Serum Potassium and Outcomes in CKD: Insights from the RRI-CKD Cohort Study

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Background and objectives: The relationship between serum potassium (S_K) and mortality in chronic kidney disease (CKD) has not been systematically investigated.

Design, setting, participants, & measurements: We examined the predictors and mortality association of S_K in the Renal Research Institute CKD Study cohort, wherein 820 patients with CKD were prospectively followed at four US centers for an average of 2.6 years. Predictors of S_K were investigated using linear and repeated measures regression models. Associations between S_K and mortality, the outcomes of ESRD, and cardiovascular events in time-dependent Cox models were examined.

Results: The mean age was 60.5 years, 80% were white, 90% had hypertension, 36% had diabetes, the average estimated GFR was 25.4 ml/min per 1.73 m^2, and mean baseline S_K was 4.6 mmol/L. Higher S_K was associated with male gender, lower estimated GFR and serum bicarbonate, absence of diuretic and calcium channel blocker use, diabetes, and use of angiotensin-converting enzyme inhibitors and/or statins. A U-shaped relationship between S_K and mortality was observed, with mortality risk significantly greater at $S_K \leq 4.0$ mmol/L compared with 4.0 to 5.5 mmol/L. Risk for ESRD was elevated at $S_K \leq 4$ mmol/L in S_K categorical models. Only the composite of cardiovascular events or death as an outcome was associated with higher S_K (≥ 5.5).

Conclusions: Although clinical practice usually emphasizes greater attention to elevated S_K in the setting of CKD, our results suggest that patients who have CKD and low or even low-normal S_K are at higher risk for dying than those with mild to moderate hyperkalemia.

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Hyperkalemia (serum potassium [S_K] ≥ 5.5 mmol/L) is common in patients with ESRD. In the dialysis population, the prevalence of hyperkalemia has been estimated to range from 5 to 10% (1). Hyperkalemia is thought to contribute to 2 to 5% of deaths among patients with ESRD and accounts for up to 24% of emergency hemodialysis sessions in this population (2–4). Hyperkalemia has also been associated with increased mortality (up to 17%) in the general hospitalized population (5). Although nephron adaptation occurs in those with progressive renal insufficiency by way of enhanced distal tubular secretion of ingested potassium (6), mildly elevated potassium levels are not uncommon and dietary restriction of potassium is frequently considered prudent for patients with advanced chronic kidney disease (CKD) to avoid dangerous hyperkalemia (7).

Adverse effects of $S_K \leq 3.5$ mmol/L have been well documented in the cardiovascular literature. Among patients with heart failure, hypokalemia is associated with ventricular arrhythmias and death (8); however, little is known about adverse effects of hypokalemia in the CKD population, which is known to be at high risk for cardiovascular disease in general and sudden death in particular (9).

We postulated that lower (<3.5 mmol/L) levels of S_K would be associated with higher risk for mortality in a CKD population. The aims of this study were to examine the distribution and predictors of S_K and association, if any, of S_K with mortality, ESRD, the composite outcome of death or ESRD, and the composite of death or any cardiovascular event in a CKD cohort.

Materials and Methods

Data Source: The Renal Research Institute CKD Study

This prospective observational study of adult patients with stages 3 through 5 CKD was conducted at four outpatient nephrology clinics in the United States. Patients were recruited between June 2000 and February 2006. The inclusion criteria were age >18 years and a creatinine clearance of ≤50 ml/min by the Cockcroft-Gault formula, although subsequently estimated GFR (eGFR) values that were recalculated by the four-variable Modification of Diet in Renal Disease (MDRD) equation were occasionally >50 ml/min per 1.73 m^2. A total

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of 834 patients enrolled in the study. Patients were followed by the study coordinators whenever they presented for routine clinical care to their nephrology clinics. The institutional review boards at all participating sites approved the study, and all patients provided written informed consent. Details of the study design have been published previously (10).

Study Variables

At enrollment and follow-up visits, data on demographic, anthropometric, cause of CKD, comorbidities, laboratory variables, medications, and outcomes (ESRD, death, and cardiovascular events/procedures) were collected. Of 834 patients, 820 had S_K values available at study entry and were included in the analyses. S_K values that were obtained from baseline and subsequent clinic visits were classified into the following categories: ≤4.0, 4.0 to 5.5, and ≥5.5 mmol/L.

Statistical Analysis

Linear regression models were used to assess predictors of S_K at baseline, with the adjusted R^2 used to compare models in an all-subsets regression analysis. The distributions of S_K values was illustrated using box plots by eGFR, gender, angiotensin-converting enzyme inhibitor (ACEI) use and quartiles of serum carbon dioxide (CO_2), using all available S_K values during follow-up time. The SAS mixed procedure (SAS Institute, Cary, NC) was used to test for differences in S_K values between groups. To predict S_K during follow-up time, we used mixed linear regression models with a spatial anisotropic exponential covariance structure (to account for correlation between follow-up visits of differing intervals). Separate Cox models evaluated the associations between S_K (as a continuous or as a categorical covariate) and time to death, time to ESRD, the composite outcome of death or ESRD, the composite of death or any cardiovascular event (defined as prespecified coronary disease–, cerebrovascular disease–, or peripheral vascular

Table 1. Patient demographics, comorbidities, medication use, and laboratory variables by serum potassium categories at enrollment

Variable	Overall (n = 820)	Hypokalemia (n = 122)	Eukalemia (n = 633)	Hyperkalemia (n = 65)	P
Demographics					
age (years; mean ± SD)	60.5 ± 15.4	60.6 ± 16.1	60.7 ± 15.4	58.4 ± 14.0	0.499
male (n [%])	448 (55)	52 (43)	346 (55)	50 (77)	<0.0001
black (n [%])	167 (20)	37 (30)	117 (19)	13 (20)	0.012
Vital signs (mean ± SD)					
BMI (kg/m^2)	29.4 ± 6.9	29.8 ± 6.9	29.3 ± 6.9	29.4 ± 7.7	0.847
SBP (mmHg)	139.7 ± 21.7	142.8 ± 23.9	139.4 ± 21.6	137.8 ± 18.8	0.211
eGFR (ml/min per 1.73 m^2)	25.4 ± 10.6	27.0 ± 13.7	25.3 ± 9.9	23.2 ± 10.1	0.059
Cause of CKD (n [%])					
diabetes	265 (32)	39 (32)	199 (32)	27 (42)	0.262
hypertension	402 (49)	60 (49)	310 (49)	32 (49)	0.99
Medication use (yes/no; n [%])					
ACEIs	332 (41)	34 (28)	260 (41)	43 (66)	<0.0001
ARBs	144 (17)	35 (29)	144 (23)	7 (11)	0.021
aspirin	304 (37)	41 (34)	236 (37)	27 (42)	0.549
β blockers	392 (47)	62 (51)	295 (47)	35 (54)	0.414
calcium channel blocker	353 (43)	64 (52)	294 (46)	23 (35)	0.083
diuretics	409 (50)	75 (61)	317 (50)	34 (52)	0.069
erythropoietin	199 (24)	30 (25)	150 (24)	19 (29)	0.609
statins	352 (42)	39 (32)	278 (44)	34 (52)	0.014
Laboratory (mean ± SD)					
serum albumin (g/dl)	3.8 ± 0.5	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	0.098
serum CO_2 (mEq/L)	24.2 ± 3.9	26.2 ± 3.7	24.1 ± 3.8	21.2 ± 3.5	<0.0001
serum potassium (mmol/L)	4.6 ± 0.9	3.7 ± 0.3	4.7 ± 0.4	5.8 ± 0.3	<0.0001
serum phosphorus (mg/dl)	4.2 ± 1.1	4.3 ± 1.5	4.1 ± 1.0	4.5 ± 1.1	0.031
Patient outcomes (n [%])					
death	86 (10)	16 (13)	64 (10)	6 (9)	0.576
ESRD	303 (36)	57 (36)	213 (35)	33 (48)	0.145
coronary artery disease	70	11 (9)	50 (8)	9 (14)	0.258
cardiovascular disease	50	8 (7)	38 (6)	4 (6)	0.977
peripheral arterial disease	70	8 (7)	55 (8)	7 (11)	0.581
any cardiovascular event	190	32 (27)	139 (22)	19 (29)	0.249

Hypokalemia: S_K ≤4.0 mmol/L; eukalemia: S_K >4.0 and <5.5 mmol/L; hyperkalemia: S_K ≥5.5 mmol/L. ARB, angiotensin II receptor blocker; BMI, body mass index; SBP, systolic BP.

disease–related events that required hospitalization or revascularization procedures in any of the named three major arterial beds). All models entered S_K as either a baseline or a time-dependent variable that changed at each measurement during the follow-up period. In baseline models, S_K was a weaker predictor than time-dependent S_K, probably because measures of S_K that are more proximate to the event have higher predictive power; therefore, only time-dependent models are presented. Cox models were adjusted for age, gender, race, and diabetes status; history of cardiovascular disease; hypertension; and eGFR. Variables that were considered but excluded as adjustments included diabetes and race, based on $P > 0.2$. Models were considered both with and without the inclusion of serum albumin. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

Results

An average of six S_K values per patient (n = 820) were available during the course of the study. The average duration of patient follow-up was 2.6 years (range 0.0 to 7.0 years), with three nephrology clinic visits per year, on average. The average number of visits for those with stage 3 CKD was 1.94 visits per year and for stage 4 CKD or more was 2.58 visits per year. Table 1 shows baseline characteristics of patients who were included in this analysis. Patients were predominantly white (80%) and had a mean ± SD age of 60.5 ± 15.4 years (range 18.0 to 93.0 years) and mean eGFR of 25.4 ± 6.9 ml/min per 1.73 m^2 (range 3.7 to 91.7 ml/min per 1.73 m^2). The majority had hypertension (90%), and 36% had diabetes. The average S_K level was 4.6 ± 0.9 mmol/L (range 2.5 to 7.0 mmol/L).

Figure 1 shows the distribution of S_K by eGFR category. There were significant differences in the average S_K values and CKD stage ($P < 0.05$ for all pairwise mean differences). Figure 2 displays the distribution of S_K by gender, ACEI use, and quartiles of serum CO_2. There were significant differences in the average S_K values between men and women ($P < 0.0001$) and between ACEI users and nonusers ($P < 0.0001$). The significant trend in average S_K by quartiles of serum CO_2 (trend $P = 0.05$) shows lower average S_K with higher serum CO_2 relationship. Figure 2 also shows the wide variation in S_K values at all levels of these strongly predictive covariates.

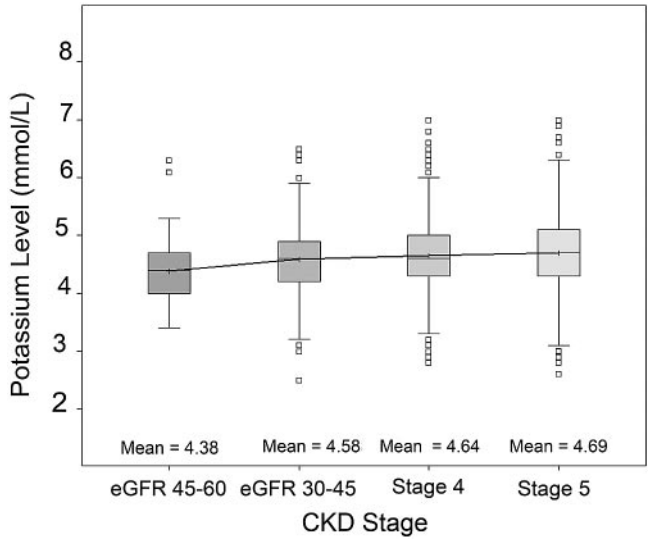

Figure 1. Box plot distributions of S_K by eGFR categories (45 to 60, 30 to 45, 15 to 30, and <15).

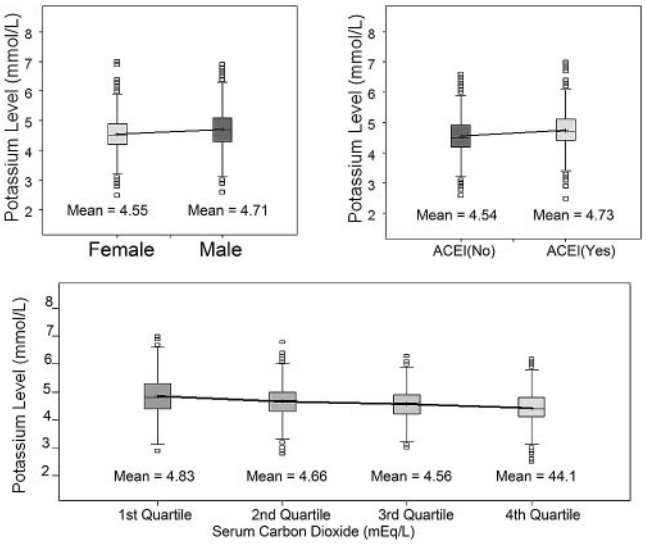

Figure 2. Box plot distributions of S_K by gender, ACEI use, and quartiles of serum CO_2.

Table 2 shows a cross-sectional model predicting baseline S_K and a longitudinal model predicting S_K during the follow-up period. In the baseline model, higher S_K was significantly associated with male gender, lower serum CO_2, diabetes, and use of ACEIs and/or statins. In time-dependent models, higher S_K was additionally associated with lower eGFR and absence of diuretic and/or calcium channel blocker use. The estimated correlation between repeated S_K values from the same patient in the longitudinal model was approximately $r = 0.53$, indicating relatively stable S_K levels for a given patient over time.

Among the 820 patients, there were 86 deaths before reaching ESRD. Using the three categories of S_K in a Cox model adjusted for age, gender, eGFR, hypertension, and history of cardiovascular disease, we found that pre-ESRD mortality was significantly higher for $S_K \leq 4.0$ mmol/L compared with $S_K > 4.0$ and < 5.5 mmol/L, but higher S_K (≥ 5.5 mmol/L) was not associated with elevated mortality (Table 3). Furthermore, when modeled as a continuous variable, a marginally significant quadratic effect was observed, with significant effects at lower S_K (≤ 4.0 mmol/L) but not at higher S_K (≥ 5.5 mmol/L; Table 3). Figure 3a displays the model-based U-shaped relationship between risk for mortality and S_K. After addition of serum albumin to the model, low S_K remained significantly associated with mortality (Table 3).

There were 303 ESRD events ($n = 263$ dialysis, $n = 40$ preemptive transplants). In the model with S_K as a categorical model, low S_K (≤ 4.0 mmol/L) but not higher S_K (≥ 5.5 mmol/L) was significantly associated with elevated risk for ESRD (Table 3). When modeled as a continuous variable, a significant quadratic effect was observed. Figure 3b displays the U-shaped relationship between risk for ESRD and S_K. After addition of serum albumin to the model, low S_K was marginally associated with ESRD (Table 3).

Table 2. Predictors of S_K at baseline and during follow-up

Predictors	Predictors of S_K at Baseline ($n = 729$)[a]		Predictors of S_K over Time ($n = 5111$)[b]	
	Estimate	*P*	Estimate	*P*
Male gender	0.18	<0.0001	0.18	<0.0001
Serum CO_2 (mEq/L)	−0.05	<0.0001	−0.03	<0.0001
eGFR (per 10 ml/min per 1.73 m^2)	−0.02	0.39	−0.06	<0.0001
Diabetes	0.10	0.029	0.06	0.030
ACEI use	0.21	<0.0001	0.17	<0.0001
Diuretic use	−0.07	0.76	−0.12	<0.0001
Calcium channel blocker use	−0.06	0.12	−0.09	<0.0001
Statin use	0.11	0.001	0.12	<0.0001

All variables from Table 1 were tested in the selection models, with significant variables retained ($\alpha = 0.05$).
[a]All variables simultaneously entered in a multiple linear regression model.
[b]All variables simultaneously entered in a repeated measures regression model. The values of all covariates (except gender) were allowed to change with follow-up time.

For the composite outcome of death or ESRD (Figure 3c), a U-shaped relationship between S_K and the composite outcome was evident. There was a significantly higher hazard for death/ESRD at lower serum S_K, the significance of which was attenuated by adjustment for serum albumin in the model. As a categorical variable, lower S_K levels remained a significant predictor of the composite outcome before and after adjustment for serum albumin (Table 3). Higher S_K was not significantly associated with the composite outcome.

A total of 190 cardiovascular events (70 coronary, 50 cerebrovascular, and 70 peripheral vascular) that required hospitalization were documented during the course of the study. A significant quadratic relationship was seen between S_K, and the relative hazard of first cardiovascular event or death (Figure 3d) was noted. Unlike overall mortality, this was statistically significant for S_K >5.5 mmol/L but not for lower potassium (<4.0 mmol/L). After addition of serum albumin to the model, higher S_K but not lower S_K was associated with the composite outcome (Table 3).

Discussion

To the best of our knowledge, this is the first study to investigate systematically the prevalence and mortality associated with S_K levels that are obtained during routine clinical practice in a large and diverse nondialysis prospective CKD cohort. Our main finding is that S_K level ≤4.0 mmol/L was associated with a higher risk for mortality and ESRD compared with S_K between 4.1 and 5.5 mmol/L. These observations are of clinical importance, because most physicians consider S_K values of 3.5 to 3.9 mmol/L to be "within normal limits." Our multivariable analyses show that the lowest risk for mortality was in the S_K range of 4.1 to 5.5 mmol/L and that mortality or ESRD risk was not significantly higher even at S_K levels of 5.5 to 5.9 mmol/L, a range of S_K values that almost always evokes clinical concern with or without intervention (*e.g.*, dietary advice, prescription of loop diuretic, discontinuation of potassium-sparing diuretics). This modest level of hyperkalemia seemed to be well tolerated in this patient population from the perspective of predicting mortality risk.

The link between relatively normal or low-normal levels of S_K (3.5 to 4.0 mmol/L) and mortality has not been previously documented in the CKD population. This finding is not altogether surprising, however. Low S_K levels affect myocardial resting membrane potential, which increases the probability of ventricular arrhythmias and sudden cardiac death (11). Hypokalemia can also predispose patients to developing diastolic dysfunction, digoxin toxicity, and insulin resistance, all of which increase the risk for cardiovascular events and death (12–16). Dietary potassium depletion has been linked to the genesis of hypertension, and supplementation can improve BP control (17–19). Data from the cardiovascular literature suggest that serum potassium levels <4.0 mmol/L portend a worse prognosis among those who have a history of heart failure or acute myocardial infarction (20,21). Current American Heart Association/American College of Cardiology guidelines recommend that serum potassium levels be maintained between 4.0 and 5.0 mmol/L in those with chronic heart failure (22). Our study provides observational evidence that necessitates similar guidelines for patients with CKD.

Not surprising, diuretic use was associated with lower S_K levels in this study. Non–potassium-sparing diuretic use has been linked with increased mortality and hospitalization that can likely be attributed to low S_K levels (23). Several case-control studies reported an increased risk for cardiac arrest among patients who received high dosages of thiazide diuretics. This risk was lowered when thiazide therapy was combined with potassium-sparing diuretics (24–26). Because diuretics are very commonly used for volume and BP control in the CKD population and hypokalemia is a frequent complication of this class of medications, these results suggest that clinicians need to monitor S_K levels closely and consider using potassium-sparing diuretics and/or potassium supplements in patients who have CKD and are prone to hypokalemia; however, clinical trials will need to be performed before formulating defin-

Table 3. Cox models to determine association between S_K (at baseline and as time dependent covariate) as continuous and categorical covariate with mortality, ESRD, and cardiovascular events

Parameter	Model 1 (without Serum Albumin)			Model 2 (with Serum Albumin)		
	HR	95% CI	*P*	HR	95% CI	*P*
Mortality						
time-dependent continuous S_K[a]						
S_K = 3.4 *versus* 5.0 mmol/L	2.40	1.13 to 5.09		2.33	0.95 to 5.71	
S_K = 3.8 *versus* 5.0 mmol/L	1.65	1.04 to 2.61		1.57	0.90 to 2.73	
S_K = 6.0 *versus* 5.0 mmol/L	1.34	0.59 to 3.03		1.59	0.62 to 4.04	
time-dependent categorical S_K (eukalemia as reference)						
hypokalemia (≤4.0 mmol/L)	1.73	1.02 to 2.95	0.04	1.90	1.00 to 3.61	0.05
hyperkalemia (≥5.5 mmol/L)	1.57	0.78 to 3.20	0.20	1.82	0.80 to 4.16	0.15
ESRD						
time-dependent continuous S_K[b]						
S_K = 3.4 *versus* 5.0 mmol/L	1.87	1.25 to 2.79		1.56	0.97 to 2.52	
S_K = 3.8 *versus* 5.0 mmol/L	1.42	1.11 to 1.82		1.28	0.95 to 1.72	
S_K = 6.0 *versus* 5.0 mmol/L	1.26	0.91 to 2.14		1.21	0.83 to 1.76	
time-dependent categorical S_K (eukalemia as reference)						
hypokalemia (≤4.0 mmol/L)	1.69	1.25 to 2.29	0.0006	1.39	0.97 to 1.99	0.07
hyperkalemia (≥5.5 mmol/L)	1.02	0.70 to 1.48	0.91	1.09	0.71 to 1.68	0.68
ESRD or death						
time-dependent continuous S_K[c]						
S_K = 3.4 *versus* 5.0 mmol/L	2.17	1.50 to 3.15		1.42	0.88 to 2.28	
S_K = 3.8 *versus* 5.0 mmol/L	1.57	1.25 to 1.97		1.24	0.92 to 1.66	
S_K = 6.0 *versus* 5.0 mmol/L	1.25	0.90 to 1.73		1.04	0.73 to 1.48	
time-dependent categorical S_K (eukalemia as reference)						
hypokalemia (≤4.0 mmol/L)	1.71	1.31 to 2.22	<0.0001	1.07	1.99 to 0.02	1.07
hyperkalemia (≥5.5 mmol/L)	1.12	0.81 to 1.57	0.46	0.81	1.74 to 0.36	0.81
Cardiovascular event or death						
time-dependent continuous S_K[d]						
S_K = 3.4 *versus* 5.0 mmol/L	1.34	0.86 to 2.09		1.04	0.62 to 1.74	
S_K = 3.8 *versus* 5.0 mmol/L	1.07	0.81 to 1.41		0.92	0.67 to 1.26	
S_K = 6.0 *versus* 5.0 mmol/L	1.84	1.24 to 2.74		1.78	1.17 to 2.70	
time-dependent categorical S_K (eukalemia as reference)						
hypokalemia (≤4.0 mmol/L)	1.33	0.95 to 1.86	0.09	1.13	0.76 to 1.67	0.54
hyperkalemia (≥5.5 mmol/L)	1.75	1.18 to 2.62	0.005	1.69	1.09 to 2.60	0.02

[a]Model 1: $\beta(S_K^2) = 0.32$, $P = 0.11$; model 2: $\beta(S_K^2) = 0.38$, $P = 0.10$.
[b]Model 1: $\beta(S_K^2) = 0.24$, $P = 0.007$; model 2: $\beta(S_K^2) = 0.18$, $P = 0.09$.
[c] Model 1: $\beta(S_K^2) = 0.72$, $P = 0.002$; model 2: $\beta(S_K^2) = 0.10$, $P = 0.32$.
[d]Model 1: $\beta(S_K^2) = 0.31$, $P = 0.003$; model 2: $\beta(S_K^2) = 0.23$, $P = 0.04$.

itive recommendations in this regard. We have no definitive explanation for why statin use should be associated with higher S_K levels; however, we speculate that statin use by virtue of its potential to cause subclinical muscle injury could be associated with release of S_K from cells, accounting for the higher S_K. Creatine phosphokinase levels, which would have allowed the testing of this hypothesis, were not measured in this CKD cohort; therefore, this potential mechanism cannot be commented on.

The association of higher S_K with lower eGFR is not surprising. As renal function declines, potassium balance is usually maintained *via* increases in potassium excretion per functioning nephron (6). Hyperkalemia stimulates aldosterone secretion, which also increases the fractional potassium excretion (27). Patients who have CKD and have been given a potassium load actually maintain their S_K levels when compared with control subjects, strongly supporting the presence of compensatory extrarenal mechanisms of potassium loss (28). Patients with

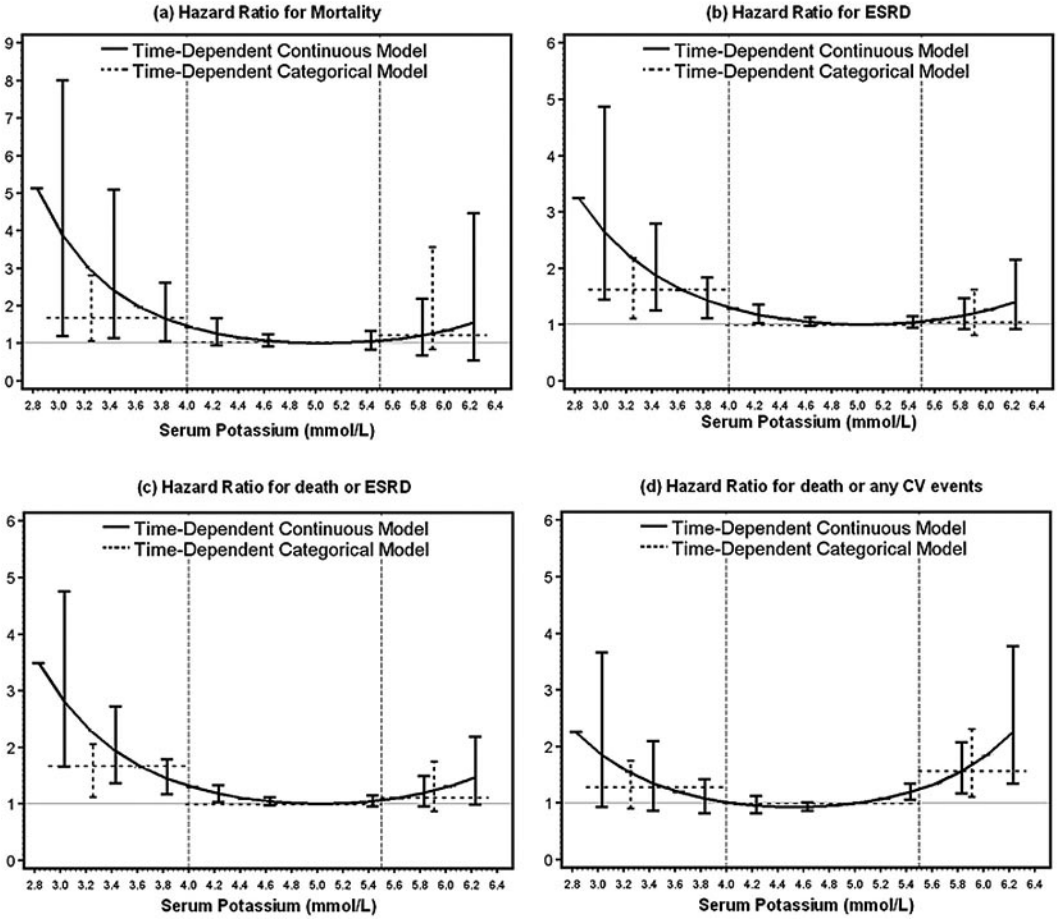

Figure 3. Relationship of S_K and risk for mortality (a), risk for ESRD (b), risk for the composite of death or ESRD (c), and risk for the composite of death or cardiovascular events that require hospitalization (d), using S_K as a time-dependent continuous covariate (smooth curves). In addition, S_K as a categorical time-dependent covariate is shown, with the middle category (S_K >4.0 and <5.5) as the reference group in the Cox model; 95% confidence intervals are given for the continuous S_K models at S_K values of 3.0, 3.4, 3.8, 4.2, 4.6, 5.4, 5.8, and 6.2, with upper limits truncated at 8.0 in panel a.

CKD also have been found to have increased extrarenal potassium excretion through both increased intestinal potassium excretion and increased potassium translocation into the intracellular component (29,30).

It has been postulated that those with diabetes are more likely to have relative aldosterone insensitivity and therefore are predisposed to the development of acidosis and hyperkalemia (31). In addition, inadequate insulin secretion may lead to extracellular potassium shifts (32). We speculate that given that this cohort of patients was being followed in nephrology clinics, concomitant diuretic use or nutritional advice to lower potassium intake may have potentially attenuated the relationship between eGFR and S_K, as well as that of diabetes status and higher potassium levels, particularly among those with stages 4 to 5 CKD. In our study, higher S_K was associated with use of renin-angiotensin-aldosterone system antagonists such as ACEIs. Hyperkalemia is a widely recognized adverse effect of the use of such agents. The risk for development of elevated potassium levels is low (<6%) in those with normal renal function but higher among those with CKD (5 to 50%) (33). In this study, a modest degree of hyperkalemia (S_K between 5.0 and 6.0 mmol/L) seemed to be well tolerated with no significantly elevated risk for mortality. In contrast, the association between higher S_K and the risk for cardiovascular events (or the composite of cardiovascular event or death) is somewhat surprising, given our findings with respect to the outcome of mortality or ESRD as the outcomes of interest; however, we speculate that this may be due to the greater documentation of cardiovascular events (related to hospitalization) among survivors in this cohort, who on average have a higher potassium level (*i.e.*, it is more likely related to a "survivor bias" than a true "causal" link, although the latter cannot be excluded on the basis of this study alone).

The association between increased risk for ESRD and hypo- and hyperkalemia has not been previously documented in the literature. In one study (34) patients with hypokalemia were less likely to be taking ACEIs, which has been shown to slow progression of CKD. In two other studies (35,36), patients with hyperkalemia were more likely to have higher phosphorous levels, lower eGFR, and lower bicarbonate levels, factors that all have been independently linked to progression of CKD.

The strengths of our study include a large prospective cohort

of CKD with availability of serum potassium in the majority of patients at multiple time points during follow-up, permitting analyses with S_K as a time-dependent covariate. The long duration of follow-up (median 3 years) and detailed medication data are additional strengths. Certain limitations merit consideration. Data on the dietary intake of potassium and protein was not collected in the Renal Research Institute CKD Study; however, we examined models with and without adjustment for serum albumin, a major marker of nutritional status. The predictive value of S_K was slightly attenuated by this adjustment, suggesting that nutritional state may be part of the explanation for the link between low S_K and mortality. In this study, death, ESRD, and cardiovascular event information was abstracted by study coordinators primarily from patient charts. It is possible that some events were not detected. The average time from the last S_K measure until death was 8.2 months, and the median was 5.8 months; therefore, we do not have values of S_K closer to the time of death.

The relatively weak association of higher S_K with mortality may be the result of dialysis initiation as "rescue" therapy in the face of emergent hyperkalemia and absence of data pertaining to serum potassium just proximate to dialysis initiation among those who reached ESRD. Similarly, the association between higher levels of S_K and cardiovascular events may reflect a survivor bias rather than a causal effect, although the latter cannot be excluded. Despite these limitations, the association, particularly at the lower end of the range of potassium levels in this patient population, could more plausibly be causally linked (based on what is known about the adverse effects of low potassium) to adverse outcomes in this and other patient populations. Causal inferences cannot be drawn with certainty, however, in the setting of an observational study such as ours.

Conclusions

Lower S_K (even less than or equal to a "normal" level of 4.0 mmol/L) seems to predict mortality to a relatively greater degree compared with the risk associated with $S_K \geq 5.5$ mmol/L. This study shows that the levels of S_K that are associated with lowest risk for mortality are between 4.1 and 5.5 mmol/L, which suggests that maintaining S_K in this range may potentially help optimize survival in patients with CKD. Practice patterns could potentially be adapted to supplement potassium (through dietary modification or pills) and avoid use of loop diuretics whenever possible. The benefits of potassium-sparing diuretics such as aldosterone receptor–blocking agents may be due in part to their ability to "normalize" serum potassium levels. Aldosterone is increasingly recognized to be important in the pathogenesis of CKD (37,38), and mineralocorticoid receptor blockade is an increasing used strategy in lowering proteinuria with the potential of both slowing renal disease progression and lowering mortality. These issues warrant future studies that specifically address the role of potassium supplementation in determining outcomes and study the deliberate optimization of serum potassium levels by use of specific drugs in randomized trials. Overall, our findings suggest that attention should be paid to patients who have CKD and are at the lower ranges of S_K as well as those with elevated serum potassium to prevent adverse outcomes such as mortality, ESRD, and cardiovascular events.

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Disclosures

None.

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