

Low Serum Potassium Levels and Clinical Outcomes in Peritoneal Dialysis—International Results from PDOPPS

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Introduction: Hypokalemia, including normal range values <4 mEq/l, has been associated with increased peritonitis and mortality in patients with peritoneal dialysis. This study sought to describe international variation in hypokalemia, potential modifiable hypokalemia risk factors, and the covariate-adjusted relationship of hypokalemia with peritonitis and mortality.

Methods: Baseline serum potassium was determined in 7421 patients from 7 countries in the Peritoneal Dialysis Outcomes and Practice Patterns Study (2014–2017). Association of baseline patient and treatment factors with subsequent serum potassium <4 mEq/l was evaluated by logistic regression, whereas baseline serum potassium levels (4-month average and fraction of 4 months having hypokalemia) on clinical outcomes was assessed by Cox regression.

Results: Hypokalemia was more prevalent in Thailand and among black patients in the United States. Characteristics/treatments associated with potassium <4 mEq/l included protein-energy wasting indicators, lower urine volume, lower blood pressure, higher dialysis dose, greater diuretic use, and not being prescribed a renin-angiotensin system inhibitor. Persistent hypokalemia (all 4 months vs. 0 months over the 4-month exposure period) was associated with 80% higher subsequent peritonitis rates (at K <3.5 mEq/l) and 40% higher mortality (at K <4.0 mEq/l) after extensive case mix/potential confounding adjustments. Furthermore, adjusted peritonitis rates were higher if having mean serum K over 4 months <3.5 mEq/l versus 4.0–4.4 mEq/l (hazard ratio, 1.15 [95% confidence interval, 0.96–1.37]), largely because of Gram-positive/culture-negative infections.

Conclusions: Persistent hypokalemia is associated with higher mortality and peritonitis even after extensive adjustment for patient factors. Further studies are needed to elucidate mechanisms of these poorer outcomes and modifiable risk factors for persistent hypokalemia.

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KEYWORDS: hypokalemia; mortality; PDOPPS; peritonitis; peritoneal dialysis; potassium

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Both high and low serum potassium concentrations have been associated with higher all-cause and cardiovascular mortality in patients receiving peritoneal dialysis (PD),^{1–5} and even at potassium levels in the lower end of the normal range.^{1–3} In The Brazilian PD Multicenter Study (BRAZPD), serum potassium <4.0

mEq/l was associated with elevated cardiovascular- and infection-related mortality and peritonitis risk.² The hypothesized mechanism(s) by which low-normal serum potassium might cause these outcomes are (i) through increasing the risk of arrhythmia in cardiovascular deaths⁶ or (ii) by hypokalemia-associated bowel motility disorders and bacterial intestinal overgrowth leading to peritonitis caused by enteric organisms.^{7,8} Alternatively, low serum potassium may be a proxy for ill health and protein-energy wasting rather than a cause of increased mortality/peritonitis.

In PD, potassium homeostasis is a balance between losses (e.g., urinary and dialysate) and dietary intake. As potassium is predominantly (98%) an intracellular ion, serum potassium concentrations also are influenced by transcellular distribution and total body potassium stores (correlated with muscle mass). This buffering capacity means that in normal health, elimination of dietary potassium will not alter serum potassium for 2 or 3 weeks.^{9,10} In contrast, protein-energy wasting is commonly observed in patients undergoing dialysis and is associated with inflammation, muscle wasting, reduced potassium intake, and total body stores, increasing the risk of hypokalemia.^{11–13} Additional factors that may potentially impact serum potassium levels in patients with PD include residual kidney function decline, dialytic removal of potassium (which may increase as clinicians prescribe more dialysis to compensate for loss of residual kidney function), diuretic use, drugs that block the renin-angiotensin aldosterone system, and the influence of glucose-containing PD solutions on transcellular shifts of potassium into cells. Cultural dietary differences may also impact potassium intake.¹⁴ Finally, interventions that alter transcellular distribution or flux (for example, glycemic control with insulin in diabetics) must also be considered.

Furthermore, questions remain regarding to what extent the relationship of hypokalemia with mortality and peritonitis may differ depending on how hypokalemia is measured/defined and over what period of time.⁴ Addressing these questions is important for informing approaches on how best to minimize poorer outcomes in relationship to hypokalemia in patients with PD. To this end, we have developed the current investigation, based on prospective, international Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) data, to (i) describe hypokalemia prevalence in patients with PD from 7 countries; (ii) identify modifiable risk factors associated with hypokalemia in patients with PD; and (iii) test the following hypotheses: (a) peritonitis and mortality will be higher with persistent hypokalemia versus a brief

hypokalemia exposure over a 4-month period; (b) low potassium levels impact intestinal motility, which increases the risk of peritonitis caused by enteric bacteria; and (c) higher mortality seen in PD patients with hypokalemia is related to poorer patient health and nutritional status.

METHODS

Study Design and Data Source

PDOPPS is an international, prospective cohort study of patients with PD ≥ 18 years of age designed to identify modifiable practices associated with improvements in PD technique and patient survival.¹⁵ Patients were randomly selected from national samples of randomly selected PD facilities treating ≥ 20 patients with PD in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom, and the United States, as described previously.¹⁵ Study approval and patient consent were obtained as required by national and local ethics committee regulations.¹⁵ The current study includes patients enrolled in PDOPPS phase 1 (2014–2017), excluding patients for reasons indicated in [Supplementary Figure S1](#).

The current study considers the 4 months before enrollment as the “baseline” period. Patient demographics, comorbidities, and medication prescriptions were captured at study enrollment. Monthly laboratory values were collected for the 4 months before enrollment and during study follow-up. Peritonitis episodes, permanent transfers to hemodialysis (HD), and deaths were identified during study follow-up. Data were abstracted from medical charts and entered into a web-based data collection tool using uniform data collection surveys and procedures.¹⁵ Data from the US patients receiving care at large dialysis organization (LDO) sites were imported from electronic health records. The current study and results are reported in accordance with the STROBE statement checklist ([Supplementary Table S4](#)).

Statistical Analysis

We described serum potassium distributions by country. Baseline patient characteristics and treatments were described by mean potassium categories averaged during the 4 months before enrollment ($K_{\text{prior-4mo}}$; [Figure 1](#)).

Association of Serum $K_{\text{prior-4mo}}$ With Peritonitis and Mortality

Cox regression was used to estimate the effect of serum potassium levels on primary outcomes of: 1) first all-cause or organism category-specific peritonitis during follow-up, and 2) all-cause mortality. For peritonitis outcomes in 1), we used cause-specific Cox models to account for

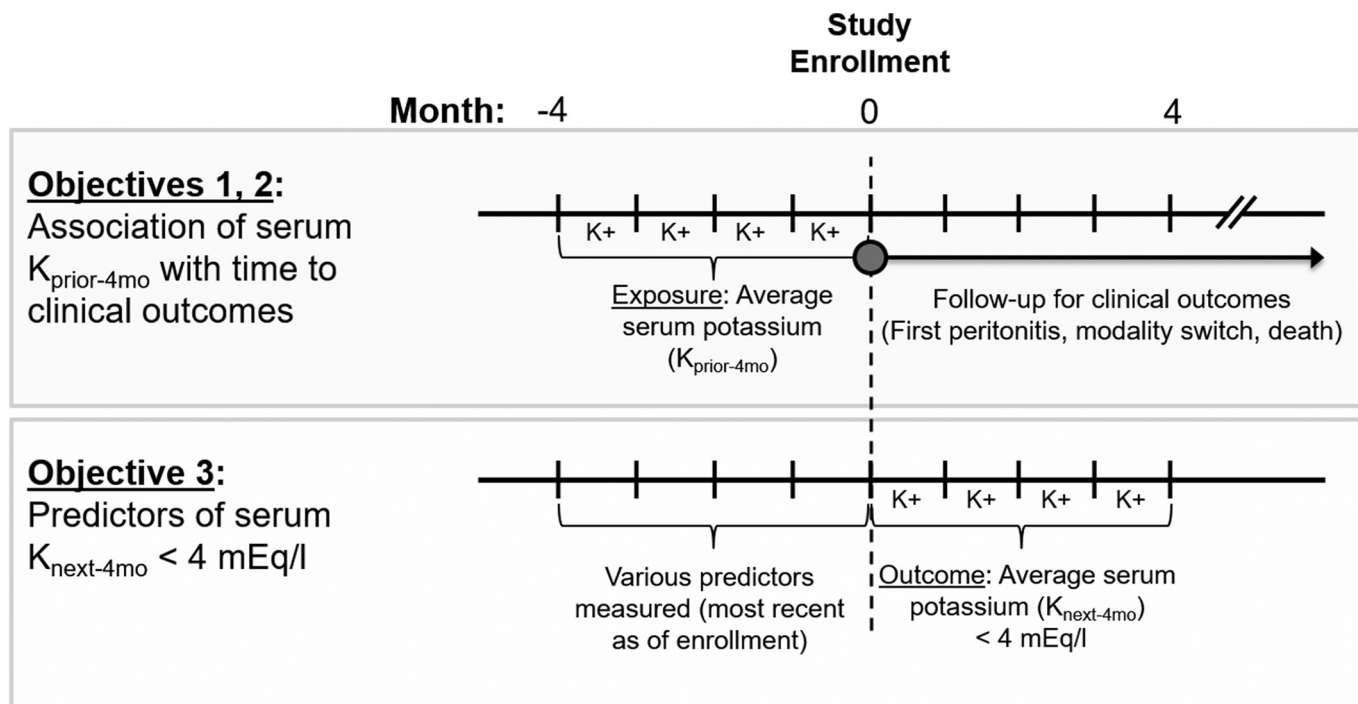


Figure 1. Timing and definition of exposures and outcomes, by study objectives.

competing risks of death, transplant, or switch to HD.^{16,17} Serum potassium exposures in all models were either mean serum $K_{\text{prior-4mo}}$ categories or number of months having a serum potassium $< 4 \text{ mEq/l}$ during the 4 months before study entry. Since elevated peritonitis risk was only seen at serum $K_{\text{prior-4mo}} < 3.5 \text{ mEq/l}$, a sensitivity analysis was performed of the association of peritonitis with number of months having a serum potassium $< 3.5 \text{ mEq/l}$. For peritonitis-related analyses, patients from facilities that did not routinely report peritonitis were excluded, and those with missing organism information were excluded from organism category-specific peritonitis analyses. As a secondary outcome, permanent transfer to HD was also investigated in relationship to the above primary exposures. All Cox models accounted for facility clustering using robust sandwich-type covariance estimators and were stratified by country, with the US represented by 4 different strata (black vs. other race [because higher rates of peritonitis have been seen in black patients with PD¹⁸] and whether or not the facility was part of an LDO). To assess the impact of covariate adjustment on primary exposure hazard ratio estimates, we applied increasing levels of covariate adjustment by fitting 3 models for each outcome. Model 1 was only stratified by country; model 2 was stratified by country and adjusted for patient age, sex, end-stage kidney disease vintage, and 13 comorbidities (listed in Table 1); and model 3 included model 2 adjustments and was also adjusted for potassium balance factors indicated as model 3 adjustments in Figures 2 and 3.

In all outcome analyses, follow-up started at study enrollment (after serum $K_{\text{prior-4mo}}$ measurements and after the baseline period). For mortality and permanent transfer to HD, follow-up ended at death or transplantation date, 7 days after permanent switch to HD, loss to follow-up, or study end. Permanent transfer to HD was defined as planned modality switch (clinician reported) or temporary transfers from PD to HD that did not return to PD within 12 weeks (84 days). Dying within 7 days of transfer to HD was counted as a death (outcome event)—not transfer. For peritonitis, patients were followed until the first recorded peritonitis episode and censored at the points noted above, in addition to the date of the last returned peritonitis questionnaire, whichever occurred first. Organism classifications for cause-specific peritonitis are listed in Supplementary Table S1. Median follow-up time for death and permanent transfer to HD was 1.2 years (interquartile range [IQR] 0.6–1.9 years) compared with 0.8 years (IQR 0.3–1.3 years) for time to first peritonitis episode.

Potassium Balance Factors Associated With Serum $K_{\text{next-4mo}} < 4 \text{ mEq/l}$

We applied logistic generalized estimating equation models to estimate the effects of potentially modifiable baseline laboratory measurements and treatments (that may potentially influence potassium balance) on the odds of subsequent mean potassium $< 4 \text{ mEq/l}$ versus $\geq 4 \text{ mEq/l}$ (reference), based on serum potassium

Table 1. Patient demographics and comorbidities by serum $K_{\text{prior-4mo}}$

	Serum $K_{\text{prior-4mo}}$, mEq/l				
	<3.5	3.5–3.9	4.0–4.4	4.5–4.9	≥5.0
Patients, n	823	2019	2368	1555	656
Demographics and clinical characteristics					
Age, yr, mean (SD)	58.7 (14.4)	60.6 (14.7)	59.1 (15.0)	57.5 (15.1)	55.3 (15.4)
Male, %	51	55	58	64	62
Black race in the US, ^a %	35	31	25	22	17
Years on PD, ^b median (IQR)	0.63 (0.07–1.80)	0.63 (0.26–1.52)	0.59 (0.27–1.49)	0.60 (0.22–1.52)	0.65 (0.16–1.54)
Years of ESKD, median (IQR)	0.97 (0.22–2.66)	1.09 (0.44–2.90)	1.09 (0.45–2.87)	1.16 (0.44–2.80)	1.19 (0.49–2.86)
Systolic blood pressure, mm Hg, mean (SD)	135 (26)	138 (24)	138 (23)	142 (24)	142 (24)
Diastolic blood pressure, mm Hg, mean (SD)	77.1 (14.9)	78.2 (14.2)	78.4 (13.3)	80.2 (13.9)	80.8 (14.0)
Caregiver(s) involved in PD exchanges, %	48	26	20	19	14
Comorbidities, ^c %					
Coronary artery disease	15	20	22	20	21
Cancer (nonskin)	5	9	10	8	8
Other cardiovascular disease	10	13	12	13	9
Cerebrovascular disease	8	7	8	7	6
Congestive heart failure	15	14	13	13	10
Diabetes	52	48	46	44	46
Gastrointestinal bleeding	2	2	2	2	2
Hypertension	88	87	86	87	86
Lung disease	4	6	5	5	5
Neurologic disease	6	3	3	3	3
Psychiatric disorder	8	12	13	14	13
Peripheral vascular disease	9	13	13	13	9
Recurrent cellulitis/gangrene	2	2	2	1	2

ESKD, end-stage kidney disease; IQR, interquartile range; $K_{\text{prior-4mo}}$, average monthly serum potassium measured during the 4 months before study enrollment; PD, peritoneal dialysis; SD, standard deviation; US, United States.

^aThe overall US population is 26% black.

^bExcludes patients from 1 large dialysis organization in the US.

^cClasses of comorbidities as defined by Pisoni *et al.*³²

measurements averaged over the 4 months after study enrollment ($K_{\text{next-4mo}}$). Baseline predictors, based on data at study enrollment, were grouped into 2 categories based on clinical judgement: 1) factors likely associated with potassium intake and 2) factors likely associated with increased/decreased potassium losses. Analyses used an exchangeable working correlation to account for clustering of patients within facilities.

Country-Specific Sensitivity Analyses

Given the high prevalence of low serum potassium in Thailand, we excluded Thailand in sensitivity analyses to test the robustness of our findings. Analyses also were carried out restricted to the United States to enable comparisons of outcomes with previously published U.S. findings.¹

Treatment of Missing Data

Missing values for all model covariates were assumed to be missing at random and therefore imputed using the sequential regression multiple imputation method by IVEware and used in models only.¹⁹ Results from 20 imputed datasets were combined for the final analysis using a formula from Little and Rubin.²⁰ The proportion of patients with PD with missing data was <15% for all

imputed covariates, with the exception of 24-hour urine volume (34% missing) and peritoneal Kt/V urea (36% missing). Caregiver involvement, icodextrin use, and PD solution glucose concentrations were not available in U.S. LDOs. All analyses were conducted with SAS software (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Study Population and Distribution of Serum $K_{\text{prior-4mo}}$ Categories

A total of 7596 patients with PD from 216 facilities enrolled in PDOPPS were included in the current study (Supplementary Figure S1). The distribution of serum $K_{\text{prior-4mo}}$ varied considerably across PDOPPS countries (Figure 4). Serum $K_{\text{prior-4mo}}$ levels <4.0 mEq/l were common in all countries, but especially in Thailand, ranging from 24%–25% of patients in the United Kingdom and Australia/New Zealand, 35% in Japan and the United States, 39% in Canada, and 76% in Thailand. Serum $K_{\text{prior-4mo}}$ <3.5 mEq/l was relatively uncommon (<12%) in all countries except Thailand (46%).

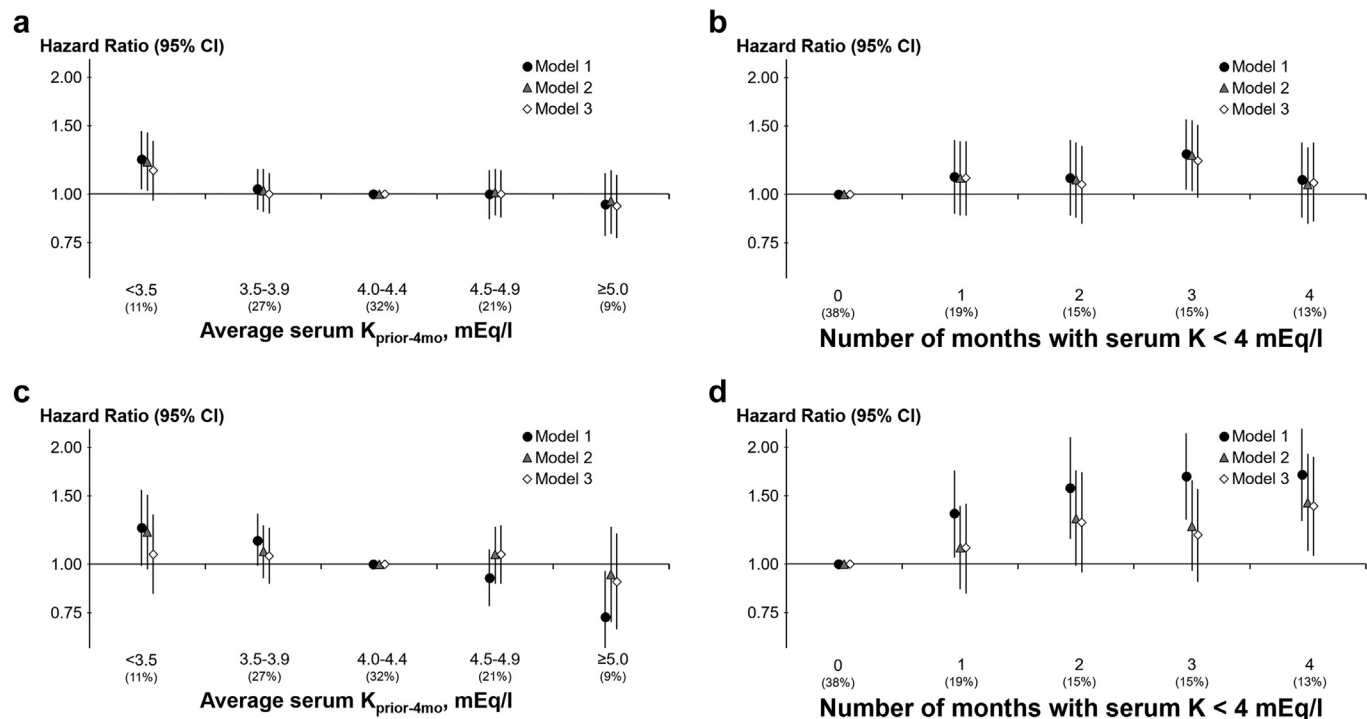


Figure 2. Associations (adjusted hazard ratio and 95% confidence interval [CI]), with progressive covariate adjustment, between (a) peritonitis and average serum $K_{\text{prior-4mo}}$ levels; (b) peritonitis and number of monthly serum $K_{\text{prior-4mo}}$ measurements <4.0 mEq/l during the 4 months before study enrollment; (c) all-cause mortality and average serum $K_{\text{prior-4mo}}$ levels; and (d) all-cause mortality and number of monthly serum $K_{\text{prior-4mo}}$ measurements <4 mEq/l during the 4 months before study enrollment.

Patient and Clinical Characteristics by $K_{\text{prior-4mo}}$ Category

Table 1 shows summary statistics of patient characteristics by mean serum $K_{\text{prior-4mo}}$ categories. The mean serum $K_{\text{prior-4mo}}$ was based upon 4, 3, 2, and 1 month of data for 50%, 22%, 18%, and 11% of patients, with 2% excluded because they had no serum potassium measurements during this period. Patients with lower $K_{\text{prior-4mo}}$ were more likely to be female, diabetic, have lower blood pressure, have a history of congestive heart failure, be black (in the United States only), and relied more on caregivers. Other comorbidities were similar across potassium levels.

Patients with lower serum $K_{\text{prior-4mo}}$ levels tended to have worse nutritional indicators (e.g., lower body mass index, body weight, serum albumin, phosphorus, and urea), reduced muscle mass (e.g., lower serum creatinine and creatinine production), higher levels of inflammatory markers (e.g., higher C-reactive protein and lower albumin), and lower residual kidney function (Table 2). Dialysis and drug prescription practices by baseline serum potassium category are summarized in Table 3. Patients with lower potassium (<3.5 mEq/l) were less likely to use automated PD, icodextrin, or PD solutions containing 2.27% or 3.86% glucose but were prescribed a higher daily total PD volume. They were less often

prescribed beta blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, but were prescribed loop diuretics more frequently compared with patients with higher potassium levels.

Serum $K_{\text{prior-4mo}}$ and Subsequent Clinical Outcomes

Peritonitis

As shown in Figure 2a, there was an overall weak inverse association between mean serum $K_{\text{prior-4mo}}$ levels and first-episode peritonitis. For the fully adjusted model (model 3), hazard ratios (HRs) for peritonitis were 1.15 (95% confidence interval [CI], 0.96–1.37) and 0.93 (95% CI, 0.77–1.12), respectively, for mean serum $K_{\text{prior-4mo}}$ of <3.5 vs. ≥ 5.0 mEq/l, respectively, compared with the reference group of 4.0–4.4 mEq/l (P for overall trend = 0.36). Progressive adjustment for patient characteristics and treatments modestly attenuated the association from model 1. Similar results were seen when including all countries except Thailand or restricted only to the United States (Supplementary Figures S2A and S3A).

Cause-specific results for enteric peritonitis (Figure 3a) or Gram-negative peritonitis (Figure 3b) showed few consistent associations with serum $K_{\text{prior-4mo}}$ levels. However, a tendency toward higher peritonitis rates was seen at $K < 3.5$ mEq/l in Gram-positive

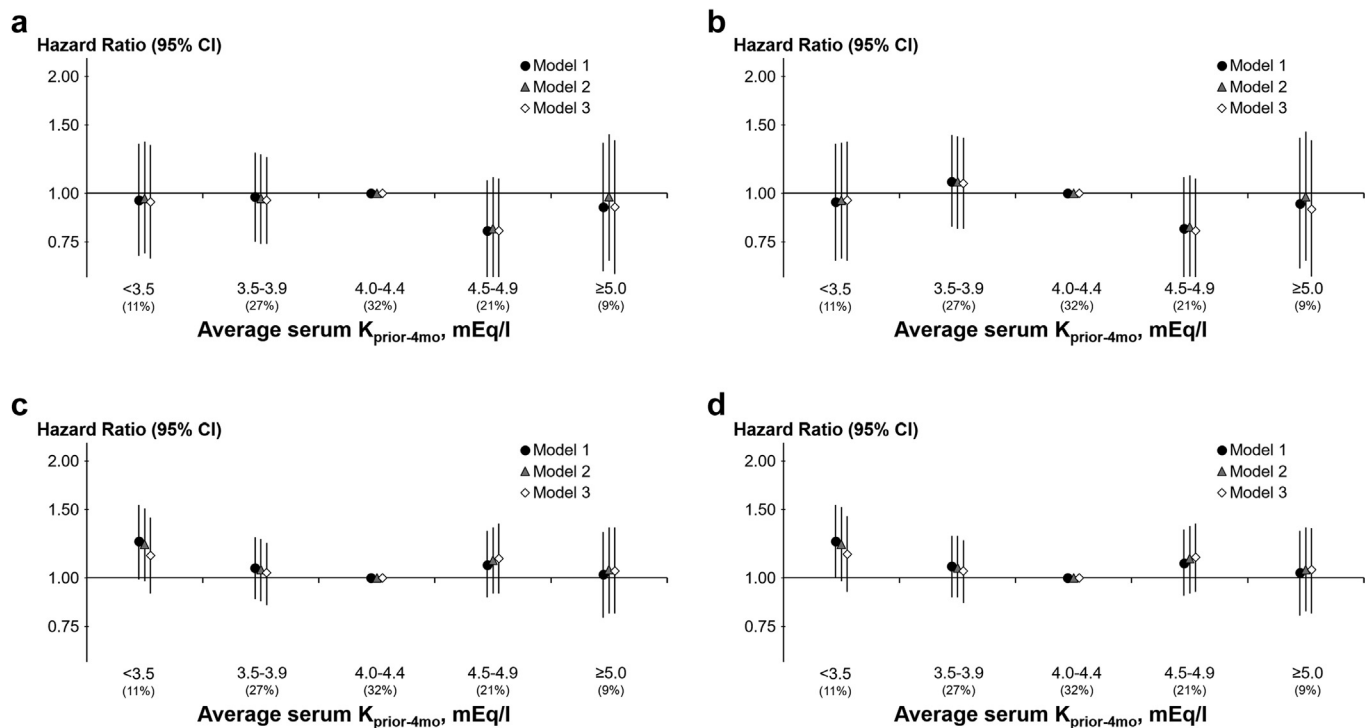


Figure 3. Associations (adjusted hazard ratio and 95% confidence interval [CI]), with progressive covariate adjustment, between (a) enteric peritonitis; (b) Gram-negative peritonitis; (c) Gram-positive peritonitis; and (d) Gram-positive or culture-negative peritonitis and average serum $K_{\text{prior-4mo}}$ level measured during the 4 months before study enrollment.

peritonitis (model 3 adjusted HR for $K_{\text{prior-4mo}} < 3.5$ vs. $K_{\text{prior-4mo}} 4.0-4.4 = 1.14$ [95% CI, 0.91–1.43]; [Figure 3c](#)) and in Gram-positive or culture-negative peritonitis (model 3 adjusted HR for $K_{\text{prior-4mo}} < 3.5$ vs. $K_{\text{prior-4mo}} 4.0-4.4 = 1.15$ [95% CI, 0.92–1.44]; [Figure 3d](#)).

We also examined the HRs of peritonitis in relationship to the number of months with serum $K_{\text{prior-4mo}}$ measurements < 4.0 mEq/l during the 4-month period

before study enrollment ([Figure 2b](#)). No strong association was found in this analysis; however, in a sensitivity analysis looking at number of months with serum $K_{\text{prior-4mo}}$ measurements < 3.5 mEq/l we found that having a potassium measurement in each of the 4 months indicated higher rates of peritonitis with persistent $K_{\text{prior-4mo}} < 3.5$ mEq/l for 3 months (HR = 1.28 [95% CI, 0.94–1.73], model 3) and 4 months (HR =

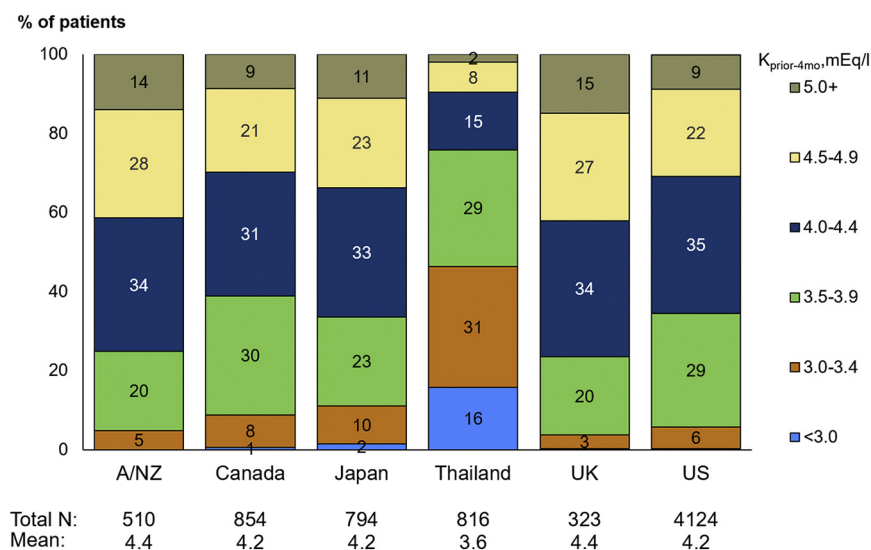


Figure 4. Proportion of patients in each potassium category across PDOPPS countries, based on average monthly potassium values measured during the 4 months before study enrollment. A/NZ, Australia/New Zealand; UK, United Kingdom; US, United States.

Table 2. Nutritional, metabolic, inflammatory, muscle mass, residual kidney function, and peritoneal clearance variables by serum $K_{\text{prior-4mo}}$

	Serum $K_{\text{prior-4mo}}$ mEq/l				
	<3.5	3.5–3.9	4.0–4.4	4.5–4.9	≥5.0
Patients, n	823	2019	2368	1555	656
Nutritional, mean (SD)					
Body mass index, kg/m ²	24.6 (5.7)	27.3 (6.2)	27.7 (6.3)	27.5 (6.0)	28.2 (6.2)
Serum bicarbonate, mEq/l	27.1 (3.5)	26.1 (3.3)	25.3 (3.3)	24.5 (3.4)	23.7 (3.5)
Serum phosphorus, mg/dl	4.27 (1.44)	4.78 (1.36)	5.13 (1.40)	5.44 (1.47)	5.97 (1.68)
Serum magnesium, mg/dl	1.96 (0.51)	2.06 (0.42)	2.15 (0.47)	2.23 (0.49)	2.27 (0.49)
Serum albumin, g/dl	3.19 (0.70)	3.39 (0.56)	3.43 (0.57)	3.48 (0.54)	3.51 (0.51)
Body weight, kg	65.5 (19.1)	76.1 (21.3)	78.4 (21.7)	78.5 (20.9)	80.4 (21.9)
Serum urea, mg/dl	86 (401)	105 (326)	128 (515)	154 (635)	267 (1032)
Metabolic, mean (SD)					
Glucose, mg/dl	144 (76)	144 (78)	141 (73)	138 (75)	134 (68)
Total cholesterol, mg/dl	178 (51)	172 (48)	176 (51)	175 (47)	170 (43)
Triglycerides, mg/dl	175 (121)	175 (106)	181 (132)	163 (103)	160 (94)
HbA1C for diabetic patients, %	7.20 (1.63)	7.44 (3.32)	7.06 (1.54)	7.09 (3.39)	6.99 (1.53)
Uric acid, mg/dl	6.38 (1.78)	6.23 (1.66)	6.14 (1.48)	6.17 (1.45)	6.07 (1.44)
Inflammatory, median (IQR)					
C-reactive protein, ^a mg/dl	0.40 (0.11–1.20)	0.33 (0.14–0.95)	0.30 (0.11–0.83)	0.25 (0.10–0.60)	0.30 (0.10–0.80)
Muscle mass, mean (SD)					
Creatinine generation rate, ^b g/d per 1.73 m ²	13.1 (19.9)	16.4 (20.9)	19.3 (20.7)	21.8 (23.9)	20.9 (22.1)
Serum creatinine, mg/dl	8.08 (3.56)	8.11 (3.70)	8.50 (3.92)	9.15 (4.12)	9.67 (4.16)
RKF, peritoneal clearance, and membrane function					
Peritoneal creatinine clearance, liter/week, mean (SD)	49.6 (26.8)	46.1 (28.0)	45.2 (33.3)	41.6 (30.1)	42.6 (28.4)
rGFR, ml/min per 1.73 m ² , mean (SD)	2.29 (3.41)	2.76 (3.73)	3.15 (3.75)	3.36 (4.00)	2.72 (3.49)
24-h urine volume, liters, mean (SD)	0.59 (0.65)	0.73 (0.69)	0.91 (0.75)	1.00 (0.82)	0.99 (0.83)
Total Kt/V urea, mean (SD)	2.21 (0.78)	2.31 (0.72)	2.33 (0.69)	2.24 (0.70)	2.20 (0.72)
Peritoneal Kt/V urea, mean (SD)	1.59 (0.57)	1.52 (0.55)	1.41 (0.50)	1.35 (0.52)	1.37 (0.57)
PSTR, mean (SD)	0.70 (0.13)	0.67 (0.14)	0.68 (0.14)	0.68 (0.14)	0.68 (0.14)
Net 24-h peritoneal ultrafiltration, ml, median (IQR)	700 (200–1191)	746 (312–1394)	719 (250–1229)	700 (201–1286)	748 (286–1510)
24-h urine volume plus net 24-hr ultrafiltration, liters, median (IQR)	1.25 (0.80–1.78)	1.50 (0.95–2.18)	1.65 (1.10–2.27)	1.75 (1.23–2.36)	1.90 (1.30–2.58)

HbA1C, glycosylated hemoglobin; IQR, interquartile ratio; $K_{\text{prior-4mo}}$, average monthly serum potassium measured during the 4 months before study enrollment; PSTR, peritoneal solute transport rate (dialysate/plasma creatinine ratio at 4 hrs); rGFR, residual glomerular filtration rate (mean of the urinary creatinine and the urea clearance); RKF, residual kidney function; SD, standard deviation.

^aRarely measured in Canada, Thailand, and the United States.

^bCalculation of the total creatinine mass removed.

1.83 [95% CI, 1.26–2.68], model 3) versus those who never had $K_{\text{prior-4mo}} < 3.5$ mEq/l (Supplementary Figure S4). A similar pattern was seen when including all countries except Thailand or restricted only to the United States (Supplementary Figures S2A and S3B).

Mortality and Permanent Transfer to HD

Mortality was inversely associated with mean serum $K_{\text{prior-4mo}}$ levels when adjusting only for country (Figure 2c; model 1, P for trend < 0.01), but this association was markedly attenuated when adjusting for other covariates, especially in model 3 (P for trend = 0.5). Sensitivity analyses excluding Thailand (Supplementary Figure S2B) or restricting to only the United States (Supplementary Figure S3B) yielded results similar to those in Figure 2c for all countries. Results also were similar in analyses exploring the impact of defining potassium < 4.0 mEq/l based upon the single most recent measurement during the 4 months before study enrollment (Supplementary

Table S2). In contrast, when mortality was examined in relationship to number of monthly serum $K_{\text{prior-4mo}}$ measurements < 4.0 mEq/l (Figure 2d), patients with a potassium level < 4 mEq/l in 2, 3, or 4 out of 4 months generally had greater mortality (HRs 1.19–1.41, model 3) compared with patients with no potassium measurements < 4 mEq/l over 4 months.

Since hypokalemia was associated with higher risks of peritonitis, and because peritonitis is one of the major causes requiring patients' permanent transfer to HD, we investigated whether permanent transfer from PD to HD was greater at low serum potassium levels. No consistent association was seen between mean serum $K_{\text{prior-4mo}}$ and permanent transfer to HD, although patients with $K_{\text{prior-4mo}}$ levels 4.5–4.9 mEq/l had a lower transfer rate than did patients in other groups (Supplementary Figure S5A). Furthermore, weak associations were seen between the number of monthly serum $K_{\text{prior-4mo}}$ measurements < 4.0 mEq/l over 4 months and permanent transfer to HD (Supplementary Figure S5B). Sensitivity analyses excluding Thailand or restricted to the United

Table 3. PD prescription and medication prescription by serum $K_{\text{prior-4mo}}$

	Serum $K_{\text{prior-4mo}}$ mEq/L				
	<3.5	3.5–3.9	4.0–4.4	4.5–4.9	≥5.0
Patients, n	823	2019	2368	1555	656
PD prescription, %					
APD	36	65	71	71	68
Wet day (APD)	51	47	43	41	40
Icodextrin	19	34	38	38	40
PD solution glucose concentrations					
Use of 2.27% but not 3.86%	32	46	50	47	46
Use of any 3.86%	11	17	14	14	15
Without any 2.27% or 3.86% use	58	37	36	39	40
Prescribed volume per BMI, l/(kg/m ²), mean (SD)	0.35 (0.14)	0.31 (0.16)	0.29 (0.17)	0.29 (0.16)	0.28 (0.16)
Prescribed volume per BSA, l/m ² , mean (SD)	4.95 (1.79)	4.36 (2.21)	4.15 (2.21)	4.08 (2.14)	3.98 (2.12)
Medication prescriptions, %					
RASi (ACEi or ARB)	38	39	44	52	56
Insulin (proportion of diabetic patients only)	50	54	53	55	52
Beta-blocker	38	50	52	54	56
Any diuretic	55	52	51	51	47
Potassium sparing diuretic (aldosterone antagonist)	4	4	3	3	2
Loop diuretic	53	49	49	49	45
Thiazide diuretic	4	6	6	6	6

ACEi, angiotensin-converting enzyme inhibitor; APD, automated peritoneal dialysis; ARB, angiotensin II receptor blockers; BMI, body mass index; BSA, body surface area; $K_{\text{prior-4mo}}$, average monthly serum potassium measured during the 4 months before study enrollment; RASi, renin-angiotensin system inhibition; SD, standard deviation.

States had similar results (Supplementary Figures S2C and S3C).

Predictors of Serum $K_{\text{next-4mo}} < 4$ mEq/l

Logistic regression was used to evaluate baseline factors associated with the odds of having a mean serum $K_{\text{next-4mo}} < 4$ vs. ≥ 4 mEq/l in the 4-month period after study entry (Table 4). The mean serum $K_{\text{next-4mo}}$ was based upon 1, 2, 3, or 4 months of data for 9%, 16%, 21%, and 54% of patients. Adjusted odds of serum $K_{\text{next-4mo}} < 4$ mEq/l were greater with higher serum bicarbonate levels (reflecting reduced protein intake), higher dialysis dose, lower serum phosphorus, creatinine, albumin, and urine volume levels, and with prescription of icodextrin or loop diuretics. Patients who were prescribed an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker were less likely to have serum $K_{\text{next-4mo}} < 4$ mEq/l. Results were similar in sensitivity analyses with $K_{\text{next-4mo}} < 3.5$ mEq/l as the outcome (Supplementary Table S3).

DISCUSSION

We observed large variations in the prevalence of hypokalaemia among the PDOPPS countries in this

large, multinational cohort study, with the highest prevalence among patients from Thailand (76%). We have no reason to suspect serum potassium measurement to meaningfully differ across any of the countries. However, cultural dietary differences could contribute to the observed national differences in serum potassium levels. Moreover, a recent meta-analysis found significant differences in the prevalence of protein-energy wasting in chronic kidney disease with a high prevalence in southeast Asia. Hypokalemia may serve as a surrogate for protein-energy wasting, which may explain our findings of a higher prevalence of hypokalemia among patients with PD in Thailand.²¹ Lower serum potassium levels in black Americans is consistent with previous observations in both healthy and chronic kidney disease populations.^{22,23}

Serum $K_{\text{prior-4mo}} < 3.5$ mEq/l—particularly if persisting over several months—was associated with higher peritonitis risk caused by any organism, as in the BRAZPD,² and tended to be associated with Gram-positive organisms. Previous studies raised concerns that hypokalemia might increase the risk for infections originating from the gastrointestinal tract, possibly by reducing gut motility.⁸ However, we found no discernible increase in enteric or Gram-negative infections, failing to support the hypothesis that higher peritonitis rates with hypokalemia occur via infections originating from the gastrointestinal tract. Adjusting for many potential confounders had a relatively modest effect on the association between peritonitis and persistent hypokalemia, such that patients with serum potassium levels < 3.5 mEq/l for 3 or 4 months over 4 months displayed 28% and 83% higher adjusted peritonitis hazards, respectively.

In contrast to previous large cohort studies,^{1–3} the effect of mean serum $K_{\text{prior-4mo}} < 4.0$ mEq/l on increased mortality was markedly attenuated in our PDOPPS cohort after adjustment for suspected confounders. We uniquely adjusted for additional potential confounders including dialysis prescriptions, residual kidney function, frailty indicators, and medications known to alter potassium excretion. These additional adjustments markedly attenuated the effect of mean serum $K_{\text{prior-4mo}} < 4.0$ mEq/l on mortality, suggesting that the association observed before adjustment, and seen in previous studies, may be explained by the additional factors (e.g., protein-energy malnutrition and other confounding factors). It is noteworthy that the relative proportions of “incident” patients (short time on PD) versus “prevalent” patients (longer time on PD) in the large previous cohort studies varied, ranging from excluding prevalent patients in the BRAZPD³ to 75% of patients on PD ≥ 1 year (IQR, 12–54 months) in the DaVita Study.¹ In contrast, our PDOPPS cohort

Table 4. Association (adjusted prevalence OR and 95% CI) between potentially modifiable baseline factors and average serum $K_{\text{next-4mo}} < 4.0$ mEq/l

Potentially modifiable factors	Adjusted model A ^a	Adjusted model B ^b
	OR (95% CI)	OR (95% CI)
Laboratory values		
Serum phosphorous, per 1 mg/dl	0.84 (0.81–0.88)	0.88 (0.84–0.93)
Serum bicarbonate, per 1 mEq/l	1.09 (1.07–1.11)	1.04 (1.02–1.06)
Serum creatinine, per 1 mg/dl	0.97 (0.95–0.98)	0.95 (0.93–0.97)
Serum albumin, per 1 g/dl	0.75 (0.68–0.84)	0.85 (0.77–0.94)
PD treatment variables		
PD modality, APD vs. CAPD	0.90 (0.79–1.03)	0.90 (0.79–1.03)
Icodextrin use	1.36 (1.16–1.59)	1.21 (1.01–1.44)
PD solution glucose concentrations		
Without any 2.27% or 3.86% use	1 (reference)	1 (reference)
Use of 2.27% but not 3.86%	1.37 (1.09–1.71)	1.22 (0.98–1.53)
Use of any 3.86%	1.31 (0.98–1.77)	1.14 (0.83–1.56)
Urine volume, per 1 liter/24 h	0.68 (0.62–0.75)	0.68 (0.60–0.78)
Loop diuretic	1.09 (0.96–1.24)	1.19 (1.05–1.36)
RASi (ACEi or ARB)	0.74 (0.65–0.84)	0.74 (0.65–0.85)
Peritoneal Kt/V urea, per 0.1	1.04 (1.03–1.06)	1.02 (1.00–1.04)
Caregiver involvement in PD exchanges, involved vs. not involved	1.17 (0.99–1.38)	1.04 (0.86–1.25)

ACEi, angiotensin-converting enzyme inhibitors; APD, automated peritoneal dialysis; ARB, angiotensin II receptor blocker; CAPD, continuous ambulatory peritoneal dialysis; CI, confidence interval; $K_{\text{next-4mo}}$, average monthly serum potassium measured during the 4 months after study enrollment; OR, odds ratio; PD, peritoneal dialysis; RASi, renin-angiotensin system inhibition.

^aEstimates in each row from separate models adjusted for patient age, sex, time since end-stage kidney disease, country, and 13 comorbidities.

^bAll estimates from a single model adjusted for all factors in the table as well as adjustments in model A.

included a mixture of incident and longer-term prevalent patients with PD, with a median of 7 months (IQR, 3–18 months) on PD therapy at enrollment. Finally, our results were robust to analyses that excluded patients from Thailand (where hypokalemia prevalence is high) or restricted to patients in the United States. These 2 countries had the highest and lowest peritonitis rates (0.40 and 0.26 episodes per patient-year in Thailand and the United States, respectively, in 2014–2017) in a recent study of PDOPPS countries by Perl *et al.*¹⁸

Previous studies variably defined hypokalemia, typically using monthly time-averaged values over an observational period.^{1,2} In the present study, patients having serum potassium levels < 4.0 mEq/l for 2, 3, or 4 months over 4 months displayed 28%, 19%, and 41% higher adjusted mortality hazards, respectively, versus 0 months < 4.0 mEq/l. Having 2–4 months with serum potassium < 4 mEq/l (vs. 0 months at this level) was a substantially stronger predictor of mortality (30%–40% higher) in fully adjusted models than having a mean serum potassium < 4 mEq/l (vs. 4.0–4.49 mEq/l) over the 4-month exposure period.

We also analyzed additional factors at PDOPPS study enrollment for their association with mean serum potassium over the subsequent 4 months ($K_{\text{next-4mo}}$

< 4.0 mEq/l). Lower serum albumin was associated with higher odds of $K_{\text{next-4mo}} < 4.0$ mEq/l, with low serum albumin known to be associated with increased peritoneal protein losses,²⁴ inflammation,²⁵ frailty,²⁶ and reduced dietary protein intake in patients with PD. Greater residual kidney function may improve dietary intake and preservation of muscle mass,²⁴ as shown in longitudinal studies of body composition.²⁷ Furthermore, in a study by Wang *et al.*,²⁸ a significant and independent effect of residual kidney function on actual daily protein intake, daily caloric intake, and other nutrient intake in patients on continuous ambulatory PD was observed.

Moreover, residual kidney function is important for potassium excretion as kidney disease progresses and similarly can benefit dialysis patients. This may explain the inverse relationship between daily urine volume and odds of $K_{\text{next-4mo}} < 4.0$ mEq/l, and with this relationship being similar whether adjusting or not for serum albumin and creatinine as nutritional and muscle mass surrogate measures. Loop diuretics were positively associated and renin-angiotensin system blockers inversely associated with $K_{\text{next-4mo}} < 4.0$ mEq/l. However, these effects are dependent on residual kidney function. Notably, a recent analysis from the BRAZPD found no association between stopping or starting renin-angiotensin system blockers and serum potassium levels.²⁹

Our study has several limitations. As with any observational analysis, we cannot control for unmeasured confounders. We did not use some established measures of nutritional status or body composition, e.g., the subjective global assessment or bioimpedance analysis, both powerful predictors of survival in patients with PD.^{30,31} However, these are not widely used in routine practice and were not part of the PDOPPS dataset. Strengths of our study include the use of many relevant factors for model adjustments, large sample size, and including countries with quite different socioeconomic circumstances and patient mix. The prospective collection of numerous patient characteristics and clinical practice patterns developed via workgroups of international experts has allowed PDOPPS to conduct the most comprehensive analysis of the associations of serum potassium to date.

How should these observations influence clinical practice? These observations suggest that clinicians should pay more attention to hypokalemia and recognize that while it is a possible risk factor for death and possibly peritonitis in PD, preventive efforts should focus on factors associated with hypokalemia (e.g., poor nutrition and wasting). Our findings of substantially stronger risks of death and peritonitis with persistent hypokalemia should stimulate investigation of interventions that minimize the duration of

hypokalemia given our identification of potentially modifiable factors. For example, increasing PD prescription or using high-dose diuretics in an attempt to maintain urine output may be appropriate but might exacerbate hypokalemia risk that could be mitigated with potassium supplements. Until appropriately designed trials have established a causative role for low serum potassium in reduced survival and greater peritonitis risk, it seems prudent that increasing PD prescription should be done with careful monitoring for the development of persistent hypokalemia. Dietary counselling to encourage the intake of vegetables and fruits, the avoidance of inappropriate dietary potassium, restriction, and nutrition support to maintain good nutritional status (from the start of PD) combined with potential interventions to increase serum potassium, if needed, seem appropriate.

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AUTHOR CONTRIBUTIONS

RLP, JAS, BB, JP, SD, and AYMW conceived and/or designed the work that led to the submission; RLP, JP, DSF, JZ, SJD, TK, and DWJ acquired data; RLP, JAS, BB, JZ, JP, DSF, JZ, SJD, TK, HM, TPM, SVB, HK, DWJ, AYMW, and AV played important roles in interpreting the results; RLP, JAS, BB, JZ, JP, DSF, JZ, SJD, TK, HM, TPM, SVB, HK, DWJ, SBo, AYMW, and AV drafted or revised the manuscript; and RLP, JAS, BB, JZ, JP, DSF, JZ, SJD, TK, HM, TPM, SVB, HK, DWJ, SBo, AYMW, and AV approved the final version. SJD confirms that he has had full access to the data in the study and final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Table S1. Peritonitis organism classifications.

Table S2. Association (adjusted hazard ratio and 95% confidence interval) between various definitions of baseline serum potassium <4.0 mEq/l and all-cause mortality.

Table S3. Association (adjusted odds ratio and 95% confidence interval) between baseline factors and serum $K_{\text{next-4mo}} < 3.5$ mEq/l

Table S4. STROBE Statement.

Figure S1. Flowchart of patients included in various analyses.

Figure S2A. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$ and all-cause peritonitis, excluding Thailand; $n = 6350$ patients and 1484 events.

Figure S2B. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$

and all-cause mortality, excluding Thailand; $n = 6576$ patients and 800 events.

Figure S2C. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$ and permanent transfer to HD, excluding Thailand; $n = 6576$ patients and 1249 events.

Figure S3A. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$ and all-cause peritonitis for US patients only; $n = 3993$ patients and 786 events.

Figure S3B. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$ and all-cause mortality for US patients only; $n = 4101$ patients and 476 events.

Figure S3C. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$ and permanent transfer to HD for US patients only; $n = 4101$ patients and 686 events.

Figure S4. Associations (adjusted hazard ratio and 95% confidence interval), with progressive covariate adjustment between peritonitis and number of monthly serum $K_{\text{prior-4mo}}$ measurements <3.5 mEq/l during 4-months before study enrollment.

Figure S5A. Association (adjusted hazard ratio and 95% confidence interval) between average serum $K_{\text{prior-4mo}}$ and permanent transfer to HD ($n = 7391$ patients and 1321 events).

Figure S5B. Association (adjusted hazard ratio and 95% confidence interval) between number of monthly serum $K_{\text{prior-4mo}}$ measurements <4 mEq/l during 4 months before study enrollment and permanent transfer to HD ($n = 3666$ patients and 633 events).

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