



# Association of pre-ESKD hyponatremia with post-ESKD outcomes among incident ESKD patients

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## ABSTRACT

**Background.** Hyponatremia is one of the most common electrolyte disturbances in advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD) patients, and has been shown to be associated with higher mortality risk. However, the relationship between hyponatremia during late-stage CKD and the risk of poor outcomes after ESKD transition is unknown.

**Methods.** We conducted a retrospective cohort study including 32 257 US veterans transitioning to ESKD from 1 October 2007 to 30 March 2015. We evaluated adjusted associations between the 3-month averaged pre-transition to ESKD serum sodium and all-cause mortality. Secondary outcomes included cardiovascular (CV) mortality, infection-related mortalities and hospitalization rate.

**Results.** Cohort mean  $\pm$  standard deviation serum sodium was  $139 \pm 3$  mEq/L, mean age was  $67 \pm 11$  years, 98% were male and 28% were African American. Over a median (interquartile range) follow-up of 702 days (296, 1301) there were 17 162 deaths. Compared with the reference of 135 to  $<144$  mEq/L, the lowest serum sodium group ( $<130$  mEq/L) had a 54% higher all-cause mortality risk [hazard ratio 1.54 (95% confidence interval 1.34–1.76)] in the fully adjusted model. Associations were similar for CV and infection-related mortality, and hospitalization outcomes.

**Conclusions.** Hyponatremia prior to ESKD transition is associated with higher risk of all-cause, CV and infection-related mortalities, and hospitalization rates after ESKD transition. Future studies evaluating management of pre-ESKD hyponatremia may be indicated to improve patient outcomes for those transitioning to ESKD.

**Keywords:** end-stage kidney disease, ESKD transition, hospitalization, mortality, serum sodium

## INTRODUCTION

Hyponatremia is one of the most common water and electrolyte disturbances in clinical practice [1] with approximately 8% of the general population aged 55 years and older being affected by hyponatremia [2]. Hyponatremia is a common sequelae of chronic kidney disease (CKD) [3–6], resulting from the nephron loss that leads to a diminished ability to appropriately handle salt and water [7, 8]. Despite these changes, the serum sodium concentration typically remains within a physiological range even in severe CKD [9].

Nonetheless, hyponatremia has been associated with higher mortality in acute kidney injury, CKD and end-stage kidney disease (ESKD), and this association remains consistent after adjustment for degree of CKD [4, 10–13]. Furthermore, even mild hyponatremia in a community-based population without underlying comorbidities has been shown to be an independent predictor of mortality [14]. This implies that abnormal serum sodium levels may be a risk factor for mortality distinct from the risk arising from the underlying cause(s) of the hyponatremia [5, 15]. Once patients transition to dialysis, serum sodium levels are affected by the dialysis procedure and it is unclear whether correcting underlying hyponatremia with hemodialysis can mitigate the poor outcomes associated with pre-existing hyponatremia.

In this study, we evaluate the association between hyponatremia in advanced CKD patients prior to ESKD transition and long-term major clinical outcomes after dialysis initiation including all-cause, cardiovascular (CV) and infection-related mortality, as well as hospitalization rate.

## MATERIALS AND METHODS

### Study population and data source

The analytical cohort was derived from the United States Renal Data System (USRDS) Special Study Center Transition of

## KEY LEARNING POINTS

### What is already known about this subject?

- Hyponatremia is one of the most common electrolyte disturbances and is associated with increased morbidity and mortality in the general population, chronic kidney disease (CKD) and end-stage kidney disease (ESKD) population;
- there is a U-shaped association between serum sodium levels and mortality in CKD and ESKD patients, with the lowest mortality being among patients with serum sodium in normonatremic range; however, it remains uncertain whether hyponatremia represents the underlying medical comorbidities or directly leads to poor clinical outcomes; and
- while serum sodium of maintenance dialysis patients is affected by dialysis, the association between baseline serum sodium of advanced CKD patients and mortality after dialysis transition is unknown.

### What this study adds?

- Average serum sodium  $<130$  mEq/L of advanced CKD patients during 3 months prior to dialysis transition was associated with greater risk of all-cause, cardiovascular (CV) and infection-related mortalities after dialysis initiation, while average serum sodium  $\geq 144$  mEq/L trended toward lower risk of all-cause and CV mortalities;
- the rate of all-cause hospitalization after dialysis initiation was inversely associated with average serum sodium during 3 months prior to dialysis transition; and
- serum sodium of advanced CKD patients with hyponatremia and hypernatremia increases and decreases toward the normal serum sodium level, respectively, after dialysis initiation and becomes plateaued after 3–6 months post-dialysis transition.

### What impact this may have on practice or policy?

- While the optimal serum sodium level during pre-dialysis initiation leading to favorable outcomes after dialysis transition remains unknown, hyponatremia in advanced CKD patients should prompt a search for an intervention of potential underlying comorbidities;
- given the highest mortality during the early phase of dialysis initiation, providers may need to pay close attention to ESKD patients with a history of hyponatremia prior to dialysis transition; and
- an appropriate time for dialysis initiation may be guided by the trend of serum sodium in advanced CKD patients and a rapidly decreased trend toward hyponatremia may require early dialysis initiation to minimize a period of hyponatremia after dialysis transition.

Care in CKD (TCCKD) database, a cohort of 102 447 US veterans who transitioned to ESKD between 1 October 2007 and 30 March 2015 [16–21].

Patients were excluded if they did not have follow-up data, were missing date of birth or if they did not have a serum sodium measurement within the 3 months prior to dialysis transition (hereby referred to as the ‘prelude’ period). Thus, our final analytical cohort consisted of 32 257 US veterans transitioning to ESKD (Supplementary data, Figure S1). Patients were followed from the initiation of ESKD until death, kidney transplantation, loss to follow-up or the date of final follow-up for all patients (1 September 2015 for all-cause mortality and hospitalization, and 31 July 2015 for CV and infection-related mortality).

Given the noninvasive nature, patient anonymity and large sample size, the requirement for written informed consent was waived and the study was approved by the Memphis and Tibor Rubin Veterans Affairs (VA) Medical Centers Institutional Review Boards.

### Demographic, clinical and laboratory measurements

Patient characteristics including demographic information and primary cause of ESKD collected during the prelude period

were extracted from a composite of USRDS, Patient and Medical Evidence files, VA databases and Centers for Medicare and Medicaid Services (CMS) databases. VA and CMS data were used to determine pre-existing comorbidity status, according to the presence of International Classification of Disease-9 (ICD-9) codes, as well as the Charlson Comorbidity Index (CCI) at the time of ESKD transition. Prescribed medication information was extracted from CMS Medicare Part D and VA pharmacy dispensation records. Medication use in this study was defined as ever having a prescription filled during the prelude period.

Laboratory measurements, including serum sodium, were obtained from the VA Decision Support System National Data Extracts Laboratory Results file. All laboratory measurements during the 3-month period prior to ESKD transition were averaged into a single measurement used as prelude levels.

### Exposure measurement

The main exposure of this study was average prelude (Q1) serum sodium. Prelude serum sodium levels were categorized into four exposure categories: (i)  $<130$  (moderate–severe hyponatremia), (ii) 130 to  $<135$  (mild hyponatremia), (iii) 135 to

<144 (referent group) and (iv)  $\geq 144$  mEq/L (hypernatremia).

### Outcome assessment

The primary outcome of interest was all-cause mortality after ESKD transition. Secondary outcomes of interest included CV mortality, infection-related mortality and hospitalization rates (Supplementary data, Table S1). Information on all outcomes and censoring events were obtained from VA, CMS and USRDS records using ICD-9 codes.

### Statistical analysis

Patient demographic and clinical characteristics are presented as mean  $\pm$  standard deviation (SD), median [interquartile range (IQR)] or percent as appropriate for the total cohort and stratified by prelude serum sodium groups.

To examine trajectories of quarterly (3-month) averaged sodium 1 year pre- and post-transition, we used a mixed-effects regression (random intercept and random slope) model to visualize trajectories stratified by prelude serum sodium groups.

Cox proportional hazards models were used to evaluate the association of the prelude serum sodium groups with all-cause, CV and infection-related mortalities. Proportional hazards assumptions were checked.

Hospitalization rates across the various sodium groups were analyzed using a Poisson model. Incidence rate ratios (IRRs) were obtained with serum sodium values between 135 and <144 as the referent range.

For each outcome, four hierarchical models of adjustment were used. Model 1: unadjusted. Model 2: Case Mix: age, sex, race, ethnicity, marital status, diabetes, cancer, CCI, cerebrovascular disease, congestive heart failure, anemia, depression, hyperlipidemia and liver disease. Model 3: Case Mix + malnutrition inflammation complex syndrome (MICS): Case Mix variables, body mass index (BMI), albumin, total serum bicarbonate ( $\text{CO}_2$ ), calcium, phosphorus, hemoglobin, white blood cells (WBCs) and glucose. Model 4: Case Mix + MICS + medication (Meds): Case Mix + MICS variables, use of antidepressants, lithium salts, thiazides, loop diuretics, potassium sparing diuretics, bicarbonate, insulin, oral hypoglycemic agents, intravenous (IV) solutions with electrolytes and IV solutions without electrolytes. Model 4 was our primary model of interest.

As a sensitivity analysis, restricted cubic spline functions were used to assess potential non-linear associations for prelude serum sodium modeled as continuous variables with all-cause mortality, CV mortality and infection-related mortality using the fully adjusted model (Model 4). Knots were placed at the 5th, 35th, 65th and 95th percentiles.

Missing categorical data on patient characteristics, including marital status, were <0.2% and were handled by creating missing categories. There were 13 patients (<0.05% of the total cohort) with missing comorbid data who were categorized as no presence of condition for each comorbidity. Missing values for laboratory measurements (including 36% of patients for phosphorus, 11% for albumin, 9% for hemoglobin, 8% for WBCs

count, 7% for BMI and <5% for others) were imputed by multiple imputation using five imputed datasets.

All analyses were conducted using SAS Enterprise Guide, version 7.1 (Cary, NC, USA) and STATA version 14.2 (StataCorp, College Station, TX, USA).

## RESULTS

### Patient demographic, clinical and laboratory characteristics

The analytical cohort consisted of 32 257 patients who had at least one serum sodium measurement in the 3-month pre-ESKD initiation. Of these patients, the mean age was  $67 \pm 11$  years, 98% were male, 75% were diabetic and 28% were African American (Table 1).

Patients with lower sodium level were more likely to be younger, not married, and have a lower prevalence of cerebrovascular disease, hyperlipidemia, cancer, anemia and dementia; however, they were more likely to have a higher prevalence of liver disease (mild and moderate-severe). Furthermore, patients with lower sodium level were more likely to have lower levels of serum albumin and lower BMI, yet higher levels of blood urea nitrogen, estimated glomerular filtration rate (eGFR), serum hemoglobin A1c, glucose, platelet count and WBCs.

Diuretics (loop and potassium-sparing) were prescribed more frequently in the lower serum sodium groups, as well as insulin, antidepressants and IV solutions with and without electrolytes.

### Sodium trajectories before and after ESKD transition

In the 1-year prior to initiation of renal replacement therapy, patients with higher 3-month pre-ESKD serum sodium showed a gradual increasing trend toward higher serum sodium concentrations, whereas the lowest 3-month pre-ESKD serum sodium group showed a decline in serum sodium concentration as they approached ESKD (Figure 1). This alteration was most pronounced within the last 6 months prior to dialysis initiation while the change in sodium was most distinct in the highest ( $\geq 144$  mEq/L) and lowest (<130 mEq/L) prelude serum sodium groups. After initiation of renal replacement therapy, there was a regression to the mean and all serum sodium groups plateaued after 3–6 months post-transition. The grading of the 3-month pre-ESKD serum sodium groups did not change during the 1 year pre- and post-transition observation period.

### Pre-ESKD serum sodium and mortality

Median (IQR) follow-up time for the total cohort was 702 (296, 1301) days and 17 162 deaths occurred during the follow-up time, with an incidence rate of 22 (22–23) deaths per 100 patient-years. Lower serum sodium was associated with higher all-cause, CV and infection-related mortality risk across all models of adjustment (Figure 2A–C and Supplementary data, Table S2A–C). Patients with a prelude serum sodium <130 mEq/L had a 54%, 37% and 144% higher all-cause, CV and infection-related mortality risks, respectively, compared with those with serum sodium 135 to <144 mEq/L in fully adjusted

**Table 1. Prelude characteristics of 32 257 veterans transitioning to dialysis stratified by 3-month pre-ESKD sodium**

Variable	Total	Serum sodium (mEq/L)				P for trend
		<130	130 to <135	135 to <144	≥144	
N (%)	32 257	341 (1)	2896 (9)	27 285 (85)	1735 (5)	
Age (years)	67 ± 11	64 ± 10	65 ± 11	67 ± 11	71 ± 11	<0.0001
Female (%)	2	2	3	2	1	0.0042
Race (%)						
White	68	75	70	64	65	<0.0001
African American	28	21	26	33	33	<0.0001
Other races	3	4	4	3	2	<0.0001
Hispanic	8	11	8	8	7	0.0421
Marital status (%)						
Single	10	11	12	9	8	<0.0001
Married	51	48	47	52	57	<0.0001
Divorced	29	33	33	29	22	<0.0001
Widowed	10	8	9	10	14	<0.0001
Comorbidities (%)						
CCI	5 (3–7)	4 (3–6)	5 (3–7)	5 (3–7)	5 (3–7)	0.8377
Myocardial infarction	28	24	30	27	30	0.6821
Congestive heart failure	59	52	61	58	63	0.1954
Peripheral vascular disease	46	38	47	47	51	<0.0001
Cerebrovascular disease	37	29	36	39	44	<0.0001
Dementia	4	3	3	4	6	<0.0001
Chronic pulmonary disease	51	46	54	50	53	0.7108
Connective tissue disease-rheumatic disease	6	6	5	6	8	0.0189
Peptic ulcer disease	10	10	9	9	11	0.0296
Liver disease	18	31	23	18	16	<0.0001
Diabetes	75	67	75	74	77	0.0070
Paraplegia and hemiplegia	5	3	5	5	7	0.0162
Cancer	28	26	26	28	32	<0.0001
AIDS/HIV	2	2	2	2	1	0.0305
Anemia	79	72	78	81	85	<0.0001
Atrial fibrillation	22	22	23	20	22	0.0636
Depression	35	36	39	36	30	<0.0001
Hyperlipidemia	82	73	81	85	89	<0.0001
Hypertension	96	91	96	98	99	<0.0001
Ischemic heart disease	60	54	61	60	65	0.0033
Laboratory tests						
Sodium (mEq/L)	138.86 ± 3.29	127.15 ± 2.69	133.25 ± 1.30	139.20 ± 2.18	145.07 ± 1.31	<0.0001
LDL (mg/dL)	84.82 ± 40.28	74.61 ± 38.96	80.16 ± 42.46	85.36 ± 40.15	85.22 ± 38.56	<0.0001
HDL (mg/dL)	39.14 ± 14.24	39.70 ± 19.10	38.48 ± 16.81	39.16 ± 13.97	39.80 ± 13.11	0.0664
Triglycerides (mg/dL)	145.22 ± 101.28	131.08 ± 79.79	149.93 ± 125.41	145.91 ± 99.97	130.17 ± 80.36	0.0024
Cholesterol (mg/dL)	152.16 ± 51.61	140.20 ± 50.70	147.28 ± 58.87	152.85 ± 51.13	151.00 ± 46.41	0.0003
Hemoglobin (g/dL)	10.23 ± 1.61	10.13 ± 1.71	10.14 ± 1.65	10.24 ± 1.60	10.33 ± 1.63	0.0001
Potassium (mEq/L)	4.49 ± 0.58	4.45 ± 0.67	4.44 ± 0.57	4.50 ± 0.58	4.53 ± 0.62	<0.0001
BUN (mg/dL)	67.21 ± 24.96	69.59 ± 31.88	69.79 ± 28.50	66.95 ± 24.44	66.51 ± 24.84	<0.0001
WBCs (× 10 <sup>9</sup> /L)	7.98 ± 4.01	9.82 ± 6.82	8.73 ± 4.03	7.89 ± 3.87	7.66 ± 5.10	<0.0001
Glucose (mg/dL)	131.04 ± 48.98	160.94 ± 119.87	153.87 ± 70.00	129.38 ± 44.40	112.86 ± 34.35	<0.0001
HgbA1c (%)	6.76 ± 1.47	7.18 ± 2.18	7.31 ± 1.94	6.71 ± 1.40	6.43 ± 1.09	<0.0001
Uric acid (mg/dL)	8.13 ± 2.29	8.18 ± 2.70	8.53 ± 2.72	8.10 ± 2.24	7.95 ± 2.08	<0.0001
Platelets (× 10 <sup>9</sup> /L)	205.79 ± 75.55	214.31 ± 98.41	212.59 ± 84.40	205.46 ± 74.63	196.63 ± 65.72	<0.0001
Thyroid stimulating hormone (mIU/L)	3.46 ± 5.41	3.86 ± 8.37	4.17 ± 6.94	3.35 ± 5.02	3.71 ± 6.94	0.0012
Alkaline phosphatase (IU/L)	98.97 ± 75.28	117.91 ± 65.01	120.27 ± 122.90	96.80 ± 69.26	91.31 ± 43.91	<0.0001
Calcium (mg/dL)	8.62 ± 0.80	8.41 ± 0.80	8.55 ± 0.74	8.62 ± 0.8	8.69 ± 0.87	<0.0001
Albumin (g/dL)	3.30 ± 0.62	3.04 ± 0.69	3.07 ± 0.64	3.31 ± 0.61	3.50 ± 0.60	<0.0001
CO <sub>2</sub> (mEq/L)	22.63 ± 4.13	21.87 ± 4.54	22.63 ± 4.25	22.60 ± 4.07	23.25 ± 4.63	<0.0001
Phosphorus (mg/dL)	5.34 ± 1.43	5.64 ± 1.91	5.39 ± 1.57	5.33 ± 1.40	5.39 ± 1.48	0.0212
eGFR (mL/min/1.73 m <sup>2</sup> )	11.8 (8.6–16.5)	14.1 (9.4–25.9)	13.4 (9.5–19.8)	11.6 (8.5–16.2)	11.5 (8.4–16.0)	<0.0001
BMI (kg/m <sup>2</sup> )	30.03 ± 6.81	28.97 ± 6.98	29.27 ± 6.95	30.08 ± 6.78	30.84 ± 6.89	<0.0001
Systolic blood pressure (mmHg)	142.73 ± 19.07	132.93 ± 22.08	137.80 ± 20.11	143.26 ± 18.72	144.86 ± 20.30	<0.0001
Diastolic blood pressure (mmHg)	74.16 ± 11.81	71.10 ± 12.53	73.50 ± 11.94	74.33 ± 311.74	73.23 ± 12.44	0.0065
Weight (lbs)	205.3 ± 50.1	199.6 ± 50.1	200.4 ± 51.4	205.6 ± 49.9	210 ± 50.6	<0.0001

*Continued*

Table 1. Continued

Variable	Total	Serum sodium (mEq/L)				P for trend
		<130	130 to <135	135 to <144	≥144	
Medications (%)						
Thiazides	20	30	30	20	14	<0.0001
Loop diuretics	72	76	76	72	66	<0.0001
K-sparing diuretics	6	19	12	6	4	<0.0001
Bicarbonate	28	31	30	28	21	<0.0001
Oral hypoglycemic	18	18	18	18	21	0.1175
Insulin	49	51	57	48	41	<0.0001
Antidepressants	33	37	41	33	24	<0.0001
Lithium salts	0.1	0	0.1	0.1	0.2	0.2574
IV solutions w/ electrolytes	35	50	49	35	19	<0.0001
IV solutions w/o electrolytes	35	50	50	34	18	<0.0001

Data presented as mean ± SD, median (IQR) or proportion where appropriate. Values might not add up to 100% due to rounding. BUN, blood urea nitrogen; CO<sub>2</sub>, bicarbonate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Hgb, hemoglobin; K, potassium; w/o, without; w/, with.

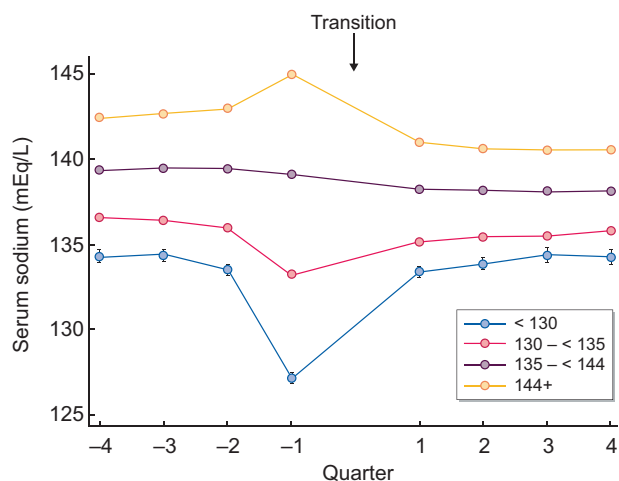


FIGURE 1: Trajectories of quarterly averaged sodium 1 year pre-transition (−4 quarters) and 1 year post-transition (4 quarters) to ESKD stratified by 3-month pre-ESKD serum sodium groups.

models (Supplementary data, Table S2A–C and Figure 2A–C). Higher serum sodium (serum sodium ≥144 mEq/L) trended toward a lower all-cause and CV mortality risk in fully adjusted models.

### Pre-ESKD serum sodium and hospitalizations

Finally, in our cohort, there were 136 302 hospitalizations over 76 464 person-years, resulting in a hospitalization rate of 1.78 [95% confidence interval (CI) 1.77–1.79] per patient year. There was an inverse linear association between serum sodium level and hospitalization rate. Compared with the reference group of 135 to <144 mEq/L, lower prelude serum sodium was associated with a 9% higher hospitalization IRR [1.09 (95% CI 1.03–1.16), for serum sodium group <130 mEq/L], while higher serum sodium was associated with a 6% lower hospitalization rate [IRR 0.94 (95% CI 0.92–0.97), for the highest serum sodium group ≥144 mEq/L] (Supplementary data, Table S2D and Figure 2D).

As a sensitivity analysis, we performed cubic spline analysis to assess the association between 3-month prelude serum sodium levels and all-cause, CV and infection-related

mortality. We did not find any significant differences in the trends that we observed in prior analyses (Supplementary data, Figure S2).

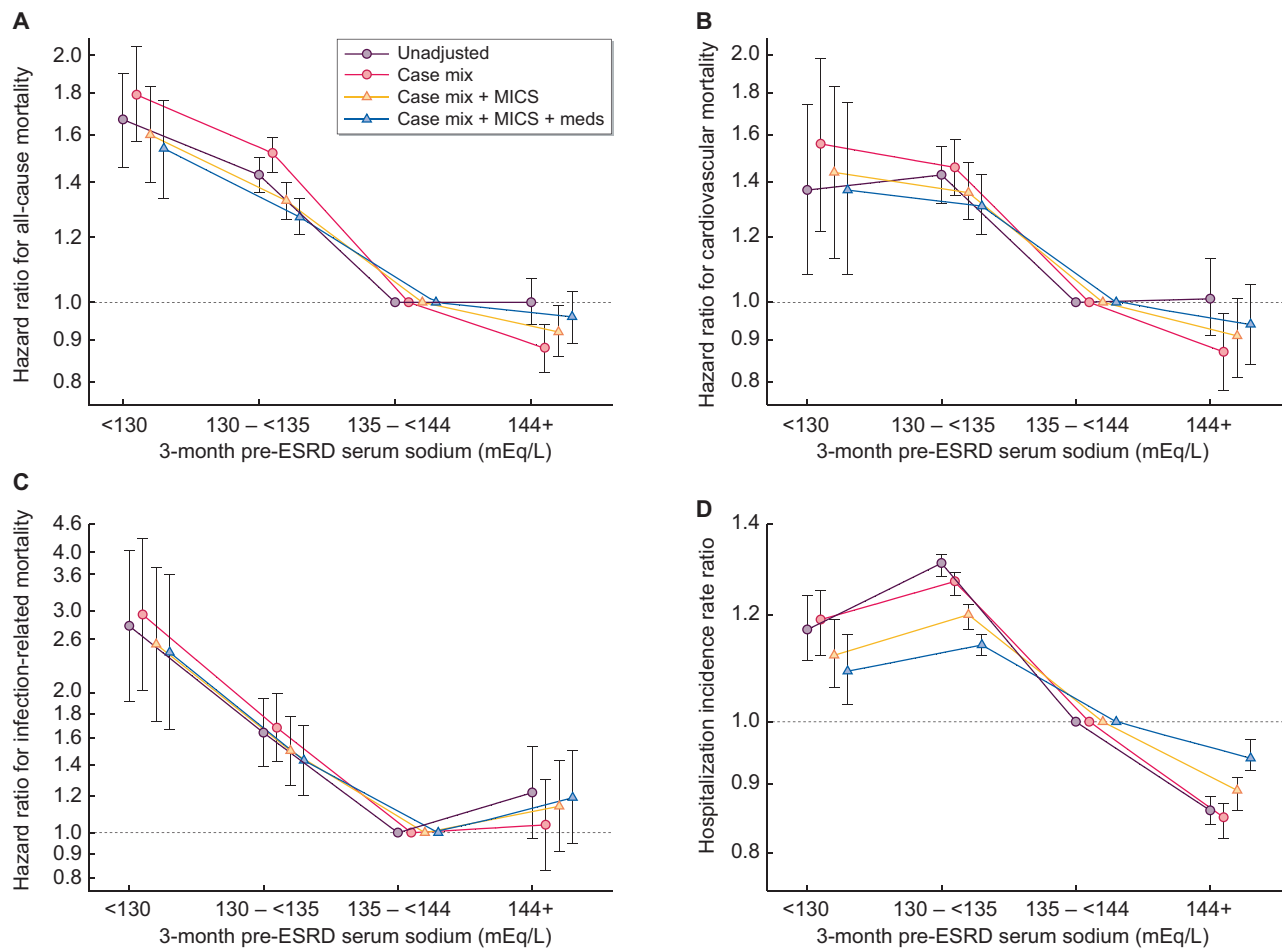
## DISCUSSION

In our cohort of 32 257 veteran patients transitioning to ESKD, we observed that moderate–severe hyponatremia (serum sodium <130 mEq/L) in the quarter prior to ESKD transition was associated with a higher risk of all-cause, CV and infection-related mortality, as well as hospitalization rate. Hypernatremia (≥144 mEq/L) was not associated with significantly different mortality and infection-related outcomes compared with our referent group but was associated with a lower risk of hospitalizations.

Our study is the first one to examine the association between serum sodium measured during the advanced CKD period (prelude) and outcomes after dialysis initiation (post-transition). Our analysis suggests that despite correction of hyponatremia with dialysis (as observed in the trajectories in Figure 1) as well as adjusting for comorbidities related to hyponatremia, hyponatremia remains associated with poor outcomes and increased rate of hospitalizations after dialysis transition.

Previously, Kovesdy *et al.* [4] demonstrated a U-shaped association between serum sodium and all-cause mortality in CKD patients, with the exception of patients with Stage 5 CKD who had lower mortality associated with hypernatremia. Our study results are similar showing higher mortality rates among patients with the lowest sodium values and suggests that even mild hyponatremia with serum sodium values between 130 and <135 are also associated with poor outcomes, even with attempting to correct hyponatremia after dialysis initiation.

Some studies have speculated that underlying causes of hyponatremia are associated with mortality, rather than the severity of hyponatremia itself [22–27]. The severity of underlying diseases may modulate serum sodium levels due to neurohormonal pathways that regulate antidiuretic hormone (ADH) secretion, which can lead to increased retention of electrolyte-free water and cause hyponatremia. Other studies have suggested that hyponatremia directly contributes to mortality [28–36].



**FIGURE 2:** Association of 3-month pre-ESKD sodium with post-ESKD (A) all-cause mortality, (B) CV mortality, (C) infection-related mortality and (D) hospitalization incidence rate ratio in 32 257 veterans transitioning to ESKD.

While it remains unclear whether hyponatremia directly contributes to higher mortality and/or is a marker of underlying comorbidities, our study suggests that there remains an association between hyponatremia and mortality even after adjusting for comorbid conditions.

Moreover, a retrospective observational study of a large cohort of incident hemodialysis patients in the USA demonstrated a graded relationship between pre-dialysis serum sodium and all-cause mortality in ESKD patients. In this study, Rhee *et al.* [12] showed that incident hemodialysis patients with pre-dialysis serum sodium of <138 had the highest all-cause mortality, whereas patients with a serum sodium of  $\geq 144$  mEq/L had the lowest mortality. However, this association became a U-shape (the lowest mortality in patients with a serum sodium of 140 to <142 mEq/L) when modeled using time-varying analysis [12]. Our study adds to this previous study by specifically investigating both moderate–severe hyponatremia levels below 130 mEq/L as well as more mild hyponatremia levels between 131 and <144 mEq/L, and shows that even patients with mild hyponatremia continue to have a higher association with poor outcomes.

Hyponatremia was also associated with higher post-ESKD hospitalization rates. Our study is consistent with several previous studies showing that hyponatremia was associated

with higher rates of infection [15], pulmonary diseases [37] and fracture [38, 39] related causes of hospitalizations. Interestingly, a higher serum sodium level ( $>144$  mEq/L) was associated with a lower rate of hospitalizations even after adjusting for confounders. The pathophysiology behind this interesting association remains unclear, though it is possible these results are prone to bias in the positive direction from the competing risk of death not being considered. Further studies are likely needed to confirm our findings and elucidate any possible biological mechanisms behind this association.

The trajectory of serum sodium concentration from 1 year prior to and 1 year after dialysis initiation deserves discussion (Figure 1). Between 6 and 12 months prior to dialysis initiation, serum sodium likely reflects underlying comorbidities and progression of CKD. As expected, patients with hyponatremia were more likely to have known underlying conditions resulting in hyponatremia such as liver disease and use of medications such as antidepressants and diuretics compared with those for groups with a baseline serum sodium concentration  $\geq 135$  mmEq/L. Serum sodium appeared stable in each group until 3 months prior to dialysis initiation, when serum sodium decreased significantly in patients with the lowest serum sodium levels. The exacerbation of hyponatremia is likely due to a combination of factors including a further decrement in the

ability of the native kidneys to excrete free water. In addition, acute illnesses are also highly prevalent around the time of dialysis initiation, which may exacerbate free water retention. After dialysis initiation, serum sodium levels appear to have normalized as a response to electrolyte control and appropriate fluid removal with dialysis treatments.

Several limitations of our study should be noted. First, as a retrospective study design, we cannot exclude the possibility of residual confounding by unmeasured variables such as inflammatory parameters (C-reactive protein), dietary patterns, other medication influencing serum sodium concentrations or the amount of excess fluid in patients prior to transition to ESKD. Second, causes of mortality and hospitalization were determined by physicians, collected in report forms and were missing in several patients. We believe these to be missing at random, which should potentially bias our results toward the null. In addition, the veteran population studied may limit external generalizability. Furthermore, our hospitalizations analysis may be prone to competing risk bias due to death, although our results are in line with other studies suggesting that there is an association between hyponatremia and increased risk of hospitalizations. We were also unable to assess individual reasons for hospitalization, especially incidence of falls and fractures, among our data. Given the known association between hyponatremia and these outcomes, further studies are necessary to see if these associations remain for patients after dialysis initiation and attempted correction of hyponatremia with dialysis.

In conclusion, we observed that hyponatremia, even mild degrees of hyponatremia (serum sodium between 130 and <135 mEq/L), in the 3-month pre-ESKD initiation period is associated with higher mortality and hospitalizations after dialysis transition despite correction of sodium levels after dialysis transition. Future studies targeting hyponatremia management in late stage CKD are needed and should help determine whether such management can improve health outcomes post-ESKD transition.

## SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org/) online.

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## CONFLICT OF INTEREST STATEMENT

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## DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated or analyzed during this study. The United States Department of Veterans Affairs (VA) places legal restrictions on access to veteran's health care data, which includes both identifying data and sensitive patient information. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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