs, or self-reported diabetes. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of CVD. Measures of albuminuria were the urine albumin-to-creatinine ratio (ACR), urine albumin excretion rate, urine protein-to-creatinine ratio, or semi-quantitative dipstick protein; urine protein-to-creatinine ratio was converted to ACR as previously described.[27]

The outcomes of interest were all-cause mortality, CVD-associated mortality and ESRD. We defined ESRD as initiation of renal replacement therapy.

Statistical analysis

We applied a two-stage meta-analysis, with each study first analyzed individually, and followed by a random-effects meta-analysis. The overview of the analysis and analytic notes for individual studies are provided in Appendix 2 in the Supplement. We imputed missing values of covariates using cohort-specific mean values. Potassium levels, serum creatinine and albuminuria, as well as the demographic variables age, gender and race were not imputed. We quantified heterogeneity with the I^2 statistic and Cochran's Q test. Since the risk of abnormal serum potassium levels and their associated outcomes might vary substantially depending on the

type of patient population, analyses were stratified by type of cohort (general population/high cardiovascular risk or CKD).

To assess the cross-sectional associations between kidney function and level of potassium, we plotted the distribution of baseline serum potassium levels within categories of eGFR using kernel density plots. Next, we modeled the risk of potassium >5.0, >5.5 and <3.5 mmol/L using logistic regression, adjusting for age, race, sex, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes mellitus, body mass index, smoking, history of coronary heart disease or stroke, history of heart failure, eGFR (linear spline with knots at 30 and 60) and albuminuria (log transformed ACR, or categories of dipstick). For eGFR and ACR, the reference point was placed at eGFR 80 ml/min/1.73 m^2 and ACR 10 mg/g in the general population/high-risk cohorts and eGFR 50 ml/min/1.73 m^2 and ACR 50 mg/g in the CKD cohorts, with statistical significance at other points determined by the meta-analyzed beta coefficient and standard error. We tested whether the relationship between kidney function and abnormal potassium levels differed by subgroups of age, race, sex, and diabetes status, by including the relevant product term in the regression model, determining statistical significance by evaluating the ratio of odds ratios between subgroups at each 1 ml/min/1.73 m^2 and 8% increment of ACR (pointwise interaction), as done previously.[20,28,29] In addition, we assessed the relationship between potassium levels >5.5 mmol/L and CKD stages (G1-G5 and A1-A3), with the reference placed as G2/A1 in the general population/high risk cohorts and G3b/A2 in CKD cohorts.

To assess the relationship between baseline serum potassium and subsequent adverse outcomes, we modeled the adjusted hazard ratios (HRs) of the studied outcomes as a spline function of serum potassium concentration, fitting piece-wise linear splines for serum potassium

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with knots placed at 3.5, 4, 4.5, 5, and 5.5 mmol/L, and adjusting for the same set of covariates. Given the importance of kidney function on potassium homeostasis, analyses were performed overall and with interaction between potassium and eGFR strata of 60+, 30-59, and <30 ml/min/1.73 m^2, albuminuria levels of <30, 30-299 and ≥300 mg/g, as well as age, race, sex, diabetes, status, RAASi use, and diuretic use, determining statistical significance for the pointwise interaction at each 0.05 mmol/L of potassium. Analyses were performed using Stata/MP 14.2 software for Windows (www.stata.com). We considered *P*-values <0.05 statistically significant.

RESULTS

There were a total of 1,217,986 participants with baseline potassium, eGFR, and albuminuria levels across 27 cohorts, followed for an average of 6.9 years (range 2.0 - 19). Average (mean ± standard deviation) age was 55±16 years, 40% were female, and 14% were black (**Table 1**). Average eGFR was 83±23 ml/min/1.73 m^2, 17% had moderate to severely-increased albuminuria, and 46% were on antihypertensive medications. Angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and potassium sparing diuretics were used in 31%, 11%, and 3% of individuals at baseline, respectively. Non-steroidal anti-inflammatory drugs (NSAID) use was reported by 15% (**Table S1**).

Prevalence and risk factors of hyperkalemia and hypokalemia

Overall, average baseline potassium was 4.2±0.4 mmol/L; potassium was higher with lower baseline eGFR in both the general population/high cardiovascular risk cohorts (**Figure 1**) and in the CKD cohorts (**Figure S1**). The prevalence of serum potassium >5.0 mmol/L, serum potassium >5.5 mmol/L, serum potassium <4.0 mmol/L, and serum potassium <3.5 mmol/L was

3.31% (95% CI: 3.28-3.34%), 0.49% (95% CI: 0.48-0.50%), 23.57% (95% CI: 23.49-23.64%), and 1.91% (95% CI: 1.89-1.94%) of individuals in general population/high cardiovascular risk cohorts and 17.94% (95% CI: 17.58-18.31%), 4.23% (95% CI: 4.03-4.42%), 12.61% (95% CI: 12.29-12.93%), and 2.03% (95% CI: 1.90-2.17%) of individuals in CKD cohorts. In the general population/high cardiovascular risk cohorts, risk factors for hyperkalemia included male gender, non-black race, diabetes mellitus, lower BMI, active smoking, history of coronary heart disease or stroke, lower eGFR, higher ACR, use of ACEi, ARB or potassium sparing diuretics, and non-use of thiazide or loop diuretics (**Table S2**). The relationship between eGFR and serum potassium >5.5 mmol/L was nearly linear; higher ACR was a weaker but independent risk factor at levels >37 mg/g (**Figure 2A & B**). There were no meaningful differences in the relationship between eGFR or ACR and potassium levels >5.5 mmol/L among patients with different age (<65 years, ≥65 years), gender, race (black, non-black), and presence/absence of diabetes mellitus (**Figures S2-S5**). Relationships between eGFR, ACR, and potassium >5.5 mmol/L were also similar in the CKD cohorts (**Figure S6**), as were the direction of associations with most risk factors (**Table S3**). Categorical analysis revealed that lower eGFR was associated with higher risk of potassium level >5.5 mmol/L independent of ACR levels, whereas the association between ACR and hyperkalemia was most apparent at higher levels of eGFR and null at eGFR <15 ml/min/1.73m^2 (**Table S4**). Similarly, in CKD cohorts, lower eGFR was a strong risk factor for potassium >5.5 mmol/L, whereas higher ACR was weak to null (**Table S5**).

Risk factors for hypokalemia in the general population/high cardiovascular risk cohorts included younger age, female gender, black race, higher systolic blood pressure, the use of thiazide or loop diuretics, lower serum cholesterol, lower BMI, and higher ACR; the use of ACEi, ARB, or potassium-sparing diuretics, the presence of diabetes mellitus, and a history of

CHD or stroke were protective (**Table S2**). The association of higher albuminuria level with the risk of hypokalemia was weak but nearly linear; the association between eGFR and potassium <3.5 mmol/L was fairly flat (**Figure 2**). Risk factor associations with potassium <3.5 mmol/L were generally consistent in direction if weaker in the CKD cohorts, with the exception of the use of RAASi medications, which was a stronger protective factor for hypokalemia <3.5 mmol/L in the CKD cohorts (**Table S3**). Neither eGFR nor ACR were significantly associated with potassium <3.5 mmol/L in CKD cohorts (**Figure S6**).

Outcomes associated with serum potassium level

We observed a total of 151,153 all-cause deaths in 26 cohorts, 9,672 cardiovascular deaths in 13 cohorts, and 14,266 ESRD events in 16 cohorts during a mean follow-up period of 6.9±4.1 years (**Table S6**). The risk-relationship between potassium and all-cause mortality demonstrated lowest risk with serum potassium levels between 4 and 4.5 mmol/L, and higher risk outside of the 3.5-5 mmol/L range (**Figure 3A**). Compared to a reference of 4.2 mmol/L, the overall adjusted hazard ratio for all-cause mortality was 1.22 (95% CI: 1.15-1.29) at serum potassium 5.5 mmol/L and 1.49 (95% CI: 1.26-1.76) at serum potassium 3.0 mmol/L. These associations were qualitatively consistent in the individual cohorts (**Figure 4**) and there was no difference in the risk of all-cause mortality associated with potassium by level of eGFR (**Figure 3B**). Risk relationships were similarly U-shaped for cardiovascular mortality and end-stage renal disease (**Figure 3C & 3D**) with qualitative consistency in point estimates (**Figures S7 & S8**). Although confidence intervals were wide, there appeared to be no difference in potassium-cardiovascular risk relationships by level of GFR (**Figure S9A**). In contrast, higher levels of potassium had a weaker relationship with ESRD in individuals with eGFR <30 ml/min/1.73 m^2

(**Figure S9B**). The associations of serum potassium with the studied outcomes were broadly

similar in individuals of different sex, race, levels of albuminuria, history of diabetes mellitus,

and ACEi/ARB/potassium-sparing diuretic use; however, the association between lower levels of

potassium and all-cause mortality appeared slightly weaker in older individuals and those using

diuretics (**Figures S10-S16**). Results were also broadly similar in CKD cohorts (**Figures S17-S25**).

DISCUSSION

In this international meta-analysis of 1,215,347 participants in 26 diverse cohorts, we

describe the prevalence, risk factors and long-term outcomes associated with abnormal

potassium concentrations. Hyperkalemia and hypokalemia were relatively infrequent in the

studied populations, especially in participants with normal kidney function. Lower eGFR was a

strong risk factor for hyperkalemia but not hypokalemia; higher albuminuria was a relatively

weak risk factor for both. Both hyper- and hypokalemia were associated with significantly higher

long-term risk of all-cause and CV mortality, and of ESRD. Ideal outcomes were observed with

serum potassium concentrations of 4-4.5 mmol/L. While abnormal potassium levels were more

common in individuals with lower estimated GFR and higher albuminuria levels, the relative

risks associated with hyperkalemia and hypokalemia were similar in patients with various levels

of kidney function, and in various subgroups divided by age, gender, race, diabetes mellitus or

treatment with ACEi or ARB.

Abnormal potassium homeostasis is often mediated by a combination of conditions

affecting potassium intake, distribution and excretion, including demographic characteristics,

comorbidities and various medications.[6,30] Our results confirm the diversity of the risk factors

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determining hyper- and hypokalemia (including comorbidities such as CHF and DM,[3] and therapeutic interventions like diuretic use and RAAS inhibitors[31]), and emphasize the central role played by the kidneys in potassium homeostasis. Similar to our findings, previous studies have found a low prevalence of hyperkalemia in patients with normal kidney function, and markedly elevated frequencies in various cohorts with CKD, especially in patients with diabetes mellitus, in those with more advanced stages of CKD[7,8,10] and in kidney transplant recipients.[9] As opposed to the widely accepted role of lower eGFR as a risk factor for hyperkalemia, the role of albuminuria in engendering this condition has not been previously studied. Our results suggest that patients with higher levels of albuminuria had a higher prevalence of both hyperkalemia and hypokalemia, although the magnitude of this association was smaller than the relationship between eGFR and potassium abnormalities, at least for hyperkalemia. This finding has important practical relevance, since patients with higher levels of albuminuria often benefit from therapy with RAAS inhibitor medications to slow progression of CKD,[32-37] but which also increase the risk of hyperkalemia.[31,38,39] A secondary analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that hyperkalemia after losartan therapy attenuated the renoprotective effect of losartan, suggesting that prevention of hyperkalemia might allow for enhanced renoprotection by RAAS inhibitors.[40] Current clinical guidelines recommend concerted efforts to resume RAAS inhibitor therapy in patients with CHF, even after episodes of severe hyperkalemia (>6 mEq/l), once the hyperkalemia was treated and precautions are taken to monitor serum potassium.[31] Recent clinical trials suggest that the use of potassium binder medications may allow the use of RAAS inhibitors in patients prone to hyperkalemia,[41-45] although the long term benefit of such strategies on clinical outcomes is yet to be demonstrated.[46]

While the prevalence of serum potassium <3.5 was relatively low, milder forms of hypokalemia were very common, especially in general population/high cardiovascular risk cohorts. Even mild hypokalemic episodes are clinically relevant in patients at high risk for ventricular arrhythmias and sudden cardiac death, such as patients with CHF or DM.[3,31,47] Correction of hypokalemia is relatively easy with dietary or medicinal measures,[48] and it is recommended as part of strategies to prevent these complications.[3]

The U-shaped association of serum potassium levels with clinical outcomes described in this study confirm findings from previous studies indicating similar associations with all-cause mortality,[8,10,14-18] and extends them to an outpatient, large and diverse international population. The association between hypo- and hyperkalemia and mortality could be explained by the induction of malignant arrhythmias[3,19] and their consequences, such as hypotension, myocardial ischemia and sudden cardiac death.[3,17] In addition, hypokalemia and low dietary potassium intake is also associated with hypertension and consequent cardiovascular outcomes such as strokes.[48] This hypothesis is also supported by the association of hypo- and hyperkalemia with cardiovascular mortality in our study. It is perhaps not surprising to see an association of serum potassium levels with ESRD, which has been inconsistently detected previously in smaller cohort studies.[8,40,49,50] Hyperkalaemia that is resistant to treatment is an indication of dialysis start and patients who require very high diuretic doses due to volume overload may have lower potassium levels and may be started earlier on dialysis. In addition to its link with hypertension, hypokalemia is also a risk factor for tubulointerstitial fibrosis and renal cyst formation,[51-54] thus contributing to the development and progression of CKD. Conversely, hyperkalemia may be a surrogate marker of more severe CKD. Further studies are needed to determine if correction of hypo- and hyperkalemia could result in improved renal outcomes.

Our study is notable for its large size, international representation and diverse patient population. Despite its advantages, this study also has limitations. Variation in design across cohorts introduces heterogeneity and prevents using time-updated potassium levels, but our consistent results across diverse cohorts suggest the robust and empirical long-term association of a single measurement, relevant to clinical practice. Our results were driven largely by findings from general population cohorts, with high cardiovascular risk and CKD cohorts contributing relatively fewer participants. However, the causes and consequences of abnormal serum potassium have been least studied in the general population, hence our emphasis on this segment fills an important void. We adjusted for many confounders, but the effect of unmeasured confounders (e.g. serum calcium, magnesium and blood pH levels) cannot be ruled out. We could not limit the studied medications (e.g. RAAS inhibitors) to new prescriptions, which may explain their lack of association with outcomes.

Conclusions

The risk factors of abnormal potassium values are diverse, and include low estimated GFR, albuminuria, the use of various medications and comorbid conditions such as diabetes mellitus. The incorporation of these findings in clinical prediction tools in future studies could enhance our ability to risk-stratify patients and to proactively manage hypo- and hyperkalemia. Hypo- and hyperkalemia are independently associated with significantly higher all-cause and CV mortality, and with higher risk of ESRD, with the best outcomes seen with serum potassium levels of 4-4.5 mmol/L. Future research is needed, preferably in the form of a randomized controlled clinical trial, to determine if correction of abnormal serum potassium levels can result in improvement in mortality and delay onset of dialysis.

Contributors:

CPK, KM, JC, SH, VS, and MEG conceived of the study concept and design. KM, JC, MEG and the CKD-PC investigators/collaborators listed below acquired the data. YS and the Data Coordinating Center members listed below analyzed the data. All authors took part in the interpretation of the data. CPK, KM, YS, and MEG drafted the manuscript, and all authors provided critical revisions of the manuscript for important intellectual content. All collaborators shared data and were given the opportunity to comment on the manuscript. JC obtained funding for CKD-PC and individual cohort and collaborator support is listed in appendix 3 in the Supplement.

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Figure Titles and Legends:

Figure 1. Distribution of serum potassium concentrations, overall and by baseline estimated glomerular filtration rate in general population and high cardiovascular risk cohorts.

Figure 2. Continuous association of estimated GFR (panel A) and albuminuria (Panel B) with the risk of serum potassium level >5.5 mmol/L, and of estimated GFR (panel C) and albuminuria (Panel D) with the risk of serum potassium level <3.5 mmol/L, in general population and high cardiovascular risk cohorts. Black dots indicate statistical significance compared with the reference (diamond) estimated GFR of 80 ml/min/1.73m^2 (panels A and C) and albuminuria of 10 mg/g (panels B and D). Adjusted for age, gender, race, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes, body mass index, smoking, history of coronary heart disease or stroke, history of heart failure.

Figure 3. Adjusted hazard ratio of all-cause mortality, cardiovascular mortality and end stage renal disease associated with serum potassium concentration in general population and high cardiovascular risk cohorts. Black dots indicate statistical significance compared with the reference (diamond) serum potassium of 4.2 mmol/L. Models adjusted for age, gender, race, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes, body mass index, smoking, eGFR, albuminuria, history of coronary heart disease or stroke, history of heart failure.

Figure 4. Adjusted relative hazard of all-cause mortality for potassium of 3.0 mmol/L (A) and 5.5 mmol/L (B), compared to a potassium of 4.2 mmol/L in individual general population/high risk cohorts