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Original Article

ORIGINAL ARTICLE

Dysnatremia and risk of bloodstream infection in dialysis patients

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ABSTRACT

Background. Emerging data suggest that sodium disarrays including hyponatremia are potential risk factors for infection ensuing from impairments in host immunity, which may be exacerbated by coexisting conditions (i.e. mucosal membrane and cellular edema leading to breakdown of microbial barrier function). While dysnatremia and infection-related mortality are common in dialysis patients, little is known about the association between serum sodium levels and the risk of bloodstream infection in this population.

Methods. Among 823 dialysis patients from the national Biospecimen Registry Grant Program who underwent serum sodium testing over the period January 2008–December 2014, we examined the relationship between baseline serum sodium levels and subsequent rate of bloodstream infection. Bloodstream infection events were directly ascertained using laboratory blood culture data. Associations between serum sodium level and the incidence of bloodstream infection were estimated using expanded case mix–adjusted Poisson regression models.

Results. In the overall cohort, ∼10% of all patients experienced one or more bloodstream infection events during the follow-up period. Patients with both lower sodium levels <134 mEq/l and higher sodium levels ≥140 mEq/l had higher incident rate ratios (IRRs) of bloodstream infection in expanded case mix analyses (reference 136–<138 mEq/l), with adjusted IRRs of 2.30 [95% confidence interval (CI) 1.19–4.44], 0.77 (95% CI 0.32–1.84), 1.39 (95% CI 0.78–2.47), 1.88 (95% CI 1.08–3.28) and 1.96 (95% CI 1.08–3.55) for sodium levels <134, 134–<136, 138–<140, 140–<142 and ≥142 Eq/l, respectively.

Conclusions. Both lower and higher baseline serum sodium levels were associated with a higher rate of subsequent bloodstream infections in dialysis patients. Further studies are needed to determine whether correction of dysnatremia ameliorates infection risk in this population.

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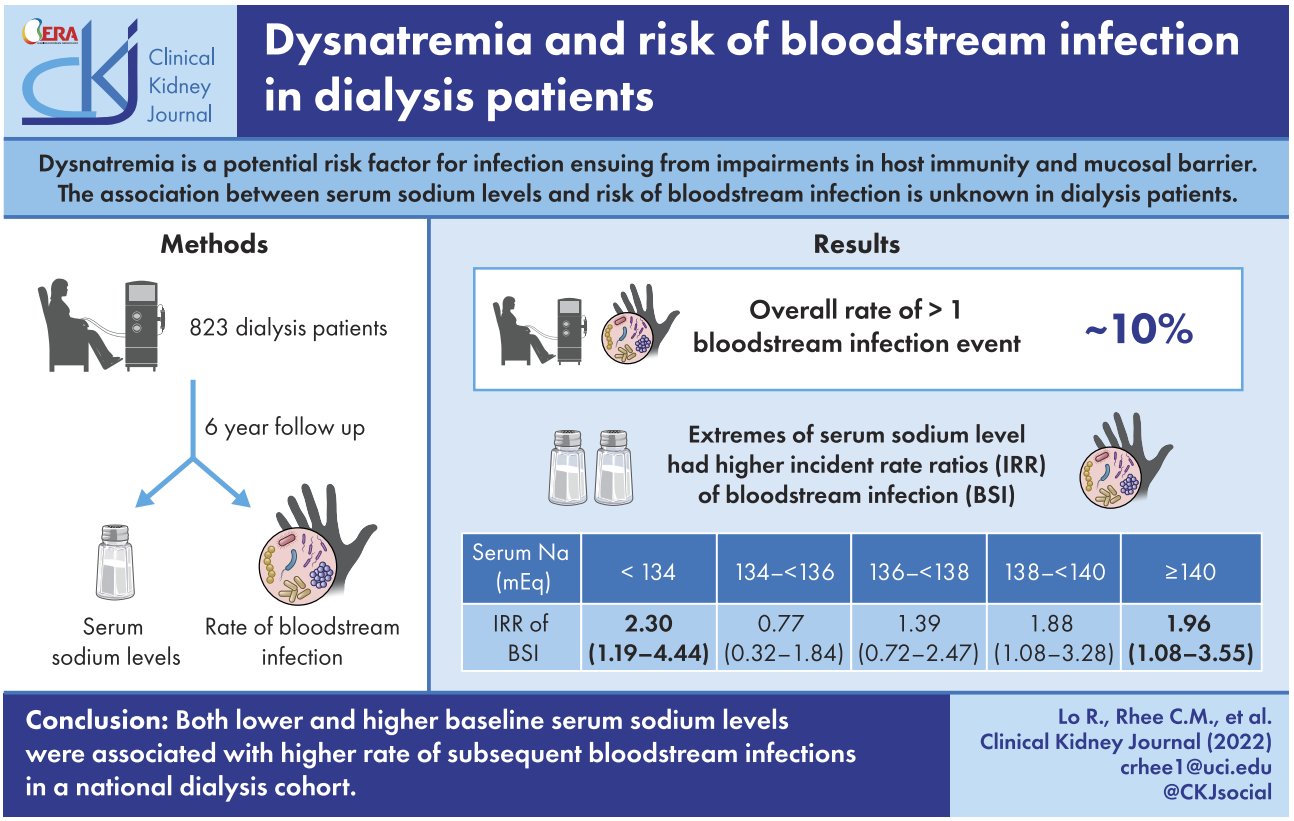
LAY SUMMARY

Hypo- and hypernatremia are among the most commonly encountered electrolyte disorders in kidney disease patients and are also independent predictors of mortality in dialysis patients. While the precise mechanisms underlying the relationship between lower and higher serum sodium levels and heightened death risk in end-stage renal disease (ESRD) patients receiving dialysis are not clear, hyponatremia has been shown to be a risk factor for infection, which is one of the leading causes of death in the dialysis population. In this study we sought to examine the relationship between serum sodium levels and the risk of bloodstream infections in a national cohort of dialysis patients. We found that both lower sodium levels <134 mEq/l and higher sodium levels ≥140 mEq/l were associated with a higher risk of bloodstream infection in the dialysis cohort. Further studies are needed to determine whether correction of lower and higher serum sodium levels reduces infection risk in the ESRD population.

GRAPHICAL ABSTRACT



Keywords: bloodstream infection, dialysis, dysnatremia, hypernatremia, hyponatremia

INTRODUCTION

Dysnatremia is the most commonly encountered electrolyte disorder in clinical practice and is frequently comorbid to a wide range of medical disorders such as chronic kidney disease (CKD), heart failure and liver cirrhosis [1–3]. For example, in CKD patients there is a 2-fold higher prevalence of hyponatremia compared with non-CKD patients [3–5]. While the relationship between hyponatremia and increased mortality has been established primarily in patients with heart failure and liver cirrhosis [6–9], a growing body of literature has suggested that both hyponatremia and hypernatremia are also independent predictors of overall mortality in end-stage renal disease (ESRD) patients [3, 10–17]. However, whether there is a direct causal relationship between altered serum sodium levels and heightened mortality in ESRD patients remains to be established. A few studies have also begun to explore specific causes of mortality in hyponatremic ESRD patients, with one study by Mandai *et al.* [18] showing increased susceptibility to infection-related hospitalizations in hemodialysis patients with lower serum sodium levels. However, there has been a paucity of research examining the relationship between dysnatremia and specific types of infection in the dialysis patients, in whom bacteremia is among the most common causes of infection [19, 20] and a major source of hospitalizations, morbidity and mortality [21].

To address this knowledge gap, we sought to examine the relationship between serum sodium concentrations and the rate of bloodstream infections in a well-characterized cohort of

dialysis patients from the national Biospecimen Registry Grant (BioReg) Program. We hypothesized that both hyponatremia and hypernatremia were independently associated with higher rates of bloodstream infections in dialysis patients.

MATERIALS AND METHODS

Study population

An observational study was conducted using data from dialysis patients in the BioReg Program with detailed patient information on sociodemographics, comorbidities, laboratory tests, dialysis treatment characteristics, clinical events and vital status. The BioReg parent cohort was comprised of 4023 maintenance hemodialysis patients from US-wide dialysis units within a large dialysis organization (DaVita, Denver, CO, USA) who provided informed consent and were prospectively enrolled and underwent specimen collections (including plasma, serum and whole blood) on a quarterly basis for up to 1 year. Following completion of the specimen collection phase, the biospecimens and patients' corresponding deidentified clinical and outcome information were allocated to four academic centers (University of California Irvine, Harvard University, Johns Hopkins University and University of Tennessee Health Science Center). The present study was comprised of 976 adult dialysis patients from the University of California Irvine BioReg cohort who were followed over a 7-year period from January 2008 to December 2014. Patients in this cohort were included provided they were ≥18 years of age and underwent one or more serum sodium measurements. Patients were excluded if they did not undergo serum sodium measurement or had a nonsensical follow-up time value (Supplemental Fig. S1). The study was approved by the Institutional Review Committee of the University of California Irvine.

Exposure ascertainment

The objective of the study was to examine the association between baseline serum sodium levels and the rate of bloodstream infections. The primary exposure of interest was the baseline serum sodium concentration obtained from patients' clinical data, which was divided into six categories: <134, 134–<136, 136–<138 (reference group), 138–<140, 140–<142 and ≥142 mEq/l. Among hemodialysis patients, serum samples were drawn predialysis within outpatient dialysis clinics and were transported to a single central laboratory for testing using automated and standardized methods, typically within 24 hours for sodium measurement.

Outcome ascertainment

The primary outcome of interest was bloodstream infection. Bloodstream infections were ascertained using laboratory data indicating the presence of a positive blood culture. At-risk time began the day after the baseline quarter of sodium measurement. Patients were censored for positive blood cultures or at the end of the study period (31 December 2014).

Statistical analyses

Baseline characteristics between exposure groups were compared using chi-squared, analysis of variance and Kruskal–Wallis tests, according to variable type. We first conducted logistic regression analyses to examine the association between relevant clinical characteristics with low serum sodium levels <134 mEq/l (versus ≥134 mEq/l). We then examined the relationship between baseline serum sodium level and the risk of bloodstream infection defined by incident rate ratios (IRRs) using Poisson regression models. Both logistic and Poisson regression analyses were conducted using four incremental levels of covariate adjustment:

- Unadjusted model: included serum sodium level as the primary exposure of interest;
- Case mix–adjusted model: included age, sex and race/ethnicity;
- Expanded case mix–adjusted model: adjusted for covariates in the case mix–adjusted model, as well as dialysis vintage, Charlson Comorbidity Index (CCI), dialysis access and diabetes comorbidity status; and
- Expanded case mix + laboratory–adjusted model: adjusted for covariates in the expanded case mix–adjusted model, as well as body mass index (BMI), serum albumin, dialysis adequacy [single-pool Kt/V (spKt/V)], serum creatinine, serum glucose and interdialytic weight gain (for hemodialysis patients).

We a priori defined the expanded case mix model as our primary model, which forced into the model core sociodemographic, dialysis treatment and comorbidity covariates. To explore the impact of other potential confounders, we also conducted expanded case mix + laboratory–adjusted models as sensitivity analyses given the high number of parameters relative to the number of bloodstream infection cases.

Effect modification of baseline serum sodium level and bloodstream infection across clinically relevant categories of sociodemographics, comorbidities, dialysis treatment characteristics and laboratory measures were explored through the addition of two-way interaction terms using likelihood ratio testing. There were no missing data for age, sex, race, dialysis vintage and diabetes status; remaining covariates had <1% missing values except for serum creatinine (3%), BMI (6%), spKt/V (7%), CCI score (13%), interdialytic weight gain (13%) and serum glucose (49%), which were addressed using multiple imputation. Analyses and figures were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), Stata version 13.1 (StataCorp, College Station, TX, USA) and SigmaPlot version 12.5 (Systat Software, San Jose, CA, USA).

RESULTS

Baseline characteristics

Among the 823 patients who met eligibility criteria for the study cohort (798 hemodialysis patients, 16 peritoneal dialysis patients and 9 with unknown modality type), the mean ± standard deviation (SD), median [interquartile range (IQR)] and minimum–maximum of observed baseline serum sodium levels were 138 ± 3 mEq/l, 138 mEq/l (136–140) and 116–147 mEq/l, respectively. Among these patients, 9.5% had serum sodium levels consistent with hyponatremia (sodium ≤134 mEq/l) (Supplemental Fig. S2). Upon comparing baseline characteristics across strata of serum sodium levels (Table 1), we observed that, compared with patients in the highest sodium category (≥142 mEq/l), those in the lowest sodium category (≤134 mEq/l) were more likely to be non-Hispanic White, had a longer dialysis vintage, were more likely to have an arteriovenous fistula or graft, were more likely to have diabetes, had lower BMI and serum creatinine levels and had higher interdialytic weight gains and serum glucose levels. Conversely, patients in the

Table 1: Baseline characteristics according to serum sodium level in dialysis patients.

Characteristics	Overall	<134	134-<136	136-<138	138-<140	140-<142	≥142
Serum sodium (mEq/l)							
Patients, *n* (%)	823	78 (9.48)	104 (12.64)	180 (21.87)	210 (25.52)	162 (19.68)	89 (10.81)
Age (years), mean ± SD	60.0 ± 13.9	59.4 ± 12.9	59.8 ± 13.4	59.8 ± 13.8	61.3 ± 13.9	58.7 ± 14.5	60.4 ± 14.1
Female, *n*	46	55	45	48	43	44	51
Race/ethnicity, *n* (%)							
Non-Hispanic White	39	49	39	38	45	29	40
Black	37	26	39	37	34	43	44
Hispanic	19	21	18	21	18	22	12
Other	4	5	3	4	3	6	3
Diabetes, *n*	53	65	51	56	49	55	43
Vintage (months), mean ± SD	48.7 ± 49.3	51.7 ± 46.3	47.3 ± 38.0	49.9 ± 52.0	50.8 ± 44.7	44.8 ± 53.2	47.3 ± 60.0
CCI, median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–7.0)	5.0 (4.0–7.0)	6.0 (4.0–6.0)	5.0 (4.0–7.0)	5.0 (4.0–6.0)
Vascular access, *n*							
AVF/AVG	29	33	31	29	26	30	27
Catheter	21	17	17	21	16	23	31
Unknown	50	50	52	49	58	46	42
BMI (kg/m^2), mean ± SD	29.7 ± 8.1	28.1 ± 7.6	28.5 ± 7.6	30.1 ± 8.0	30.1 ± 8.7	30.6 ± 8.0	29.1 ± 8.1
Weight gain (kg), mean ± SD	2.7 ± 1.6	3.1 ± 2.4	2.8 ± 1.0	2.8 ± 1.8	2.5 ± 1.6	2.5 ± 1.2	2.4 ± 1.2
Laboratory tests, median (IQR)							
Serum albumin (g/dl)	3.9 (3.6–4.1)	3.8 (3.5–3.9)	3.9 (3.5–4.1)	3.9 (3.7–4.2)	3.9 (3.6–4.1)	3.9 (3.7–4.1)	3.9 (3.6–4.2)
spKt/V	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.6 (1.4–1.7)	1.6 (1.4–1.7)
Serum creatinine (g/dl)	8.0 (6.0–10.5)	7.5 (5.8–9.7)	8.1 (6.1–0.0)	8.1 (6.2–10.9)	8.2 (6.2–10.6)	7.9 (6.2–10.5)	8.0 (5.7–10.5)
Serum glucose (mg/dl)	131 (102–183)	164 (117–266)	157 (109–219)	139 (102–189)	126 (96–167)	126 (96–160)	124 (88–166)

AVF, arteriovenous fistula; AVG, arteriovenous graft.

lowest sodium category were less likely to be Black and have a catheter venous access. Both the lowest and highest sodium categories had a higher proportion of females to males compared with the intervening serum sodium categories.

Clinical characteristics associated with hyponatremia

In logistic regression analyses examining clinical characteristics associated with low serum sodium levels ≤134 mEq/l (versus >134 mEq/l) (Table 2), we observed that patients of Black race and with higher serum albumin levels were less likely to have hyponatremia across all levels of covariate adjustment. In contrast, patients with higher serum glucose levels and interdialytic weight gains were more likely to have hyponatremia across all levels of covariate adjustment.

Serum sodium level and risk of bloodstream infection

Patients contributed a total of 1976 patient-years of follow-up, during which time 141 total bloodstream infection events occurred among 83 patients (10.1%). The median at-risk time was 1.4 years (IQR 1.2–3.6). Across all levels of covariate adjustment, serum sodium levels <134 mEq/l and >140 mEq/l were associated with significantly higher IRRs of bloodstream infection compared with the reference sodium level of 136–<138 mEq/l (Fig. 1), exhibiting a J-shaped association between sodium concentration and rate of bloodstream infection. The primary expanded case mix model showed IRRs of 2.30 (95% CI 1.19–4.44), 0.77 (0.32–1.84), 1.39 (0.78–2.47), 1.88 (1.08–3.28) and 1.96 (1.08–3.55) for sodium categories <134, 134–<136, 138–<140, 140–<142 and ≥142 mEq/l, respectively (Supplemental Table S1). A similar pattern of findings were observed for unadjusted, case mix and expanded case mix + laboratory models.

Serum sodium level and bloodstream infection risk across clinically relevant subgroups

We then examined the relationship between serum sodium level, categorized as <134, 134–140 and >140 mEq/l (reference 134–140 mEq/l), and bloodstream infection rates across clinically relevant subgroups (Fig. 2 and Supplemental Table S2). In expanded case mix analyses we found there was effect modification of the serum sodium–bloodstream infection rate relationship on the basis of age and dialysis vintage, such that both lower and higher sodium levels <134 mEq/l and >140 mEq/l were each associated with a higher rate of infection in those of younger versus older age (<60 versus ≥60 years) and longer versus shorter dialysis vintage (≥1 versus <1 year) (*P* interaction values = .005 and .01, respectively). We also observed a differential sodium–bloodstream infection relationship across the level of comorbidity burden, such that higher sodium levels >140 mEq/l were associated with a higher rate of infection in those with lower versus higher CCI scores (<5 versus ≥5) (*P* interaction value = .007). We did not detect effect modification on the basis of sex, race, BMI, serum albumin, dialysis adequacy or serum glucose level (all *P* interaction values >.05).

Across all subgroups the nominal IRRs for risk of bloodstream infection for sodium levels <134 mEq/l were >1 in the expanded case mix models, except among patients who were ≥60 years of age, had a dialysis vintage <1 year, had a BMI ≥25 kg/m^2 and had a serum glucose ≥140 mg/dl. Nominal associations for sodium levels <134 mEq/l were statistically significant among patients who were <60 years of age or who had a dialysis vintage ≥1 year. Conversely, in expanded case mix analyses, across all subgroups the nominal IRRs of bloodstream infection for sodium levels >140 mEq/l were >1 except among patients who were ≥60 years of age or had a CCI score ≥5. Nominal associations for sodium levels >140 mEq/l were statistically significant among patients who were <60 years of age, of non-Black race, with a dialysis

Table 2: Clinical characteristics associated with low serum sodium <134 mEq/l (versus ≥134 mEq/l) in dialysis patients, using logistic regression.

Characteristics	Unadjusted, OR (95% CI)	Case mix, OR (95% CI)	Expanded case mix, OR (95% CI)	Expanded case mix + laboratory, OR (95% CI)
Age (Δ10 years)	0.97 (0.82–1.14)	0.92 (0.77–1.09)	1.00 (0.75–1.33)	1.03 (0.76–1.39)
Male (versus female)	0.68 (0.43–1.09)	0.65 (0.41–1.05)	0.65 (0.40–1.06)	0.55 (0.31–0.96)
Race/ethnicity (versus non-Hispanic White)				
Black	0.52 (0.30–0.92)	0.49 (0.28–0.88)	0.47 (0.26–0.85)	0.44 (0.23–0.83)
Hispanic	0.85 (0.46–1.57)	0.80 (0.43–1.51)	0.76 (0.40–1.44)	0.80 (0.41–1.57)
Other	1.00 (0.34–3.01)	1.06 (0.35–3.19)	0.95 (0.31–2.88)	1.11 (0.35–3.53)
Diabetes (versus non-diabetes)	1.78 (1.09–2.89)	1.72 (1.05–2.83)	2.07 (1.13–3.80)	1.85 (0.95–3.61)
Vintage (Δ6 months)	1.01 (0.98–1.04)	1.01 (0.99–1.04)	1.01 (0.99–1.04)	1.02 (0.99–1.05)
CCI score	1.00 (0.88–1.15)	1.04 (0.86–1.26)	0.89 (0.69–1.14)	0.84 (0.63–1.09)
Vascular access (versus AVF/AVG)				
Catheter	0.68 (0.34–1.37)	0.66 (0.33–1.34)	0.70 (0.34–1.44)	0.54 (0.24–1.20)
Unknown	0.85 (0.50–1.44)	0.86 (0.50–1.45)	0.84 (0.49–1.44)	0.81 (0.46–1.44)
BMI (Δ5 kg/m^2)	0.86 (0.73–1.01)	0.84 (0.71–1.00)	0.80 (0.67–0.96)	0.76 (0.63–0.92)
Weight gain (Δ0.5 kg)	1.08 (1.02–1.16)	1.10 (1.03–1.18)	1.10 (1.03–1.19)	1.10 (1.01–1.19)
Serum albumin (Δ0.5 mg/dl)	0.69 (0.55–0.87)	0.67 (0.53–0.85)	0.60 (0.46–0.78)	0.65 (0.48–0.86)
spKt/V (Δ0.2)	1.04 (0.92–1.16)	0.99 (0.87–1.12)	0.99 (0.87–1.12)	0.97 (0.84–1.13)
Serum creatinine (Δ1.0 g/dl)	0.94 (0.87–1.02)	0.96 (0.88–1.05)	0.94 (0.85–1.04)	1.01 (0.90–1.13)
Serum glucose (Δ100 mg/dl)	2.25 (1.60–3.17)	2.19 (1.55–3.09)	2.28 (1.58–3.30)	2.44 (1.63–3.67)
Hemodialysis session length (Δ30 minutes)	0.96 (0.81–1.13)	0.96 (0.82–1.13)	0.96 (0.81–1.14)	1.00 (0.83–1.20)
Predialysis weight (Δ0.5kg)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.01 (1.00–1.02)
Post-dialysis weight (Δ0.5 kg)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.01 (1.00–1.02)
Predialysis SBP (Δ20 mmHg)	0.94 (0.80–1.11)	0.93 (0.79–1.11)	0.92 (0.78–1.10)	0.95 (0.79–1.14)
Postdialysis SBP (Δ20 mmHg)	0.98 (0.82–1.17)	0.97 (0.81–1.16)	0.95 (0.79–1.15)	0.87 (0.71–1.06)

AVF, arteriovenous fistula; AVG, arteriovenous graft; SBP, systolic blood pressure.

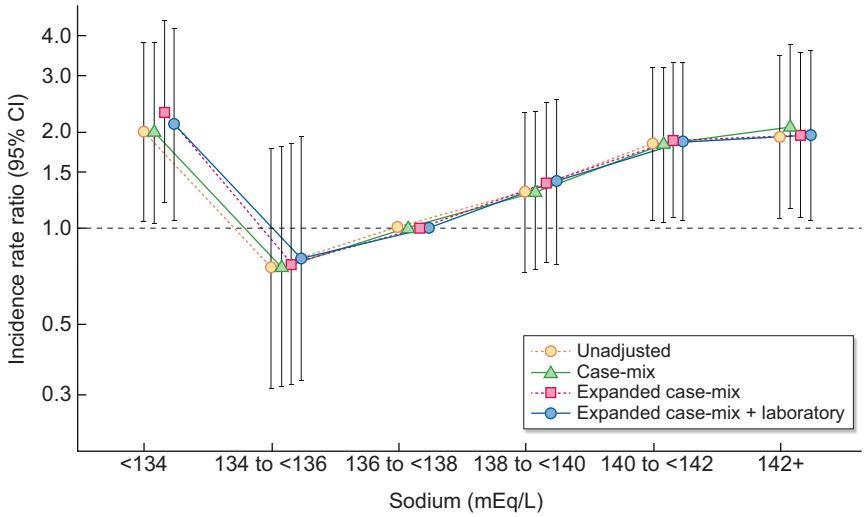


Figure 1: Association between baseline serum sodium level and IRRs of bloodstream infection risk in dialysis patients.

vintage ≥1 year, CCI score <5, serum albumin ≥4 g/dl or spKt/V ≥1.4.

DISCUSSION

In this well-characterized, contemporary cohort of dialysis patients from the national BioReg Program, we found that both lower and higher serum sodium levels were independently associated with a >2-fold higher rate of bloodstream infection. These associations were robust across multiple levels of covariate adjustment that accounted for differences in sociodemographics, comorbidities, dialysis treatment characteristics and laboratory test profiles, including markers for nutritional and inflammatory status (e.g. serum albumin).

While multiple prior studies have demonstrated that derangements in serum sodium in dialysis patients have been associated with heightened mortality risk [3, 10–17], few have examined the risk of cause-specific mortality, thus the causal

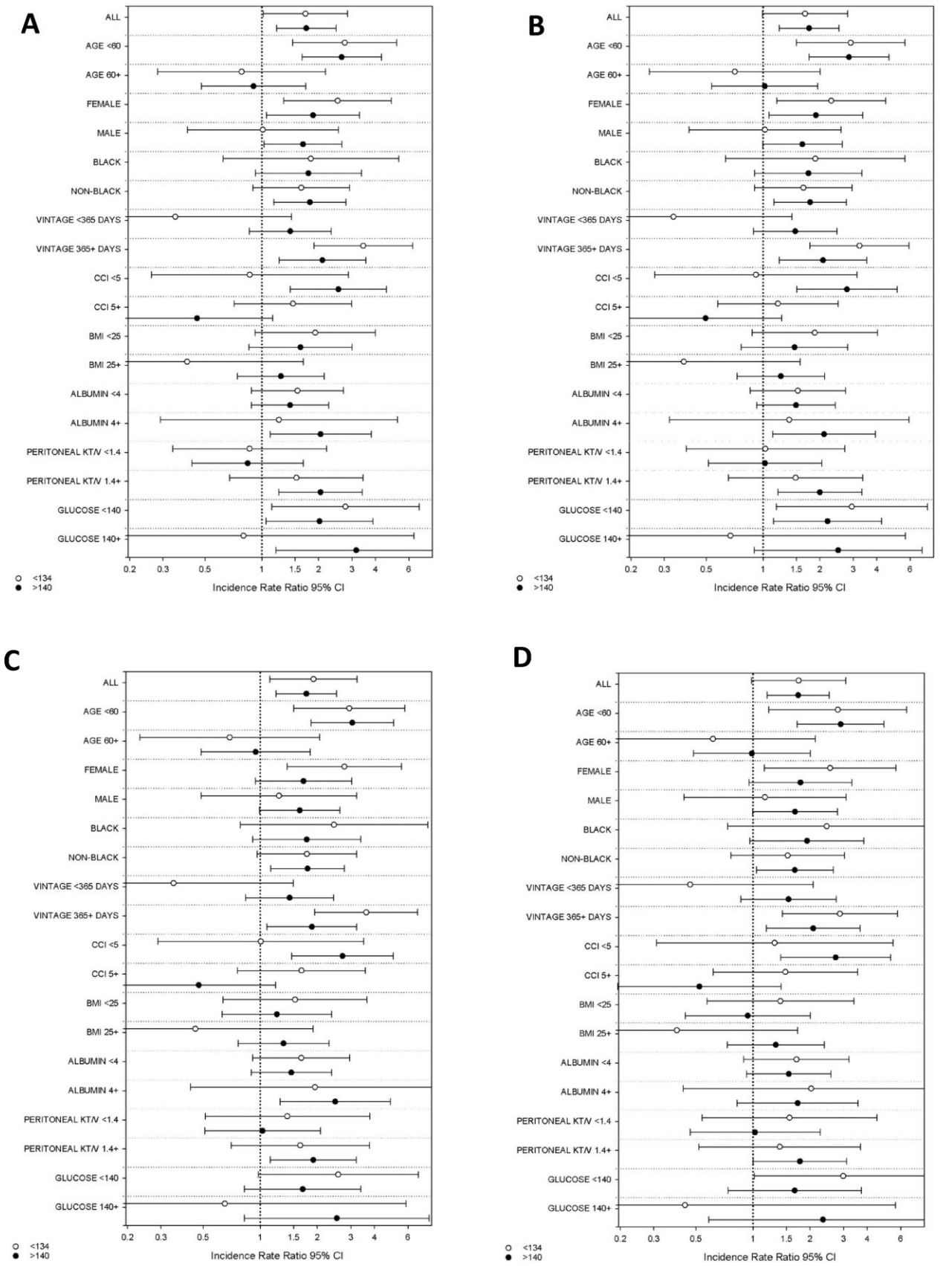


Figure 2: Association between baseline serum sodium level and bloodstream infection rate in dialysis patients across clinically relevant subgroups in **(A)** unadjusted, **(B)** case mix, **(C)** expanded case mix and **(D)** expanded case mix + laboratory–adjusted analyses.

relationship between dysnatremia and mortality remains unclear. Despite the fact that cardiovascular mortality is the largest contributor to mortality in ESRD patients overall [22], one report from the HEMO study [16] suggests that the higher mortality risk in hyponatremic hemodialysis patients stems from noncardiovascular-related causes of death. These findings have prompted greater scrutiny of infection-related mortality (i.e. the second most common cause of death in dialysis patients overall [22]) as a potential adverse complication of hyponatremic dialysis patients.

To date, there have been few studies that have examined serum sodium concentrations with infection in the dialysis population. Among these is a study of 332 maintenance hemodialysis patients by Mandai *et al.* [18] that showed those with lower serum sodium levels in the lowest two tertiles were associated with a 2.4-fold higher risk of infection-related hospitalizations. In another study, by Chang *et al.* [23], of 441 incident peritoneal dialysis patients, each 1-mEq/l higher time-averaged serum sodium level was associated with a 33% lower risk of infection-related death. These findings were corroborated in a subsequent study of 1656 peritoneal dialysis patients by Qiu *et al.* [24], which showed that hyponatremia (defined as serum sodium $<$135 mEq/l) was associated with a higher risk of infection-related death among those who were $\geq$50 years of age. However, there remain major knowledge gaps with respect to the relationship between dysnatremia and the risk of specific types of infection in dialysis patients, including bacteremia as one of the dominant sources of infection in this population [19, 20].

To our knowledge, ours is the first study to granularly examine the association between fine gradations of serum sodium levels with subsequent bloodstream infection incidence rigorously ascertained by laboratory blood culture data among a large contemporary dialysis cohort. Given that prior research of serum sodium levels and other outcomes (i.e. all-cause mortality) in hemodialysis patients have shown that incrementally higher levels even in the high-normal range as well as incrementally lower levels in the low-normal range are associated with increasingly higher death risk, we sought to granularly examine serum sodium concentrations in order to more precisely determine the threshold at which a higher risk of bloodstream infections is observed [14]. While it is still unclear as to whether dysnatremia is an indicator of versus a direct contributor to increased susceptibility to infection, there may be several pathophysiological mechanisms by which alterations in serum sodium promote bloodstream infection. There is an increasing body of literature that has reported the negative impact of hypernatremia on immune cell function, particularly macrophages and T cell subsets. Hypersalinity has been shown to impact macrophage chemotaxis *in vitro* [25], as well as promote pro-inflammatory or M1 macrophage differentiation [26–28] while suppressing wound-healing M2 macrophage activity *in vivo* [29]. Hypersalinity has also been shown to promote differentiation of T helper 17 (Th17) cells [30, 31] and suppress the inhibitory action of regulatory T cells on Th17 cells [32], causing further dysregulation of the immune response and increased susceptibility for infectious processes. With respect to hyponatremia, changes in extracellular tonicity often drive fluid shifts into and out of intracellular compartments, resulting in cellular edema or shrinkage that may impair the inherent antimicrobial barrier and structure of mucosal surfaces [27, 28, 33].

The strengths of our study include its examination of a well-characterized dialysis cohort with detailed collection of sociodemographic, comorbidity, dialysis treatment and laboratory test data; more granular examination of serum sodium levels as compared with prior studies; and rigorous adjudication of bloodstream infection events using laboratory blood culture data. However, several limitations of the study bear mention. First, while we were able to adjust for a large number of confounders of the sodium–bloodstream infection association, we were unable to account for dietary factors (i.e. sodium and fluid intake) and differences in dialysate sodium concentrations, which may have resulted in residual confounding. Second, it is possible that some of the lower sodium values may have been observed in the context of hyperglycemia, which is an independent risk factor for infection. However, we accounted for serum glucose derangements in multivariable models, which showed a robust association between dysnatremia and bloodstream infection risk. Third, there were variable degrees of missingness for some of the covariates that may confound the serum sodium–bloodstream infection association (e.g. serum creatinine, glucose, etc.), which we sought to address with multiple imputation. Given that the laboratory data were obtained as part of routine clinical care from the dialysis clinics of a large national dialysis organization, it is possible that selection of certain laboratory measurements may have been at the discretion of the various clinics/providers and/or there may have been missed measurements among patients. Fourth, due to the limited availability of repeated serum sodium measurements, we were restricted to examine sodium levels measured at a single point in time, and further corollary studies are needed to determine the longitudinal impact of dysnatremia upon the risk of bloodstream infection in dialysis patients. Lastly, as with all observational research, we are unable to confirm a causal relationship between dysnatremia and bloodstream infection, and further studies are needed to determine if hypo- and hypernatremia are markers or mediators of infection in dialysis patients.

In summary, our study found that both lower and higher serum sodium levels are each associated with a heightened risk of bloodstream infection in a well-characterized national cohort of dialysis patients. Future studies are needed to define underlying mechanisms, establish whether sodium derangements predispose to other types of infections and determine whether correction of dysnatremia attenuates the risk for infection in this population.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

R.H.L., A.S.Y. and C.M.R. were responsible for the research idea and study design and original draft preparation and editing. C.M.R. and K.K.Z. were responsible for data acquisition. C.M.R. was responsible for the investigation and supervision and mentorship. A.S.Y. and C.M.R. were responsible for the statistical analysis. All authors were responsible for review of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly to protect the privacy of individuals who participated in the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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