

Dialysate Potassium and Mortality in a Prospective Hemodialysis Cohort

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Keywords

Dialysate potassium · Serum potassium · Gradient · Hemodialysis · Mortality

Abstract

Background: Studies examining the association of dialysate potassium concentration and mortality in hemodialysis patients show conflicting findings. We hypothesized that low dialysate potassium concentrations are associated with higher mortality, particularly in patients with high pre-dialysis serum potassium concentrations. **Methods:** We evaluated 624 hemodialysis patients from the prospective Malnutrition, Diet, and Racial Disparities in Kidney Disease study recruited from 16 outpatient dialysis facilities over 2011–2015 who underwent protocolized collection of dialysis treatment characteristics every 6 months. We examined the association of dialysate potassium concentration, categorized as 1, 2, and 3 mEq/L, with all-cause mortality risk in the overall cohort, and stratified by pre-dialysis serum potassium (<5 vs. ≥5 mEq/L) using case-mix adjusted Cox models. **Results:** In

baseline analyses, dialysate potassium concentrations of 1 mEq/L were associated with higher mortality, whereas concentrations of 3 mEq/L were associated with similar mortality in the overall cohort (reference: 2 mEq/L): adjusted hazard ratios (aHRs; 95% CI) 1.70 (1.01–2.88) and 0.95 (0.64–1.39), respectively. In analyses stratified by serum potassium, baseline dialysate potassium concentrations of 1 mEq/L were associated with higher mortality in patients with serum potassium ≥5 mEq/L but not in those with serum potassium <5 mEq/L: aHRs (95% CI) 2.87 (1.51–5.46) and 0.74 (0.27–2.07), respectively (*p* interaction = 0.04). These findings were robust with incremental adjustment for serum potassium, potassium-binding resins, and potassium-modifying medications. **Conclusion:** Low (1 mEq/L) dialysate potassium concentrations were associated with higher mortality, particularly in hemodialysis patients with high pre-dialysis serum potassium. Further studies are needed to identify therapeutic strategies that mitigate inter-dialytic serum potassium accumulation and subsequent high dialysate serum potassium gradients in this population.

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Introduction

Regulation of serum potassium is essential to health and survival, given the potent association between hyperkalemia and hypokalemia with cardiovascular complications, particularly ventricular arrhythmias [1–6]. Daily potassium intake typically ranges between 60 and 150 mmol in the typical Western diet, with 92 and 8% excreted in urine and stool, respectively, in order to maintain total body potassium homeostasis [7]. In the context of normal kidney function, serum potassium levels can be maintained within normal ranges with up to a 10-fold higher intake of potassium, albeit with gradual increases in consumption. However, as kidney function declines, there is a compensatory increase in the fecal excretion of potassium up to a certain threshold below which hyperkalemia eventually ensues [8, 9].

While it is well established that hemodialysis is a critical intervention for maintaining potassium homeostasis among end-stage renal disease patients, there remains a wide debate regarding the appropriate prescription of dialysate potassium concentrations in this population. Although clinical practice guidelines do not currently provide recommendations on the prescription of dialysate potassium, many clinicians apply a “Rule of 7’s” in which the sum of a patient’s serum potassium and dialysate potassium concentrations should approximate 7 mEq/L [10]. However, there is limited data supporting these methods of dialysate potassium concentration selection.

There is particular controversy regarding the safety of low dialysate potassium concentrations utilized in the maintenance hemodialysis population, particularly among patients with high pre-dialysis serum potassium levels. To date, several studies have observed that patients prescribed low dialysate potassium concentrations of 0 and 1 mEq/L experience higher all-cause and cardiovascular mortality risk [10–13]. Adding to these aforementioned uncertainties, there has also been concern that abrupt changes in potassium kinetics during hemodialysis ensuing from a high serum-to-dialysate potassium gradient may increase risk of cardiovascular morbidity and mortality. For example, serum potassium levels decline most precipitously during the first 2–3 h of hemodialysis, and following completion of dialysis treatment. In addition, while the vast majority of the body’s potassium is intracellular (98 vs. 2% stored in the intracellular vs. extracellular space, respectively) [4–6], dialysis has greater influence upon extracellular vs. intracellular potassium concentrations, post-dialysis rebound is frequently observed (i.e., 35 and 65% attenua-

tion in intra-dialytic serum potassium reductions within 1 and 6 h after hemodialysis treatment, respectively) [8]. Thus, it has been hypothesized that a large differential between serum and dialysate potassium concentrations may exacerbate rapid changes in potassium kinetics, leading to instability in cardiac conduction and heightened risk of malignant arrhythmias in hemodialysis patients [14, 15].

However, studies of the serum-to-dialysate potassium gradient and mortality in hemodialysis patients have shown mixed findings to date [2, 10, 11, 16, 17]. Thus, to better inform the field, we examined repeated measures of dialysate and serum potassium concentrations among a prospective multi-center cohort of hemodialysis patients in Southern California. We aimed to test the hypothesis that lower dialysate potassium concentrations prescribed to hemodialysis patients with higher serum potassium levels (i.e., high serum-to-dialysate potassium gradient) were associated with higher mortality risk.

Methods

Study Population

The study population was comprised of adult hemodialysis patients in the ongoing Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease (MADRAD) study (ClinicalTrials.gov study: NCT01415570), a prospective cohort study examining the differential association between dietary factors and nutritional status across racial and ethnic subgroups [18–20]. In the ongoing MADRAD study, patients undergo protocolized assessment of sociodemographics, comorbidities, medications, dialysis treatment characteristics, laboratory tests, nutritional status, and body anthropometry every 6 months (designated as study rounds) [18–20]. The study population was a subcohort of MADRAD study patients recruited from 16 outpatient dialysis clinics in the Southern California region over October 2011 to February 2015, with follow-up through November 2016.

Patients were included in the study provided that they had available dialysate and serum potassium data collected during the same round, were age 18 years or older at the time of study entry (i.e., date of first dialysate potassium concentration assessment), were receiving thrice-weekly in-center hemodialysis for at least 4 weeks, and signed a local institutional review board approved consent form. Patients were excluded if they were actively receiving treatment with peritoneal dialysis, had life expectancy less than 6 months, or were unable to provide consent. The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA and the University of California Irvine School of Medicine.

Exposure Ascertainment

The exposure of interest was the dialysate potassium concentration ascertained every 6 months by MADRAD research coordinators while patients were undergoing routine dialysis treatments, categorized as 1, 2, and 3 mEq/L. In co-primary analyses, we eval-

uated the association between (1) dialysate potassium concentration and all-cause mortality in the overall cohort, as well as (2) dialysate potassium concentration and all-cause mortality stratified by serum potassium level dichotomized as <5 vs. ≥ 5 mEq/L. A cutoff of 5 mEq/L was selected as the approximate median and mean serum potassium level in our study population, as well as an established threshold for higher mortality risk in previous studies [13]. Serum potassium levels were performed by the outpatient dialysis clinics on a minimum monthly basis, and other routine dialysis laboratory measurements were conducted on a monthly or quarterly basis.

In primary analyses, we sought to examine the association between baseline dialysate potassium concentration and all-cause mortality. In secondary analyses, we examined the association between time-dependent dialysate potassium concentration and all-cause mortality, in which we examined repeated measures of time-updated dialysate potassium concentrations.

Sociodemographic, Comorbidity, Dialysis Treatment, and Medication Measures

Baseline sociodemographic, comorbidity, medication, and dialysis treatment data were collected at the time of enrollment and every 6 months by MADRAD research coordinators. We considered medication data prescribed within 1 year of study entry (i.e., date of first dialysate potassium concentration assessment) as collected by the MADRAD research coordinators and staff from participating dialysis units.

Body Anthropometry and Nutritional Score Measures

MADRAD research coordinators conducted measurements of body composition surrogates during routine hemodialysis treatments, including body mass index, subcutaneous fat (determined from biceps and triceps skinfold), visceral fat (determined from waist circumference), lean muscle mass (determined from mid-arm circumference and mid-arm muscle circumference), and body fat percentage (measured by near-infrared interactance) as has been previously described [18]. Data on Subjective Global Assessment, a nutritional scoring tool, body mass index, serum albumin, and total iron binding capacity were also used to estimate the Malnutrition Inflammation Score as a proxy of protein-energy wasting (scores ranging from 0 to 30 with higher Malnutrition Inflammation Scores reflecting more severe degrees of protein-energy wasting) [21–26].

Outcome Ascertainment

All-cause mortality was the primary outcome of interest. At-risk time began the day after dialysate potassium concentration assessment, and patients were censored for kidney transplantation, transfer to a non-participating dialysis facility, peritoneal dialysis, or at the end of the study period (November 22, 2016). Every 6 months, information regarding mortality, censoring events, and associated dates from prior study rounds were collected from event forms completed by the MADRAD research coordinators and were reviewed by 2 MADRAD study nephrologists (C.M.R. and K.K.-Z.).

Statistical Methods

Patients' baseline characteristics stratified by baseline dialysate potassium concentrations were compared with analysis of variance, chi-square, or Kruskal-Wallis tests as appropriate. We first

examined the relationship of relevant clinical characteristics with the likelihood of being prescribed a low (1 mEq/L) dialysate potassium concentration (reference: 2–3 mEq/L) using logistic regression.

We then estimated the association between dialysate potassium concentration and all-cause mortality using Cox proportional hazards models. Logistic regression and Cox proportional hazards models were conducted using 5 incremental levels of covariate adjustment:

1. Unadjusted model: included dialysate potassium concentration;
2. Case-mix model: covariates in the unadjusted model, as well as age (at the time of dialysate potassium concentration), sex, race (black vs. non-black), and ethnicity (Hispanic vs. non-Hispanic);
3. Case-mix + serum potassium model: covariates in the case-mix adjusted model, as well as serum potassium concentration;
4. Case-mix + serum potassium + potassium-binding resins model: covariates in the case-mix + serum potassium model, as well as potassium-binding resins (e.g., sodium polystyrene);
5. Case-mix + serum potassium + potassium-modifying medications model: covariates in the case-mix + serum potassium + potassium-binding resin model, plus non-steroidal anti-inflammatory drugs, potassium sparing diuretics, angiotensin converting enzyme inhibitors, and aldosterone receptor blockers.

We defined the case-mix adjusted model as our primary model, which forced into the model core sociodemographic measures. Analyses incrementally adjusted for serum potassium, potassium-binding resins, and potassium-modifying medications were conducted as secondary analyses. To determine the impact of key confounders upon estimates of the dialysate potassium concentration-mortality association, namely comorbidity burden and nutritional status/dietary compliance, we implemented an expanded case-mix + serum potassium + potassium-modifying medications model that further adjusted for history of diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, any cardiovascular disease, and Malnutrition Inflammation Score [22, 23, 25] as sensitivity analyses. The proportional hazards assumption was confirmed graphically and by Schoenfeld residual function testing. There were no missing covariate data except for Malnutrition Inflammation Score (i.e., 14% of patients with missing data), which was addressed using multiple imputation. Analyses were carried out using the statistical software Stata version 12.0 (Stata-Corp LP, College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Cohort Description

Among 624 patients who met eligibility criteria (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000489961), the mean \pm SD age of the cohort was 54.5 ± 14.5 years, among whom 43% were women; 35% were black, and 47% were of Hispanic ethnicity; and of whom 51% had underlying diabetes. At

study entry, 8% ($n = 47$), 72% ($n = 449$), and 21% ($n = 128$) were prescribed 1, 2, and 3 mEq/L dialysate concentrations, respectively. Compared to patients who were prescribed 2 or 3 mEq/L dialysate concentrations, those prescribed 1 mEq/L dialysate concentrations were more likely to be female and Hispanic; had longer dialysis vintage; and had higher normalized protein catabolic rates (nPCR), serum phosphorus, and serum creatinine levels (Table 1).

Clinical Characteristics Associated with Dialysate Potassium Concentration

In case-mix adjusted logistic regression models, we observed that patients who were female; Hispanic; of longer dialysis vintage; and with higher nPCR, serum potassium, and serum creatinine levels had higher likelihood of receipt of a low (i.e., 1 mEq/L) dialysate potassium concentration. Associations with female sex, Hispanic ethnicity, higher nPCR, and higher serum creatinine levels with low dialysate concentration persisted across all models of covariate adjustment (Table 2).

Dialysate Potassium Concentration and Mortality

Patients contributed a total of 1,867 person-years of follow-up during which time 161 death events were observed. Median (IQR) at-risk time was 3.2 (1.8–4.3) years. In analyses of baseline dialysate potassium concentration in the overall cohort, compared to patients prescribed a 2 mEq/L dialysate concentration, those prescribed a 1 mEq/L concentration had higher mortality risk in case-mix, case-mix + serum potassium, case-mix + serum potassium + potassium-binding resin, and case mix + serum potassium + potassium-modifying medication adjusted analyses (adjusted hazard ratios [aHRs; 95% CI] 1.70 [1.01–2.88], 1.71 [1.01–2.90], 1.70 [1.00–2.88], and 1.72 [1.01–2.93], respectively), whereas patients prescribed a 3 mEq/L bath had similar mortality risk (aHR [95% CI] 0.95 [0.64–1.39], 0.94 [0.63–1.40], 0.94 [0.63–1.39], and 0.91 [0.6–1.36], respectively; Fig. 1; online suppl. Table 1). In sensitivity analyses adjusted for expanded case-mix + serum potassium + potassium-modifying medications covariates, point estimates for receipt of a 1 mEq/L dialysate potassium concentration suggested higher mortality risk, although associations narrowly missed statistical significance: aHR (95% CI) 1.70 (0.97–2.96), $p = 0.06$ (online suppl. Table 1).

We observed that pre-dialysis serum potassium level was an effect modifier of the association between dialysate potassium concentration and mortality risk. In

analyses stratified by serum potassium, patients prescribed a 1 mEq/L bath had higher mortality among those with serum potassium levels ≥ 5 mEq/L in case-mix adjusted analyses (reference: 2 mEq/L): aHR (95% CI) 2.87 (1.51–5.46). However, we did not observe a significant association between patients prescribed a 1 mEq/L bath and mortality among those with serum potassium levels < 5 mEq/L: aHR (95% CI) 0.74 (0.27–2.07), p interaction = 0.04. These patterns of association persisted in models incrementally adjusted for case-mix, case-mix + serum potassium, case-mix + serum potassium + potassium-binding resin, case-mix + serum potassium + potassium-modifying medications covariates (Fig. 2; online suppl. Table 2). Sensitivity analyses adjusted for expanded case-mix + serum potassium + potassium-modifying medications covariates also showed that a 1 mEq/L dialysate potassium concentration was associated with higher mortality in patients with serum potassium levels ≥ 5 mEq/L but not in those with serum potassium < 5 mEq/L: aHRs (95% CI) 2.51 (1.24–5.06) and 0.76 (0.26–2.23), respectively; p interaction = 0.04 (online suppl. Table 2).

In analyses of time-dependent dialysate and serum potassium concentrations adjusted for case-mix covariates, there was a trend between receipt of 1 mEq/L dialysate potassium concentrations and higher mortality risk, although associations did not achieve statistical significance (online suppl. Table 3). Similar patterns were observed when analyses of time-dependent dialysate potassium concentration and mortality were stratified by time-dependent serum potassium level (online suppl. Table 4).

Discussion

In a prospective, multi-center cohort of maintenance hemodialysis patients across Southern California, we observed that patients who were prescribed a dialysate potassium concentration of 1 mEq/L had higher mortality risk compared to those receiving a 2 or 3 mEq/L dialysate potassium concentration bath. However, in a priori defined analyses stratified by serum potassium level, we found that low dialysate potassium concentrations of 1 mEq/L were associated with higher mortality risk only among patients with high pre-dialysis serum potassium levels (≥ 5 mEq/L) but not in those with low serum potassium levels (< 5 mEq/L). These observations persisted across sensitivity analyses with incremental levels of multivariable adjustment for case-

Table 1. Baseline characteristics according to dialysate potassium concentration

	Dialysate potassium concentration			<i>p</i> value*
	1 mEq/L	2 mEq/L	3 mEq/L	
Patients, <i>n</i> (%)	47 (8)	449 (72)	128 (21)	N/A
Age, years, mean ± SD	50.1±15.5	54.1±14.3	57.3±14.4	0.02
Female, %	58	44	35	0.03
Black race, %	32	35	38	0.69
Hispanic ethnicity, %	64	47	41	0.03
Vintage, months, mean ± SD	71.9±48.3	52.2±48.5	35.0±36.2	<0.001
Vascular access, %				0.52
AVF/AVG	79	79	85	
Catheter	21	21	15	
Marital status, %				0.28
Non-married	62	56	52	
Married	38	43	46	
Unknown/other	0	0	2	
Primary insurance, %				0.18
Medicare/Medicaid	77	77	67	
Private	11	10	17	
Other/unknown	13	13	16	
BMI, kg/m ² , mean ± SD	27.5±7.1	27.7±6.1	28.0±5.5	0.46
Comorbidities				
Diabetes, %	50	52	50	0.86
CHF, %	13	10	9	0.81
CAD, %	13	9	13	0.34
CVA/TIA, %	2	0	1	0.17
CVD, %	23	18	19	0.64
MIS, mean ± SD	3.9±2.0	4.5±2.9	4.6±3.1	0.64
Laboratory results, median (IQR)				
Serum potassium, mEq/L	5.21 (4.7–5.6)	5.0 (4.6–5.3)	4.7 (4.4–5.0)	<0.001
Bicarbonate, mEq/L	23 (20–26)	23 (21–26)	23 (21–25)	0.80
spKt/V, single pool	1.66 (1.54–1.93)	1.63 (1.43–1.86)	1.58 (1.41–1.87)	0.37
Serum albumin, g/dL	4.1 (3.9–4.3)	4.0 (3.8–4.2)	4.0 (3.9–4.2)	0.24
nPCR, g/kg/day	1.2 (1.0–1.3)	1.0 (0.9–1.2)	0.9 (0.8–1.1)	<0.001
Phosphorus, mg/dL	5.2 (4.0–7.1)	4.9 (4.1–5.7)	4.7 (3.8–5.3)	0.01
Serum creatinine, mg/dL	10.8 (9.3–12.7)	9.9 (7.9–12.0)	8.2 (6.1–10.4)	<0.001
Hemoglobin, g/dL	10.5 (9.7–11.2)	10.7 (10.1–11.3)	10.8 (10.3–11.5)	0.23
Body anthropometry, median (IQR)				
Waist circumference, cm	88 (83–99)	96 (85–107)	97 (90–109)	0.02
Triceps skinfold, mm	23 (14–31)	17 (10–28)	19 (12–28)	0.12
Biceps skinfold, mm	14 (8–21)	11 (6–19)	11 (6–18)	0.16
Mid-arm muscle circumference, cm	23 (21–25)	24 (21–27)	25 (22–28)	0.25
Mid-arm circumference, cm	31 (27–34)	30 (27–34)	31 (28–35)	0.55
NIR body fat, <i>n</i> (%)	30 (20–38)	29 (22–38)	30 (21–39)	0.99
Medication use, %				
Sodium polystyrene	0	<1	<1	0.84
ACEi and ARB	30	37	37	0.60
NSAIDs	19	33	32	0.15
Potassium sparing diuretics	0	0	<1	0.14
Other (trimethoprim-sulfamethoxazole, heparin, potassium supplement)	2	<1	0	0.29

* *p* value calculated by analysis of variance, chi-square, or Kruskal-Wallis tests.

Categorical variables are given as percentages; continuous variables as mean ± SD or median (IQR).

N/A, not applicable; AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; CHF, congestive heart failure; MI, myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; TIA, transient ischemic attack; CVD, cardiovascular disease; nPCR, normalized protein catabolic rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Clinical characteristics associated with receipt of 1 mEq/L dialysate potassium concentrations (reference: 2–3 mEq/L)

	Unadjusted		Case-mix adjusted		Case-mix + serum K adjusted		Case-mix + serum K + potassium-binding resin adjusted		Case-mix + serum K + potassium-modifying medication adjusted	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age (Δ 10 years)	0.80 (0.65–0.98)	0.03	0.81 (0.66–0.99)	0.04	0.84 (0.68–1.05)	0.12	0.84 (0.68–1.05)	0.13	0.86 (0.69–1.07)	0.17
Female (vs. male)	1.87 (1.02–3.14)	0.04	2.09 (1.13–3.85)	0.02	1.92 (1.04–3.57)	0.04	1.90 (1.03–3.53)	0.04	2.01 (1.07–3.78)	0.03
Black (vs. non-black)	0.84 (0.45–1.60)	0.60	2.47 (0.85–7.20)	0.10	2.66 (0.86–8.18)	0.09	2.66 (0.87–8.17)	0.09	2.72 (0.92–8.02)	0.07
Hispanic (vs. non-Hispanic)	2.08 (1.12–3.85)	0.02	3.97 (1.41–11.2)	0.01	3.67 (1.24–10.9)	0.02	3.69 (1.24–10.9)	0.02	3.69 (1.3–10.5)	0.01
Vintage (Δ 6 months)	1.05 (1.02–1.08)	0.002	1.04 (1.01–1.07)	0.01	1.04 (1.00–1.07)	0.03	1.04 (1.00–1.07)	0.03	1.03 (1.00–1.06)	0.06
Vascular access										
AVF/AVG (vs. catheter)	0.91 (0.38–2.17)	0.83	0.86 (0.35–2.10)	0.74	0.83 (0.33–2.06)	0.68	0.84 (0.34–2.09)	0.71	0.78 (0.31–1.96)	0.60
Marital status (ref.: married)										
Non-married	1.28 (0.69–2.36)	0.43	1.20 (0.62–2.32)	0.60	1.38 (0.71–2.71)	0.34	1.39 (0.71–2.73)	0.33	0.78 (0.31–1.96)	0.60
Insurance (ref. Medicare/Medicaid)										
Private	0.88 (0.34–2.32)	0.80	1.13 (0.42–3.05)	0.82	1.33 (0.48–3.68)	0.58	1.36 (0.49–3.77)	0.56	1.33 (0.47–3.71)	0.59
Other/unknown	0.95 (0.39–2.33)	0.91	0.97 (0.38–2.45)	0.95	1.12 (0.44–2.87)	0.81	1.13 (0.44–2.91)	0.80	1.13 (0.44–2.92)	0.80
MIS (Δ 1)	0.92 (0.80–1.05)	0.22	0.92 (0.80–1.05)	0.21	0.91 (0.79–1.05)	0.19	0.91 (0.79–1.05)	0.19	0.91 (0.79–1.05)	0.20
Diabetes	0.90 (0.50–1.63)	0.72	1.02 (0.52–1.99)	0.96	0.96 (0.49–1.89)	0.91	0.96 (0.49–1.90)	0.91	1.10 (0.55–2.21)	0.79
CHF	1.31 (0.54–3.13)	0.56	1.45 (0.57–3.65)	0.43	1.61 (0.63–4.13)	0.32	1.63 (0.64–4.16)	0.31	1.60 (0.62–4.11)	0.33
CAD	1.39 (0.56–3.42)	0.47	1.58 (0.63–3.99)	0.33	1.54 (0.60–3.96)	0.37	1.52 (0.59–3.92)	0.38	1.75 (0.67–4.57)	0.25
CVA/TIA	6.25 (0.56–70.2)	0.14	9.60 (0.81–114)	0.07	16.2 (1.29–203)	0.03	15.9 (1.27–200)	0.03	19.6 (1.52–254)	0.03
CVD	1.39 (0.69–2.82)	0.36	1.55 (0.75–3.21)	0.23	1.61 (0.77–3.35)	0.21	1.60 (0.77–3.35)	0.21	1.71 (0.81–3.60)	0.16
Laboratory data										
Serum potassium (Δ 1 mEq/L)	3.71 (1.93–7.11)	<0.001	3.16 (1.61–6.21)	0.001	3.16 (1.61–6.21)	0.001	3.16 (1.61–6.21)	0.001	3.24 (1.64–6.42)	0.001
Bicarbonate (Δ 1 mEq/L)	0.98 (0.90–1.06)	0.57	1.01 (0.92–1.09)	0.91	1.02 (0.94–1.11)	0.68	1.02 (0.93–1.11)	0.70	1.01 (0.93–1.10)	0.81
spKt/V (Δ 0.2)	1.07 (0.90–1.27)	0.47	1.01 (0.83–1.22)	0.95	1.02 (0.83–1.25)	0.85	1.02 (0.83–1.26)	0.84	1.00 (0.82–1.23)	0.97
Serum albumin (Δ 0.2 g/dL)	1.13 (0.95–1.34)	0.17	1.13 (0.95–1.36)	0.17	1.14 (0.95–1.38)	0.16	1.14 (0.95–1.37)	0.17	1.13 (0.94–1.36)	0.21
nPCR (Δ 0.2 g/kg/day)	1.40 (1.14–1.71)	0.001	1.39 (1.13–1.71)	0.002	1.32 (1.06–1.64)	0.01	1.32 (1.06–1.63)	0.01	1.31 (1.05–1.63)	0.02
Phosphorus (Δ 1 mg/dL)	1.22 (1.04–1.45)	0.02	1.19 (1.00–1.42)	0.05	1.12 (0.93–1.34)	0.22	1.12 (0.94–1.35)	0.21	1.13 (0.94–1.36)	0.18
Creatinine (Δ 1 mg/dL)	1.18 (1.07–1.31)	0.001	1.26 (1.10–1.43)	0.001	1.20 (1.05–1.38)	0.01	1.20 (1.05–1.38)	0.01	1.19 (1.04–1.37)	0.01
Hemoglobin (Δ 1 g/dL)	0.91 (0.69–1.20)	0.50	0.926 (0.70–1.23)	0.60	0.96 (0.71–1.27)	0.76	0.95 (0.71–1.27)	0.71	0.95 (0.70–1.27)	0.71
Body anthropometry										
Waist circumference (Δ 5 cm)	0.93 (0.86–1.02)	0.12	0.94 (0.85–1.03)	0.18	0.94 (0.85–1.03)	0.19	0.94 (0.85–1.03)	0.19	0.95 (0.86–1.04)	0.28
Triceps skinfold (Δ 10 mm)	1.21 (0.95–1.54)	0.12	1.14 (0.88–1.48)	0.31	1.19 (0.92–1.55)	0.19	1.19 (0.92–1.55)	0.19	1.29 (0.98–1.04)	0.07
Biceps skinfold (Δ 10 mm)	1.26 (0.94–1.69)	0.13	1.13 (0.83–1.55)	0.44	1.15 (0.84–1.58)	0.39	1.15 (0.84–1.57)	0.40	1.24 (0.89–1.72)	0.20
Mid-arm muscle circumference (Δ 5 cm)	0.83 (0.60–1.16)	0.28	0.91 (0.64–1.28)	0.58	0.88 (0.62–1.25)	0.48	0.88 (0.62–1.24)	0.46	0.87 (0.61–1.23)	0.43
Mid-arm circumference (Δ 5 cm)	1.01 (0.78–1.32)	0.92	1.02 (0.78–1.34)	0.87	1.03 (0.78–1.36)	0.82	1.03 (0.78–1.35)	0.84	1.07 (0.81–1.42)	0.63
NIR body fat (Δ 10%)	0.97 (0.73–1.29)	0.84	0.77 (0.52–1.13)	0.18	0.77 (0.52–1.13)	0.18	0.77 (0.72–1.19)	0.17	0.79 (0.53–1.18)	0.25
BMI (Δ 5 kg/m ²)	0.97 (0.75–1.25)	0.81	0.95 (0.74–1.23)	0.71	0.93 (0.72–1.19)	0.55	0.92 (0.72–1.19)	0.54	0.95 (0.73–1.22)	0.68
Medications										
ACEi and ARB	0.72 (0.38–1.38)	0.32	0.68 (0.35–1.31)	0.25	0.64 (0.33–1.24)	0.18	0.64 (0.33–1.24)	0.19	0.71 (0.36–1.41)	0.33
NSAIDs	0.49 (0.23–1.03)	0.06	0.48 (0.22–1.02)	0.06	0.47 (0.22–1.02)	0.05	0.47 (0.22–1.03)	0.06	0.51 (0.23–1.11)	0.09
Other (trimethoprim-sulfamethoxazole, heparin, potassium supplement)	4.16 (0.42–40.8)	0.22	6.57 (0.59–73.56)	0.13	5.31 (0.46–61.7)	0.18	5.25 (0.45–61.1)	0.19	6.06 (0.52–70.39)	0.15

Bold values indicate statistically significant estimates.

mix covariates, serum potassium levels, potassium-binding resins, and potassium-modifying medications.

There has been considerable debate regarding the safety of low dialysate potassium concentrations particularly in the setting of high pre-dialysis serum potassium levels [27]. An early report by Karnik et al. [12] and a more recent study by Pun et al. [11] have both shown that receipt of low dialysate potassium concentrations (defined as 0–1 and <2 mEq/L, respectively) were associated with higher risk of cardiac arrest among in-center

hemodialysis patients. However, a study of 81,013 prevalent dialysis patients from a large national dialysis organization by Kovesdy et al. [2] observed that higher dialysate potassium concentrations (>3 mEq/L) were associated with higher mortality among those with elevated pre-dialysis serum potassium levels (>5 mEq/L), whereas an analysis of 55,183 patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort who were administered a dialysate potassium concentration of 2 vs. 3 mEq/L showed no associations with

all-cause mortality or cardiovascular events [10]. Most recently, Brunelli et al. [17] examined hemodialysis patients from a national LDO and found an incremental association between higher serum-to-dialysate potassium gradients ≥ 3 mEq/L with higher risk of hospitalizations and emergency department visits.

To our knowledge, our study is the first to show that low dialysate potassium concentrations are associated with higher mortality risk among patients with high serum potassium concentrations (≥ 5 mEq/L) but not in those with normal serum potassium (< 5 mEq/L), supporting findings from the recent Brunelli et al. [15] study suggesting that high serum-to-dialysate potassium gradients may be harmful [14]. While the majority of total body potassium exists in intracellular compartments, potassium removal during dialysis is largely driven by the extracellular serum-to-dialysate potassium concentration gradient, which is highest in the first hour of dialysis, dissipates over treatment, and may be further attenuated post dialysis due to a rebound effect (i.e., post-dialysis extracellular potassium movement) [8]. It has been suggested that rapid changes in serum potassium levels, primarily during the first hour of dialysis, can lead to de-stabilization of cell membranes, QTc interval dispersion, ventricular ectopy, and arrhythmogenicity [28–30].

The heterogeneous findings across studies may potentially be explained by a differential relationship between the serum-to-dialysate potassium gradient with short-term vs. long-term risk [17]. While a small serum-to-dialysate potassium gradient among patients with higher serum potassium levels may bear long-term risk (i.e., potassium accumulation/overload leading to eventual death), it is also possible that a large gradient may lead to malignant arrhythmias, sudden cardiac death, and hence short-term risk. Based on these collective data, further studies are needed to determine whether alternative methods of dialysis prescription (i.e., potassium profiling), pharmacotherapies (e.g., sodium zirconium cyclosilicate, patiromer), and dietary interventions that prevent inter-dialytic accumulation of serum potassium can improve the survival of hemodialysis patients.

The strengths of our study include its examination of a prospective cohort of hemodialysis patients who underwent protocolized collection of sociodemographic, comorbidity, laboratory, and medication data; longitudinal information on dialysis prescription characteristics; and rigorous adjudication of mortality events. However, there are several limitations of the study that should be noted. First, while we observed a robust association between baseline dialysate potassium and se-

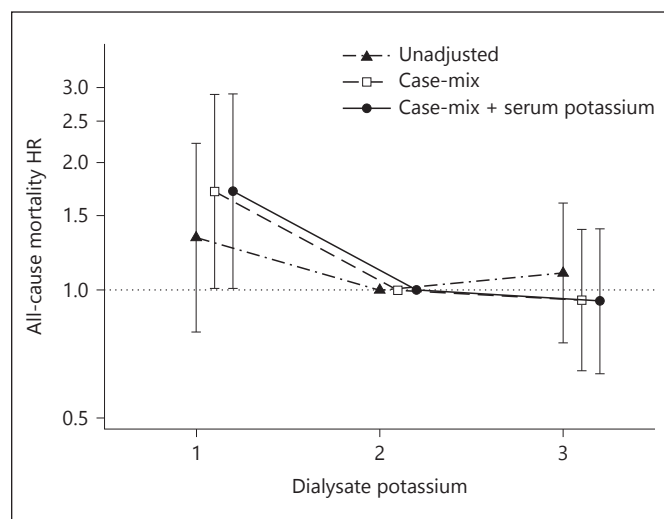


Fig. 1. Baseline dialysate potassium concentration and all-cause mortality risk in the overall cohort using case-mix adjusted Cox models. HR, hazard ratio.

rum potassium levels with mortality, these findings do not reflect how changes in dialysate and serum potassium concentrations over time influence mortality. However, we found that the vast majority (~73%) of our study maintained the same dialysate potassium concentration during follow-up. Second, as we do not know the clinical indications for which specific dialysate potassium concentrations were prescribed, it is possible that those receiving 1 mEq/L dialysate potassium concentrations were those who were less compliant with dialysis and dietary prescriptions and with worse underlying ill health status. While we observed robust associations between receipt of a 1 mEq/L dialysate potassium concentration and higher mortality among patients with serum potassium levels ≥ 5 mEq/L but not in those with serum potassium < 5 mEq/L after accounting for differences in pre-dialysis serum potassium levels, multiple comorbidities, and nutritional status, we cannot exclude confounding by indication on this basis. Third, our study population's observed pre-dialysis serum potassium levels were largely within a narrow range (4–6 mEq/L; only 8 patients had serum potassium levels ≥ 6 mEq/L), which may limit generalizability to patients with very low or high serum potassium levels. However, our findings do apply to the vast majority of patients in clinical practice whose serum potassium generally ranges between 4 and 6 mEq/L. Fourth, we lacked data on cause-specific death in providing insights into underlying pathways towards mortality. Lastly, as with all observa-

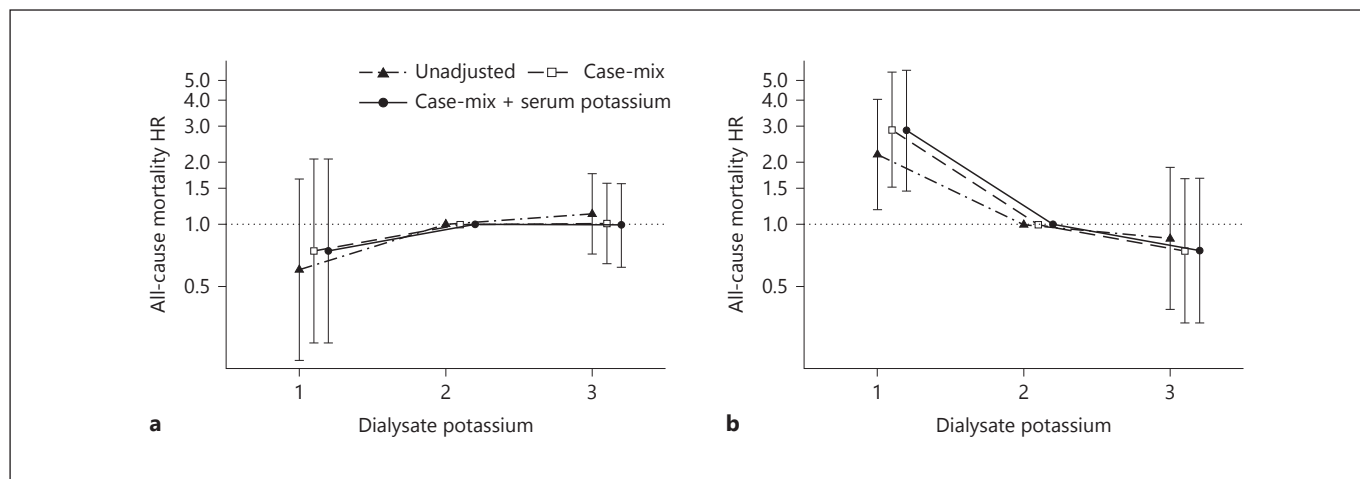


Fig. 2. Baseline dialysate potassium concentration and all-cause mortality, stratified according to pre-dialysis serum potassium level, using case-mix adjusted Cox models: serum potassium <5 mEq/L (a) vs. serum potassium ≥5 mEq/L (b). HR, hazard ratio.

tional studies, we cannot exclude the possibility of residual confounding, and our findings do not confirm a causal association of dialysate and serum potassium with mortality risk.

In conclusion, our study is the first to show that the prescription of low (1 mEq/L) potassium dialysate concentrations is associated with higher mortality risk, particularly among hemodialysis patients with high pre-dialysis serum potassium concentrations, which may relate to large serum-to-dialysate potassium gradients leading to rapid changes in potassium during the dialysis procedure. Further studies are needed to verify the risk associated with rapid potassium removal during dialysis, as well as the potential role for interventions (i.e., potassium binding resins) obviating the need and risk of excessive potassium removal during dialysis.

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