Hyponatremia, Hypernatremia and Mortality in Patients with Chronic Kidney Disease with and without Congestive Heart Failure

Running title: Kovesdy et al.; Serum sodium level and outcomes in CKD

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Abstract:

**Background** - Hyponatremia is common in patients with conditions such as congestive heart failure, and is associated with increased mortality in hospitalized patients. Congestive heart failure is common in patients with chronic kidney disease (CKD), but the association of serum sodium concentration with mortality in such patients is not well characterized.

**Methods and Results** - We examined the association of serum sodium concentration (SeNa) with all-cause mortality in a nationally representative cohort of 655,493 US veterans with non-dialysis dependent CKD (95,961 (15%) of them with congestive heart failure). Associations were examined in time-dependent Cox models with adjustment for potential confounders. During a median follow-up of 5.5 years a total of 193,956 patients died (mortality rate, 95% confidence interval [CI]: 62.5/1000 patient-years, 62.2-62.8). The association of serum sodium level with mortality was U-shaped, with the lowest mortality seen in patients with sodium level of 140 mEq/l, and with both lower and higher levels showing significant associations with increased mortality. Patients with serum sodium levels of <130, 130-135.9, 145.1-150 and ≥150 compared to 136-145 mEq/l had multivariable adjusted mortality hazard ratios (95%CI) of 1.93 (1.83-2.03), 1.28 (1.26-1.30), 1.33 (1.28-1.38) and 1.56 (1.33-1.83), p<0.001 for all. The associations remained consistent in subgroups of patients with and without congestive heart failure.

**Conclusions** - Both lower and higher serum sodium levels are independently associated with higher mortality in patients with non-dialysis dependent CKD, irrespective of the presence of absence of congestive heart failure.

**Key words**: hyponatremia, hypernatremia, kidney, heart failure, epidemiology
Introduction

Hyponatremia is one of the most common electrolyte abnormalities that has been described primarily in hospitalized patients; the prevalence of hyponatremia in hospitalized patients has been reported to be as high as 42% in some studies.\textsuperscript{1, 2} Hyponatremia has been associated with various adverse clinical outcomes such as increased mortality,\textsuperscript{3-20} length of inpatient stay,\textsuperscript{20, 21} gait imbalance and falls,\textsuperscript{22} rhabdomyolysis\textsuperscript{23} and bone fractures.\textsuperscript{24-26} Additionally, hyponatremia has also been linked to significantly increased healthcare costs.\textsuperscript{27-29}

Most of the studies that examined outcomes associated with hyponatremia studied hospitalized patients at single medical centers and many restricted their analyses to patients with various pre-existing pathologic conditions known to cause hyponatremia, such as CHF and liver cirrhosis. While most studies that examined outcomes associated with abnormal serum sodium levels have focused on low serum sodium (hyponatremia), elevated serum sodium (hypernatremia) has also been associated with an increase in mortality in hospitalized patients.\textsuperscript{20}

Patients with chronic kidney disease (CKD) may be more susceptible to the development of dysnatremias by virtue of their diminished ability to maintain water homeostasis in the face of decreasing kidney function. In spite of this, short of a single study in hemodialysis patients\textsuperscript{19} to our knowledge there have been no attempts to explore the association of abnormal serum sodium levels in patients with CKD. We examined the association of serum sodium levels measured repeatedly over time with all-cause mortality in a large, nationally representative cohort of US veterans with non-dialysis dependent CKD. We examined associations both with mild and moderate-to-severe hyponatremia and hypernatremia.
Methods

Cohort definition

We used laboratory data on serum creatinine from the VA Decision Support System (DSS) National Data Extracts Laboratory Results file (a VA-wide database containing select laboratory results obtained in the clinical setting) to identify patients with CKD based on a stable estimated GFR (eGFR) and the presence of an elevated spot urine microalbumin/creatinine ratio (for those with eGFR ≥60). GFR was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The algorithm for cohort definition is shown in Figure 1. Of a total of 4,381,049 patients with any available eGFR between October 1, 2004 and September 30, 2006 we identified 655,493 patients with non-dialysis dependent CKD and available serum sodium measurements.

Socio-demographic characteristics and comorbidities

Data on patient age, gender, race, geographic location (Veteran Integrated Service Network (VISN) number) and blood pressure was obtained through the VA Corporate Data Warehouse (CDW). Information on race was complemented with data obtained from Medicare through the VA-Medicare data merge project. All blood pressure values available from the October 1, 2004-October 1, 2009 time period were recorded and grouped by calendar quarters, and their quarterly-averaged values were used for analyses. Data on comorbidities (including the presence of CHF, liver disease, malignancies and depression) was collected from the VA Inpatient and Outpatient Medical SAS Datasets using International Classification of Diseases, Ninth Revision (ICD-9) diagnostic and procedure codes and Current Procedural Terminology codes recorded during the October 1, 2004 to September 30, 2006 time period.
These databases contain up to 12 diagnostic and/or procedure codes for every inpatient, long-term care and outpatient VA encounter, as well as non-VA encounters. Prevalent cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina or myocardial infarction, or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We calculated the Charlson comorbidity index using the Deyo-modification for administrative datasets, without including kidney disease.36

**Laboratory characteristics**

Data on laboratory variables was collected from the October 1, 2004-September 30, 2009 time period by using the DSS National Data Extracts Laboratory Results file.30 To minimize random variability all available laboratory values (including all serum sodium levels) were grouped by calendar quarters, and their quarterly-averaged values were used in analyses.

**Statistical analyses**

Descriptive analyses were performed and skewed variables were log-transformed. Due to the large sample size traditional statistical testing of differences in baseline characteristics was statistically significant for all variables; hence the significance of differences was established based on what we deemed to be biologically meaningful differences. Data points were missing for race (1.4%), blood pressure (17.5%), serum albumin (13.0%), hemoglobin (13.2%), white blood cell count (WBC, 16.1%), aspartate aminotransferase (AST, 7.4%), alanine aminotransferase (ALT, 5.3%), total bilirubin (9.4%), alkaline phosphatase (10.3%) and blood glucose (0.5%). There were a total of 509,906 patients (78% of the total study population) with complete data available for the fully adjusted multivariable analyses. Compared to patients with missing data, patients with complete data were of similar age (73.8±9.6 vs. 74.0±10.1 years), gender (2.7% vs. 3.1% females), race (87% vs. 91% white, 10% vs. 7% black), and had similar
prevalence of diabetes mellitus (44% vs. 41%), cardiovascular disease (44% vs. 39%) and congestive heart failure (15% vs. 12%). Missing values were not imputed in primary analyses, and were substituted by using multiple imputation procedures in sensitivity analyses. Missing values were replaced by multiple imputations with a multivariate normal regression method using data augmentation with an iterative Markov chain Monte Carlo procedure\textsuperscript{37, 38} in Stata’s “mi” command suite. Ten imputed datasets were generated, primary analyses were performed on each imputed dataset and Rubin’s combination rules were used to form one set of results.\textsuperscript{39}

The start of the follow-up period was the date of the first available serum sodium measurement after October 1, 2004. Patients were followed until death or were censored at the date of the last health care or administrative VA encounter, as documented in the VA Vital Status Files (VSF). The VA VSF is a registry containing dates of death or last medical/administrative encounter from all available sources in the VA system (the Beneficiary Identification Records Locator Subsystem (BIRLS), the Patient Treatment File (PTF), Medicare and Social Security Administration (SSA)). The sensitivity and specificity of the Vital Status Files using the National Death index as gold standard were shown to be very high (98.3% and 99.8% respectively).\textsuperscript{40} For 2,956 patients (0.005%) with missing VSF data the date of the last available laboratory measurement was used as the censoring date. The association of serum sodium level with all-cause mortality was examined in time-dependent Cox models, with adjustment for potential confounders. Variables were included in multivariable models if they could be considered confounders\textsuperscript{41} based on theoretical considerations and after examination of baseline associations with serum sodium. Associations were examined sequentially in models with incremental multivariable adjustments: unadjusted (Model 1), age, gender, race and geographic location (Model 2), model 2 plus comorbid conditions (diabetes, ASCVD, CHF, liver disease,
malignancy, depression and Charlson comorbidity index) (Model 3) and model 3 plus systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, AST, ALT, total bilirubin, blood hemoglobin, glucose and white blood cell count (Model 4). Variables which were measured repeatedly during follow-up (serum sodium, blood pressure and all other laboratory covariates) were handled as time-dependent variables in Cox models. We hypothesized that the association of serum sodium with mortality will be non-linear; hence we examined sodium by using restricted cubic splines. Due to the small number of patients with serum sodium levels <115 mEq/liter (N=76) and >160 mEq/liter (N=61) the spline models were limited to patients with serum sodium levels of 115-160 mEq/liter. We also compared patients with mild-moderate and severe hyponatremia (serum sodium <130 and 130-135 mEq/l) and hypernatremia (serum sodium 146-150 and >150 mEq/l) to those with normal serum sodium (serum sodium 136-145 mEq/l). Due to their smaller numbers patients with hypernatremia were analyzed as a single category (serum sodium >145 mEq/l) in subgroup analyses. In order to better assess the short term vs. the long term effects of serum sodium levels on mortality time-stratified Cox models were constructed to examine 1-year mortality hazard ratios associated with baseline hypo- and hypernatremia (defined by serum sodium levels at the cohort entry and maintained constant throughout the examined time periods) and with time-varying hypo-and hypernatremia (defined based on repetitive quarterly serum sodium measurements in each examined year) in the first, second, third, fourth and fifth years of follow-up, conditional on surviving to the beginning of the examined (first, second, etc.) year.42

The association of serum sodium with mortality was examined separately in subgroups of patients categorized by CKD stage, by key sociodemographic characteristics, presence or absence of key comorbid conditions and by their levels of relevant laboratory values. Sensitivity
analyses were performed by using imputed values of independent variables and by using serum sodium levels corrected for serum glucose level. Statistical analyses were performed using STATA MP version 11 (STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

Role of the Funding Source

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Results

The mean±SD age of the cohort at baseline was 73.9±9.8 years, 87% and 9% of patients were white and black, respectively, and the mean estimated GFR (eGFR) was 50.2±14.1 ml/min/1.73m². The mean±SD baseline serum sodium was 140±3 mEq/l. At baseline 85,855 patients (13.5%) had hyponatremia (serum sodium <136 mEq/l) and 13,289 (2%) had hypernatremia (serum sodium of >145 mEq/l); during the entire duration of follow-up 169,158 patients (26%) had at least one episode of hyponatremia and 45,666 (7%) had at least one episode of hypernatremia. Baseline characteristics in patients categorized by their baseline serum sodium levels are shown in Table 1. Patients with hyponatremia were younger, more likely to be diabetic and to have CHF, liver disease and depression, had a higher eGFR, blood glucose and white blood cell count, and a lower serum albumin and blood hemoglobin. Patients with hypernatremia on the other hand were older, and had a lower eGFR, serum total bilirubin and blood glucose.
Mortality

A total of 193,956 patients died (mortality rate: 62.5/1000 patient-years, 95% confidence interval [CI]: 62.2-62.8) during a median follow-up of 5.5 years. The number of deaths in patients with different serum sodium levels were 1,773 (<130); 30,199 (130-135.9); 158,103 (136-144.9); 3,680 (145-149.9) and 201 (≥150 mEq/liter). The association of serum sodium with mortality was U-shaped, with both lower and higher serum sodium showing a significant association with higher mortality even after multivariable adjustment (Figure 2). Patients with serum sodium levels of <130, 130-135.9, 145.1-150 and ≥150 compared to 136-145 mEq/l had unadjusted mortality hazard ratios (95%CI) of 2.49 (2.38-2.61), 1.43 (1.41-1.44), 1.40 (1.34-1.35) and 2.17 (1.89-2.49), p<0.001 for all; after full multivariable adjustment the hazard ratios (95%CI) for the same groups were 1.93 (1.83-2.03), 1.28 (1.26-1.30), 1.33 (1.28-1.38) and 1.56 (1.33-1.83), p<0.001 for all (Figure 3). In time-stratified Cox models concomitantly assessing 1-year mortality rates associated with both baseline and time-varying serum sodium categories, time-varying hypo-and hypernatremia both showed stronger associations with mortality compared to baseline hypo- and hypernatremia, which displayed weak or non-significant associations (Table 2).

The association of lower and higher serum sodium with mortality was present in all examined subgroups, including patients with and without CHF, liver disease, malignancy and depression, in patients with high and with low levels of the composite Charlson comorbidity index, and in patients with normal or elevated serum levels of hepatic enzymes (Figure 4). There was no linear trend in the mortality hazard ratios associated with hyponatremia in patients with different stages of CKD (Figure 4, panel A); however, mortality associated with hypernatremia...
appeared to be relatively lower in patients with more advanced stages of CKD (Figure 4, panel B).

Results of analyses using imputed values for missing variables yielded similar results: the multivariable adjusted hazard ratios (95%CI) in patients with serum sodium levels of <130, 130-135.9, 145.1-150 and ≥150 compared to 136-145 mEq/l were 1.94 (1.85-2.03), 1.28 (1.27-1.30), 1.29 (1.25-1.34) and 1.58 (1.38-1.82), p<0.001 for all. The results of analyses examining serum sodium levels that were adjusted for blood glucose levels were also not different from the results detailed above (data not shown).

**Discussion**

We describe an association between abnormally decreased and elevated levels of serum sodium and higher all-cause mortality in a large, nationally representative group of US veterans with non-dialysis dependent CKD. These associations were linearly proportional with the severity of the underlying hyponatremia and hypernatremia, and were independent from comorbid conditions such as CHF or liver disease. Both lower and higher serum sodium were associated more strongly with mortality when modeling them in a time-dependent manner, with weak or no effects associated with baseline levels of the same factors, suggesting that both hypo- and hypernatremia represent acute (short term), rather than chronic (long term) risk factors for mortality. Severity of kidney disease did not appear to affect the mortality associated with hyponatremia, but patients with more advanced CKD displayed a relatively lower mortality associated with hypernatremia compared to patients with less severe stages of CKD.
Studies examining the predictive value of serum sodium level have concentrated largely on hyponatremia, have examined mostly patients who were hospitalized, and were usually derived from data obtained from single medical centers. Such studies have described associations of hyponatremia with a variety of adverse outcomes including all-cause mortality, length of inpatient stay, gait imbalance and falls, rhabdomyolysis, bone fractures and higher hospitalization costs. Some of the studies examined unselected groups of patients, but others focused on groups with some underlying comorbid condition such as CHF, cardiovascular or liver disease. Irrespective of the setting or the patients included, all studies have found that hyponatremia is associated with an increased risk of the studied end points. Similar associations were reported for hypernatremia too, although this abnormality has been in general under-emphasized.

Ours is the first study that examined patients with non-dialysis dependent CKD, and the first to provide data that is nationally representative for the US. The uniqueness of the CKD population is that kidney disease affects the organ responsible for maintaining water homeostasis, and as such it is possible that both the prevalence of dysnatremias and their clinical consequences could be magnified. While we did report a relatively high prevalence and incidence of hyponatremia (13% of the patients in our study had hyponatremia at baseline, and twice as many had at least one episode of hyponatremia during follow-up), the lack of information about the general population prevents us from determining whether CKD results in an increased incidence or prevalence of dysnatremias. Regarding outcomes, we did not find differences in the association of hyponatremia with mortality in patients with different severities of CKD, but hypernatremia appeared to predict less severe outcomes in patients with more advanced stages of CKD. This latter observation could be the result of end-organ adaptation to a
state of increased extracellular osmolality in patients with advanced CKD who experience a gradual accumulation of various uremic solutes with advancing severity of kidney disease.

One implication of our results is that it establishes hypo- and hypernatremia as robust outcome predictors in patients with all stages of CKD. On the other hand, it is unclear yet if these abnormalities should be considered treatment targets in these patients. Both hypo- and hypernatremia can have direct adverse effects on various organs’ function, most notably on the central nervous system.\textsuperscript{43-46} This underlying pathophysiology could serve as one potential explanation of why abnormal serum sodium level is associated with increased mortality; our results indicating a more marked association with short term, rather than long term mortality also supports this hypothesis. Since abnormal water homeostasis usually develops as a result of another underlying pathology it is also possible that hyponatremia and hypernatremia are merely surrogate markers of more severe disease states. Similar to other studies, we did not detect any effect modification by known disease states that affect serum sodium level, which makes it more likely that abnormal serum sodium level has an independent effect on survival. Furthermore, a study of maintenance hemodialysis patients enrolled in the Hemodialysis (HEMO) study also reported a significant association of hyponatremia with mortality, even though in anuric dialysis patients the development of low serum sodium is unrelated to the stimulation of arginine-vasopressin by underlying comorbidities.\textsuperscript{19} Arguing against a causal effect of hyponatremia was a recent study in hospitalized patients in whom the authors could link fatalities associated with severe hyponatremia (<120 mEq/l) to more severe underlying disease processes rather than the hyponatremia itself.\textsuperscript{47} Nevertheless, observational studies cannot completely overcome the problem of residual confounding, which can be better addressed by randomized controlled trials. One such large trial in patients that examined the effects of the vasopressin V2 receptor
antagonist tolvaptan on mortality in patients with CHF did not detect a significant benefit on mortality,\textsuperscript{48} but more interventional studies are needed to determine if other patient populations, other treatment regimens, or patients with different severities of hyponatremia might show different outcomes.

Our study is notable for its very large sample size and event numbers, and for it being representative of the entire geographic United States. Our study also has a number of limitations that need to be considered when interpreting its results. Our study population consisted mostly of male patients; hence the results may not apply to females. We used data obtained during the course of clinical practice, hence selection bias is possible. However, the key laboratory variables used for cohort definition (serum creatinine and sodium) are part of routine panels that are measured in most patients receiving healthcare, hence it is unlikely that a significant proportion of actively enrolled veterans would have been excluded. We defined CKD using the CKD-EPI equation as it is more accurate than other estimating equations (such as the Modification of Diet in renal Disease (MDRD) equation) in patients with normal and mildly decreased GFR. The CKD-EPI equation was, however, meant to be used with serum creatinine measured by the IDMS-traceable method, which was not ubiquitous at the time when our cohort was defined (2005-2006), and hence it is unclear how accurate the staging of CKD in our cohort was. The associations between serum sodium and mortality did not change, however, if we used the MDRD equation to estimate GFR in our cohort participants (data not shown). We did not collect information about hospitalizations, hence we cannot determine if the mortality associated with hypo- or hypernatremia occurred in context of hospitalizations. We adjusted our analyses for a significant number of potential confounders, but we cannot rule out the presence of residual confounding. We used diagnostic codes to define comorbid conditions that could act as
confounders in the association of serum sodium with mortality, which may have resulted in underestimation of their prevalence. By including laboratory variables reflecting abnormal liver function and/or structure we were able to alleviate this concern as far as the confounding imparted by liver disease, but we did not have similar data to assess the presence and/or severity of the other relevant comorbid conditions. We had relatively few patients with extremely high or extremely low serum sodium levels, hence our ability to characterize outcomes associated with very severe degrees of hypo- and hypernatremia may be limited.

Conclusions

Both hyponatremia and hypernatremia are associated with increased all-cause mortality in patients with non-dialysis dependent CKD. This association is independent of comorbid conditions and severity of kidney disease. Abnormal serum sodium levels can be used as predictors of outcomes in this patient population, and could be considered as treatment targets that need to be tested in clinical trials.

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Conflict of Interest Disclosures: Dr. Kalantar-Zadeh has received honoraria from Otsuka Pharmaceuticals. The other authors declared no conflicts of interest.
References:


Table 1. Baseline characteristics of individuals stratified by baseline serum sodium level

<table>
<thead>
<tr>
<th>Serum sodium (mEq/l)</th>
<th>&lt;130 (N=2,729)</th>
<th>130-135.9 (N=83,126)</th>
<th>136-144.9 (N=556,349)</th>
<th>145-149.9 (N=12,807)</th>
<th>≥150 (N=482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.5 ± 11.3</td>
<td>71.7 ± 10.7</td>
<td>74.1 ± 9.6</td>
<td>75.5 ± 8.9</td>
<td>76.1 ± 8.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>2,346 (87)</td>
<td>70,905 (87)</td>
<td>482,718 (88)</td>
<td>11,245 (89)</td>
<td>423 (89)</td>
</tr>
<tr>
<td>black</td>
<td>217 (8)</td>
<td>8,206 (10)</td>
<td>51,704 (9)</td>
<td>1,163 (9)</td>
<td>40 (8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>49 (2)</td>
<td>998 (1)</td>
<td>7,107 (1)</td>
<td>146 (1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>other</td>
<td>76 (3)</td>
<td>1,566 (2)</td>
<td>7,694 (1)</td>
<td>136 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>2,631 (96)</td>
<td>80,637 (97)</td>
<td>541,195 (97)</td>
<td>12,430 (97)</td>
<td>474 (98)</td>
</tr>
<tr>
<td>DM</td>
<td>1,302 (48)</td>
<td>45,761 (55)</td>
<td>230,989 (42)</td>
<td>4,873 (38)</td>
<td>185 (38)</td>
</tr>
<tr>
<td>ASCVD</td>
<td>1,112 (41)</td>
<td>34,868 (42)</td>
<td>237,429 (43)</td>
<td>5,778 (45)</td>
<td>221 (46)</td>
</tr>
<tr>
<td>CHF</td>
<td>556 (20)</td>
<td>14,076 (17)</td>
<td>79,374 (14)</td>
<td>1,880 (15)</td>
<td>75 (16)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>101 (4)</td>
<td>1,257 (2)</td>
<td>3,390 (0.6)</td>
<td>51 (0.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>454 (17)</td>
<td>13,949 (17)</td>
<td>98,068 (18)</td>
<td>2,445 (19)</td>
<td>82 (17)</td>
</tr>
<tr>
<td>Depression</td>
<td>205 (8)</td>
<td>5,740 (7)</td>
<td>30,295 (5)</td>
<td>692 (5)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Comorbidity index</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137 ± 20</td>
<td>137 ± 18</td>
<td>137 ± 18</td>
<td>138 ± 18</td>
<td>135 ± 19</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 11</td>
<td>72 ± 11</td>
<td>72 ± 11</td>
<td>72 ± 11</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>55.2 ± 19.3</td>
<td>53.1 ± 17.3</td>
<td>49.8 ± 13.5</td>
<td>47.1 ± 12.6</td>
<td>47.0 ± 13.1</td>
</tr>
<tr>
<td>Serum Albumin (g/dl)</td>
<td>3.8 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>4.0 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>173 ± 67</td>
<td>178 ± 46</td>
<td>173 ± 39</td>
<td>171 ± 38</td>
<td>170 ± 37</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.1 ± 0.5</td>
<td>9.2 ± 0.5</td>
<td>9.3 ± 0.5</td>
<td>9.5 ± 0.5</td>
<td>9.5 ± 0.6</td>
</tr>
<tr>
<td>Serum AST (U/L)</td>
<td>24 (19-31)</td>
<td>22 (18-28)</td>
<td>22 (19-27)</td>
<td>24 (20-29)</td>
<td>25 (21-30)</td>
</tr>
<tr>
<td>Serum ALT (U/L)</td>
<td>22 (16-32)</td>
<td>22 (16-31)</td>
<td>22 (16-30)</td>
<td>25 (18-32)</td>
<td>26 (19-33)</td>
</tr>
<tr>
<td>Serum total bilirubin (mg/dl)</td>
<td>0.7 (0.5-0.9)</td>
<td>0.7 (0.5-0.9)</td>
<td>0.7 (0.5-0.9)</td>
<td>0.6 (0.4-0.7)</td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>Serum ALP (U/l)</td>
<td>91 ± 46</td>
<td>81 ± 38</td>
<td>79 ± 32</td>
<td>85 ± 30</td>
<td>87 ± 31</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/l)</td>
<td>26.0 ± 3.0</td>
<td>26.6 ± 2.8</td>
<td>27.4 ± 2.9</td>
<td>27.9 ± 3.3</td>
<td>28.0 ± 4.2</td>
</tr>
<tr>
<td>Blood Hgb (g/dl)</td>
<td>13.1 ± 1.9</td>
<td>13.7 ± 1.8</td>
<td>13.9 ± 1.7</td>
<td>13.9 ± 1.7</td>
<td>14.0 ± 1.7</td>
</tr>
<tr>
<td>Blood WBC (1000/mm³)</td>
<td>7.9 ± 3.0</td>
<td>7.8 ± 3.6</td>
<td>7.3 ± 4.1</td>
<td>7.3 ± 3.4</td>
<td>7.4 ± 2.2</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>166 ± 126</td>
<td>151 ± 48</td>
<td>119 ± 40</td>
<td>109 ± 28</td>
<td>110 ± 32</td>
</tr>
</tbody>
</table>

Data is presented as means ± SD, number (% of total) or median (Q1-Q3). DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Hgb, hemoglobin; WBC, white blood cell count.

All p values for comparing differences between categories were statistically significant.
Table 2. One-year unadjusted mortality hazard ratios (95% confidence intervals) associated with baseline and with time-dependent serum sodium levels of <130, 130-135.9 and >145 mEq/L, compared to 136-145 mEq/L in the first, second, third, fourth and fifth year of follow-up, conditional on surviving to the beginning of the examined year.

<table>
<thead>
<tr>
<th>Serum sodium (mEq/L)</th>
<th>Year of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Baseline &lt;130</td>
<td>1.14 (0.93-1.40)</td>
</tr>
<tr>
<td>Time-dependent &lt;130</td>
<td>2.00 (1.67-2.38)</td>
</tr>
<tr>
<td>Baseline 130-135.9</td>
<td>1.03 (0.98-1.09)</td>
</tr>
<tr>
<td>Time-dependent 130-135.9</td>
<td>1.34 (1.27-1.41)</td>
</tr>
<tr>
<td>Baseline &gt;145</td>
<td>1.09 (0.94-1.27)</td>
</tr>
<tr>
<td>Time-dependent &gt;145</td>
<td>1.40 (1.20-1.64)</td>
</tr>
</tbody>
</table>

Hazard ratios are estimated from Cox models that included both baseline and time-dependent serum sodium categories, and were adjusted for age, gender, race, geographic location, diabetes mellitus, ASCVD, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferase, total bilirubin, blood hemoglobin, glucose and white blood cell count. Baseline serum sodium categories were established based on measurements in the first three months of cohort participation for all models and kept constant throughout follow-up. Time-dependent serum sodium categories were established using repetitive quarterly serum sodium levels measured throughout follow-up.
Figure Legends:

Figure 1. Algorithm used to define the study cohort. eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease.

Figure 2. Multivariable adjusted log hazard ratios (95% confidence intervals) of all-cause mortality associated with serum sodium levels in a time-dependent Cox model using restricted cubic splines, adjusted for age, gender, race, geographic location, diabetes mellitus, ASCVD, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferase, total bilirubin, blood hemoglobin, glucose and white blood cell count. The bars represent the number of deaths in patients with serum sodium levels grouped in increments of 5 mEq/liter from 115 to 160 mEq/liter, on a logarithmic scale.

Figure 3. Unadjusted and multivariable adjusted hazard ratios (95% confidence intervals) of all-cause mortality associated with various levels of serum sodium in time-dependent Cox models. The groups with serum sodium 136-145 served as referent. Models represent unadjusted association (Model 1) and associations after adjustment for age, gender, race and geographic location (Model 2), Model 2 variables + diabetes mellitus, ASCVD, CHF, liver disease, malignancy, depression and the Charlson comorbidity index (Model 3) and Model 3 variables + systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferase, total bilirubin, blood hemoglobin, glucose and white blood cell count (Model 4). All comparisons were significant at p<0.001 level.
Figure 4. Forest plot of the multivariable adjusted natural log-transformed mortality hazard ratios (95% CI) associated with mild (130-135.9 mEq/l) and moderate-to-severe (<130 mEq/l) hyponatremia (Panel A), and with hypernatremia (serum sodium >145 mEq/l, Panel B) in various pre-specified subgroups of patients. Groups with normal (136-145 mEq/l) serum sodium levels served as referent. Estimates are from time-dependent Cox models adjusted for age, gender, race, geographic location, diabetes mellitus, ASCVD, CHF, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferase, total bilirubin, blood hemoglobin, glucose and white blood cell count.
Serum sodium concentration:

- ▲ <130 mmol/l
- ▴ 130-<136 mmol/l

Age:
- ▲ <70 years
- ▴ ≥70 years

Gender:
- Male
- Female

Race:
- White
- Black

Diabetes:
- Absence
- Presence

Heart Failure:
- Absence
- Presence

Liver Disease:
- Absence
- Presence

Malignancy:
- Absence
- Presence

Depression:
- Absence
- Presence

CKD Stages:
- Stage 5
- Stage 4
- Stage 3B
- Stage 3A
- Stage 2
- Stage 1

Liver Enzymes:
- AST ≥ 41 U/l
- AST < 41 U/l
- ALT ≥ 47 U/l
- ALT < 47 U/l

Alkaline Phosphatase:
- ≥ 128 U/l
- < 128 U/l

Total Bilirubin:
- ≥ 1.3 mg/dl
- < 1.3 mg/dl

Hazard Ratio of Mortality:

0.9 1.1 1.3 1.6 2.0 2.5
Hyponatremia, Hypernatremia and Mortality in Patients with Chronic Kidney Disease with and without Congestive Heart Failure

Csaba P. Kovesdy, Evan H. Lott, Jun Ling Lu, Sandra M. Malakauskas, Jennie Z. Ma, Miklos Z. Molnar and Kamyar Kalantar-Zadeh

_Circulation_, published online January 5, 2012;

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저나트륨혈증과 고나트륨혈증은 모두 심부전의 동반 유무에 관계없이 만성 신질환자의 사망률을 높인다

최 동 주 교수 분당서울대학교병원 순환기내과

Summary

배경
울혈성 심부전 환자에서 저나트륨혈증은 매우 흔하며, 이는 입원 환자의 사망률을 증가시킨다. 만성 신질환자에서 울혈성 심부전은 매우 흔하며, 이 환자들을 대상으로 혈중 나트륨의 농도와 사망률에 대해서는 잘 알려져 있지 않다.

방법 및 결과
본 연구는 미국 재향군인협회에 소속된 투석을 받지 않는 만성 신질환자의 국가 전체의 코호트 655,493명(15%인 95,961명이 울혈성 심부전 환자임)을 대상으로 혈중 나트륨의 농도와 전체 사망률과의 연관성을 조사하고자 하였다. 연관성은 시간-의존 콕스 모델을 사용하였고, 중요한 교란 인자는 보정하였다. 5.5년 평균 관찰기간 동안 193,956명의 환자가 사망하였다(사망률, 62.5/1,000 patient-year; 95% CI, 62.2-62.8).

사망률과 혈중 나트륨 농도와의 연관성은 혈중 나트륨 농도 140mEq/L에서 가장 낮은 사망률을 보였고, 140mEq/L 이상과 이하에서 사망률이 유의하게 증가하여 U-형태를 보이고 있었다. 혈중 나트륨 농도가 <130, 130-135.9, 145.1-150, ≥150mEq/L군이 136-145mEq/L에 비해 다변량-보정 사망 위험도(multivariable-adjusted mortality hazard ratios) 및 95% CI는 각각 1.93(1.83-2.03), 1.28(1.26-1.30), 1.33(1.28-1.38) 및 1.56(1.33-1.83)였다(모두 P<0.001).

이런 연관성은 울혈성 심부전의 동반유무와 상관없이 모든 소그룹에서 일정하게 관찰되었다.

결론
낮거나 높은 혈중 나트륨 농도는 투석에 의존하지 않는 만성 신질환 환자에서 울혈성 심부전 동반유무와 관계없이 사망률과 독립적인 관련성이 있다.
저나트륨혈증은 입원 환자 중에서 가장 흔히 볼 수 있는 전해질 이상일 뿐 아니라, 입원 사망률이나 입원기간 연장 등의 나쁜 임상 결과를 가져온다. 그러나 대부분 저나트륨혈증의 임상 연구는 입원 환자를 대상으로 하였을 뿐 아니라, 저나트륨혈증에 초점을 두고 있다. 특히, 연구의 대상 환자 수가 매우 많을 뿐 아니라 사망률도 높아 미국 전역의 형편을 대변한다 할 수 있다. 그러나 연구의 대상이 재향군인협회의 등록 환자를 대상으로 하였기 때문에 남성 환자들을 대상으로 하여 여성 환자에게 그 결과를 적용할 수 없다는 제한점이 있다. 또한, 임상 경과 중 데이터를 수집하였으므로 환자의 선별 오류 (selection bias)가 있을 수 있으며, 입원기간에 수집하지 않아 사망률이 저나트륨혈증과 관련이 있는지 고나트륨혈증과 관련이 있는지 여부는 정확히 파악할 수 없다는 연구의 제한점이 있다. 그러나 655,493명의 대규모 환자를 대상으로 하였으며, 그 중 15%가 심부전을 동반하고 있었고 5.5년 관찰기간 동안 26%가 1회 이상의 저나트륨혈증, 7%가 1회 이상의 고나트륨혈증이 발생하여 동반되는 심부전, 간질환과 무관하게 저나트륨혈증, 고나트륨혈증 모두가 단기 사망률과 밀접한 상관성이 있다는 것을 밝혔다는 데 가치가 있다.

비록 이 연구가 저나트륨혈증과 고나트륨혈증이 높은 사망률의 직접적인 원인임을 밝히지는 못했으나, 만성 신질환 환자에서 심부전 유무에 관계없이 혈중 나트륨 농도가 중요한 예후 예측인자임을 강조하였으므로, 향후 이 환자군에서 혈중 나트륨 농도를 교정 목표로 하는 임상 연구가 진행될 수 있는 이론적인 근거가 될 것으로 사료된다.
Hyponatremia, Hypernatremia, and Mortality in Patients With Chronic Kidney Disease With and Without Congestive Heart Failure

Csaba P. Kovesdy, MD; Evan H. Lott; Jun Ling Lu, MD; Sandra M. Malakauskas, PhD, MD; Jennie Z. Ma, PhD; Miklos Z. Molnar, MD, PhD; Kamyar Kalantar-Zadeh, MD, PhD

Background—Hyponatremia is common in patients with conditions such as congestive heart failure and is associated with increased mortality in hospitalized patients. Congestive heart failure is common in patients with chronic kidney disease, but the association of serum sodium concentration with mortality in such patients is not well characterized.

Methods and Results—We examined the association of serum sodium concentration with all-cause mortality in a nationally representative cohort of 655,493 US veterans with non–dialysis-dependent chronic kidney disease (95,961 [15%] of them with congestive heart failure). Associations were examined in time-dependent Cox models with adjustment for potential confounders. During a median follow-up of 5.5 years, a total of 193,956 patients died (mortality rate, 62.5/1000 patient-years; 95% confidence interval, 62.2–62.8). The association of serum sodium level with mortality was U-shaped, with the lowest mortality seen in patients with sodium level of 140 mEq/L and with both lower and higher levels showing significant associations with increased mortality. Patients with serum sodium levels of <130, 130 to 135.9, 145.1 to 150, and ≥150 mEq/L compared with 136 to 145 mEq/L had multivariable-adjusted mortality hazard ratios (95% confidence interval) of 1.93 (1.83–2.03), 1.28 (1.26–1.30), 1.33 (1.28–1.38), and 1.56 (1.33–1.83) (P<0.001 for all). The associations remained consistent in subgroups of patients with and without congestive heart failure.

Conclusions—Both lower and higher serum sodium levels are independently associated with higher mortality in patients with non–dialysis-dependent chronic kidney disease, irrespective of the presence or absence of congestive heart failure. (Circulation. 2012;125:677-684.)

Key Words: epidemiology ■ heart failure ■ hypernatremia ■ hyponatremia ■ kidney

Hyponatremia is one of the most common electrolyte abnormalities that has been described primarily in hospitalized patients; the prevalence of hyponatremia in hospitalized patients has been reported to be as high as 42% in some studies.1,2 Hyponatremia has been associated with various adverse clinical outcomes such as increased mortality, length of inpatient stay,20,21 gait imbalance and falls,22 rhabdomyolysis,23 and bone fractures.24–26 Additionally, hyponatremia has also been linked to significantly increased healthcare costs.27–29 Most of the studies that examined outcomes associated with hyponatremia studied hospitalized patients at single medical centers, and many restricted their analyses to patients with various preexisting pathological conditions known to cause hyponatremia, such as congestive heart failure (CHF) and liver cirrhosis. Although most studies that examined outcomes associated with abnormal serum sodium levels have focused on low serum sodium (hyponatremia), elevated serum sodium (hypernatremia) has also been associated with an increase in mortality in hospitalized patients.20

Clinical Perspective on p 152

Patients with chronic kidney disease (CKD) may be more susceptible to the development of dysnatremias by virtue of their diminished ability to maintain water homeostasis in the face of decreasing kidney function. Despite this, other than a single study in hemodialysis patients,19 to our knowledge there have been no attempts to explore the association of abnormal serum sodium levels in patients with CKD. We examined the association of serum sodium levels measured repeatedly over time with all-cause mortality in a large, nationally representative cohort of US veterans with non–

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dialysis-dependent CKD. We examined associations with both mild and moderate to severe hyponatremia and hypernatremia.

Methods

**Cohort Definition**

We used laboratory data on serum creatinine from the Veterans Affairs (VA) Decision Support System National Data Extracts Laboratory Results file (a VA-wide database containing select laboratory results obtained in the clinical setting) to identify patients with CKD on the basis of a stable estimated glomerular filtration rate (eGFR) and the presence of an elevated spot urine microalbumin/creatinine ratio (for those with eGFR $\leq 60$). GFR was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration equation. The algorithm for cohort definition is shown in Figure 1. Of a total of 4,381,049 patients with any available eGFR between October 1, 2004, and September 30, 2006, we identified 655,493 patients with non–dialysis-dependent CKD and available serum sodium measurements.

**Sociodemographic Characteristics and Comorbidities**

Data on patient age, gender, race, geographic location (Veteran Integrated Service Network number), and blood pressure were obtained through the VA Corporate Data Warehouse. Information on race was complemented with data obtained from Medicare through the VA-Medicare data merge project. All blood pressure values available from the time period of October 1, 2004, to September 30, 2009, were recorded and grouped by calendar quarters, and their quarterly-averaged values were used for analyses. Data on comorbidities (including the presence of CHF, liver disease, malignancies, and depression) were collected from the VA Inpatient and Outpatient Medical SAS Datasets with the use of International Classification of Diseases, Ninth Revision diagnostic and procedure codes and Current Procedural Terminology codes recorded during the time period of October 1, 2004, to September 30, 2006. These databases contain up to 12 diagnostic and/or procedure codes for every inpatient, long-term care, and outpatient VA encounter, as well as non-VA encounters. Prevalent cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, or myocardial infarction or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We calculated

![Figure 1. Algorithm used to define the study cohort. eGFR indicates estimated glomerular filtration rate; ESRD, end-stage renal disease; and CKD, chronic kidney disease.](image-url)
the Charlson comorbidity index using the Deyo modification for administrative data sets, without including kidney disease.36

Laboratory Characteristics
Data on laboratory variables were collected from the time period of October 1, 2004, to September 30, 2009, by using the Decision Support System National Data Extracts Laboratory Results file.30 To minimize random variability, all available laboratory values (including all serum sodium levels) were grouped by calendar quarters, and their quarterly-averaged values were used in analyses.

Statistical Analyses
Descriptive analyses were performed, and skewed variables were log-transformed. Because of the large sample size, traditional statistical testing of differences in baseline characteristics was statistically significant for all variables; hence, the significance of differences was established on the basis of values that we deemed to be biologically meaningful differences. Data points were missing for race (1.4%), blood pressure (17.5%), serum albumin (13.0%), hemoglobin (13.2%), white blood cell count (16.1%), aspartate aminotransferase (7.4%), alanine aminotransferase (5.3%), total bilirubin (9.4%), alkaline phosphatase (10.3%), and blood glucose (0.5%). There were a total of 509,906 patients (78% of the total study population) with complete data available for the fully adjusted multivariable analyses. Compared with patients with missing data, patients with complete data were of similar age (73.8 ± 9.6 years versus 74.0 ± 10.1 years), gender (2.7% versus 3.1% female), and race (87% versus 91% white, 10% versus 7% black) and had similar prevalence of diabetes mellitus (44% versus 41%), cardiovascular disease (44% versus 39%), and CHF (15% versus 12%). Missing values were not imputed in primary analyses and were substituted with the use of multiple imputation procedures in sensitivity analyses. Missing values were replaced by multiple imputations with a multivariate normal regression method with data augmentation by an iterative Markov chain Monte Carlo procedure31 in STATA’s “mi” command suite. Ten imputed data sets were generated; primary analyses were performed on each imputed data set, and the combination rules of Rubin39 were used to form 1 set of results.

The start of the follow-up period was the date of the first available serum sodium measurement after October 1, 2004. Patients were followed until death or were censored at the date of the last healthcare or administrative VA encounter, as documented in the VA Laboratory Characteristics. The VA Vital Status Files is a registry containing dates of death or last medical/administrative encounter from all available sources in the VA system (Beneficiary Identification Records Locator Subsystem, Patient Treatment File, Medicare, and Social Security Administration). The sensitivity and specificity of the Vital Status Files with the National Death Index used as gold standard were shown to be very high (98.3% and 99.8%, respectively).40 For 2936 patients (0.005%) with missing Vital Status Files data, the date of the last available laboratory measurement was used as the censoring date. The association of serum sodium level with all-cause mortality was examined in time-dependent Cox models, with adjustment for potential confounders. Variables were included in multivariable models if they could be considered confounders on the basis of theoretical considerations and after examination of baseline associations with serum sodium. Associations were examined sequentially in models with incremental multivariable adjustments: unadjusted (model 1); age, gender, race, and geographic location (model 2); model 2 plus comorbid conditions (diabetes mellitus, atherosclerotic cardiovascular disease, CHF, liver disease, malignancy, depression, and Charlson comorbidity index) (model 3); and model 3 plus systolic blood pressure, eGFR, serum albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood hemoglobin, glucose, and white blood cell count (model 4). Variables that were measured repeatedly during follow-up (serum sodium, blood pressure, and all other laboratory covariates) were handled as time-dependent variables in Cox models. We hypothesized that the association of serum sodium with mortality will be nonlinear; hence, we examined sodium by using restricted cubic splines. Because of the small number of patients with serum sodium levels <115 mEq/L (n = 76) and >160 mEq/L (n = 61), the spline models were limited to patients with serum sodium levels of 115 to 160 mEq/L. We also compared patients with mild to moderate and severe hyponatremia (serum sodium <130 and 130–135 mEq/L) and hypernatremia (serum sodium 146–150 and >150 mEq/L) with those with normal serum sodium (serum sodium 136–145 mEq/L). Because of their smaller numbers, patients with hypernatremia were analyzed as a single category (serum sodium >145 mEq/L) in subgroup analyses. To better assess the short-term versus the long-term effects of serum sodium levels on mortality, time-stratified Cox models were constructed to examine 1-year mortality hazard ratios associated with baseline hyponatremia and hypernatremia (defined by serum sodium levels at the cohort entry and maintained constant throughout the examined time periods) and with time-varying hyponatremia and hypernatremia (defined on the basis of repetitive quarterly serum sodium measurements in each examined year) in the first, second, third, fourth, and fifth years of follow-up, conditional on surviving to the beginning of the examined (first, second, etc.) year.42

The association of serum sodium with mortality was examined separately in subgroups of patients categorized by CKD stage, by key sociodemographic characteristics, by presence or absence of key comorbid conditions, and by their levels of relevant laboratory values. Sensitivity analyses were performed with the use of imputed values of independent variables and serum sodium levels corrected for serum glucose level. Statistical analyses were performed with the use of STATA MP version 11 (STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VA Medical Center.

Results
The mean ± SD age of the cohort at baseline was 73.9 ± 9.8 years; 87% and 9% of patients were white and black, respectively; and the mean eGFR was 50.2 ± 14.1 mL/min per 1.73 m². The mean ± SD baseline serum sodium was 140 ± 3 mEq/L. At baseline, 85,855 patients (13.5%) had hyponatremia (serum sodium <136 mEq/L), and 13,289 (2%) had hypernatremia (serum sodium >145 mEq/L); during the entire duration of follow-up, 169,158 patients (26%) had at least 1 episode of hyponatremia, and 45,666 (7%) had at least 1 episode of hypernatremia. Baseline characteristics in patients categorized by their baseline serum sodium levels are shown in Table 1. Patients with hyponatremia were younger; were more likely to be diabetic and to have CHF, liver disease, and depression; had a higher eGFR, blood glucose, and white blood cell count; and had a lower serum albumin and blood hemoglobin. Patients with hypernatremia, on the other hand, were older and had a lower eGFR, serum total bilirubin, and blood glucose.

Mortality
A total of 193,956 patients died (mortality rate, 62.5/1000 patient-years; 95% confidence interval, 62.2–62.8) during a median follow-up of 5.5 years. The number of deaths in patients with different serum sodium levels were 1773 (<130 mEq/L); 30,199 (130–135.9 mEq/L); 158,103 (136–144.9 mEq/L); 3680 (145–149.9 mEq/L); and 201 (≥150 mEq/L). The association of serum sodium with mortality was U-shaped, with both lower and higher serum sodium showing a significant association with higher mortality even after multivariable adjustment (Figure 2). Patients with serum sodium levels of <130, 130 to 135.9, 145.1 to 149.9, and ≥150 mEq/L compared with 136 to 145 mEq/L had unadjusted mortality hazard ratios (95% confidence interval) of...
Table 1. Baseline Characteristics of Individuals Stratified by Baseline Serum Sodium Level

<table>
<thead>
<tr>
<th>Serum Sodium, mEq/L</th>
<th>&lt;130 (n=2729)</th>
<th>130–135.9 (n=83 126)</th>
<th>136–144.9 (n=556 349)</th>
<th>145–149.9 (n=12 807)</th>
<th>≥150 (n=482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.5±11.3</td>
<td>71.7±10.7</td>
<td>74.1±9.6</td>
<td>75.5±8.9</td>
<td>76.1±8.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2346 (87)</td>
<td>70 905 (87)</td>
<td>482 718 (88)</td>
<td>11 245 (89)</td>
<td>423 (89)</td>
</tr>
<tr>
<td>Black</td>
<td>217 (8)</td>
<td>8206 (10)</td>
<td>51 704 (9)</td>
<td>1163 (8)</td>
<td>40 (8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>49 (2)</td>
<td>998 (1)</td>
<td>7107 (1)</td>
<td>146 (1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>76 (3)</td>
<td>1566 (2)</td>
<td>7694 (1)</td>
<td>136 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>2631 (96)</td>
<td>80 905 (87)</td>
<td>541 195 (97)</td>
<td>12 430 (97)</td>
<td>474 (98)</td>
</tr>
<tr>
<td>Deposition</td>
<td>205 (8)</td>
<td>5740 (7)</td>
<td>30 295 (5)</td>
<td>692 (5)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Comorbidity index</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>137±20</td>
<td>137±18</td>
<td>137±18</td>
<td>138±18</td>
<td>135±19</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72±11</td>
<td>72±11</td>
<td>72±11</td>
<td>72±11</td>
<td>70±12</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>55±2.193</td>
<td>53±17.3</td>
<td>49.8±13.5</td>
<td>47.1±12.6</td>
<td>47.0±13.1</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>3.8±0.5</td>
<td>3.9±0.5</td>
<td>4.0±0.4</td>
<td>4.1±0.4</td>
<td>4.2±0.5</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>173±67</td>
<td>178±46</td>
<td>173±39</td>
<td>171±38</td>
<td>170±37</td>
</tr>
<tr>
<td>Serum calcium, mg/dL</td>
<td>9.1±0.5</td>
<td>9.2±0.5</td>
<td>9.3±0.5</td>
<td>9.5±0.5</td>
<td>9.5±0.6</td>
</tr>
<tr>
<td>Serum AST, U/L</td>
<td>24 (19–31)</td>
<td>22 (18–28)</td>
<td>22 (19–27)</td>
<td>24 (20–29)</td>
<td>25 (21–30)</td>
</tr>
<tr>
<td>Serum ALT, U/L</td>
<td>22 (16–32)</td>
<td>22 (16–31)</td>
<td>22 (16–30)</td>
<td>25 (18–32)</td>
<td>26 (19–33)</td>
</tr>
<tr>
<td>Serum total bilirubin, mg/dL</td>
<td>0.7 (0.5–0.9)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.6 (0.4–0.7)</td>
<td>0.5 (0.4–0.7)</td>
</tr>
<tr>
<td>Serum ALP, U/L</td>
<td>91±46</td>
<td>81±38</td>
<td>79±32</td>
<td>85±30</td>
<td>87±31</td>
</tr>
<tr>
<td>Serum bicarbonate, mEq/L</td>
<td>26.0±3.0</td>
<td>26.6±2.8</td>
<td>27.4±2.9</td>
<td>27.9±3.3</td>
<td>28.0±4.2</td>
</tr>
<tr>
<td>Blood hemoglobin, g/dL</td>
<td>13.1±1.9</td>
<td>13.7±1.8</td>
<td>13.9±1.7</td>
<td>13.9±1.7</td>
<td>14.0±1.7</td>
</tr>
<tr>
<td>Blood WBC, 1000/mm³</td>
<td>7.9±3.0</td>
<td>7.8±3.6</td>
<td>7.3±4.1</td>
<td>7.3±3.4</td>
<td>7.4±2.2</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>166±126</td>
<td>151±48</td>
<td>119±40</td>
<td>109±28</td>
<td>110±32</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. No. (% of total), or median (quartiles 1–3). CVD indicates cardiovascular disease; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; and WBC, white blood cell count. All P values for comparing differences between categories were statistically significant.

The association of lower and higher serum sodium with mortality was present in all examined subgroups, including patients with and without CHF, liver disease, malignancy, and depression; patients with high and low levels of the composite Charlson comorbidity index; and patients with normal or elevated serum levels of hepatic enzymes (Figure 4). There was no linear trend in the mortality hazard ratios associated with hyponatremia in patients with different stages of CKD (Figure 4A); however, mortality associated with hypernatremia appeared to be relatively lower in patients with more advanced stages of CKD (Figure 4B).

Results of analyses in which imputed values for missing variables were used yielded similar results: The multivariable adjusted hazard ratios (95% confidence interval) for the same groups were 1.93 (1.83–2.03), 1.28 (1.26–1.30), 1.33 (1.28–1.38), and 1.56 (1.33–1.83) (P<0.001 for all) (Figure 3). In time-stratified Cox models concomitantly assessing 1-year mortality rates associated with both baseline and time-varying serum sodium categories, time-varying hyponatremia and hypernatremia both showed stronger associations with mortality compared with baseline hyponatremia and hypernatremia, which displayed weak or nonsignificant associations (Table 2).

**Discussion**

We describe an association between abnormally decreased and elevated levels of serum sodium and higher all-cause mortality in a large, nationally representative group of US individuals.
Results from various studies have described associations of hyponatremia with a variety of adverse outcomes including all-cause mortality, length of inpatient stay, gait imbalance and falls, rhabdomyolysis, bone fractures, and higher hospitalization costs. Some of the studies examined unselected groups of patients, but others focused on groups with some underlying comorbid condition such as CHF or liver disease. Irrespective of the setting or the patients included, all studies have found that hyponatremia is associated with an increased risk of the studied end points. Similar associations were reported for hypernatremia as well, although in general this abnormality has been underemphasized.

Ours is the first study that examined patients with non–dialysis-dependent CKD and the first to provide data that are nationally representative for the United States. The uniqueness of the CKD population is that kidney disease affects the organ responsible for maintaining water homeostasis, and as such it is possible that both the prevalence of dysnatremias and their clinical consequences could be magnified. Although we reported a relatively high prevalence and incidence of hyponatremia (13% of the patients in our study had hyponatremia at baseline, and twice as many had at least 1 episode of hyponatremia during follow-up), the lack of information about the general population prevents us from determining whether CKD results in an increased incidence or prevalence of dysnatremias. In regard to outcomes, we did not find differences in the association of hyponatremia with mortality in patients with different severities of CKD, but hypernatremia appeared to predict less severe outcomes in patients with more advanced stages of CKD. This latter observation could be the result of end-organ adaptation to a state of increased extracellular osmolality in patients with advanced CKD who experience a gradual accumulation of various uremic solutes with advancing severity of kidney disease.

One implication of our results is that they establish hyponatremia and hypernatremia as robust outcome predictors in patients with all stages of CKD. On the other hand, it is unclear whether these abnormalities should be considered treatment targets in these patients. Both hyponatremia and hypernatremia can have direct adverse effects on the function of various organs, most notably on the central nervous system. This underlying pathophysiology could serve as a potential explanation of why an abnormal serum sodium level is associated with increased mortality; our results indicating a more marked association with short-term rather than long-term mortality also support this hypothesis. Because abnormal water homeostasis usually develops as a result of another underlying pathology, it is also possible that
Hyponatremia and hypernatremia are merely surrogate markers of more severe disease states. Similar to other studies, we did not detect any effect modification by known disease states that affect serum sodium level, which makes it more likely that an abnormal serum sodium level has an independent effect on survival. Furthermore, a study of maintenance hemodialysis patients enrolled in the Hemodialysis (HEMO) study also reported a significant association of hyponatremia with mortality, even though in patients with anuric dialysis the development of low serum sodium is unrelated to the stimulation of arginine vasopressin by underlying comorbidities. Arguing against a causal effect of hyponatremia was a

<table>
<thead>
<tr>
<th>Serum Sodium, mEq/L</th>
<th>Year of Follow-Up</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline &lt;130</td>
<td>1.14 (0.93–1.40)</td>
<td>0.99 (0.85–1.17)</td>
<td>1.04 (0.90–1.21)</td>
<td>1.30 (1.11–1.51)</td>
<td>1.13 (0.95–1.33)</td>
<td></td>
</tr>
<tr>
<td>Time-dependent &lt;130</td>
<td>2.00 (1.67–2.38)</td>
<td>2.04 (1.81–2.30)</td>
<td>2.05 (1.82–2.30)</td>
<td>1.63 (1.43–1.86)</td>
<td>1.32 (1.15–1.51)</td>
<td></td>
</tr>
<tr>
<td>Baseline 130–135.9</td>
<td>1.03 (0.98–1.09)</td>
<td>1.05 (1.01–1.09)</td>
<td>1.06 (1.03–1.10)</td>
<td>1.04 (1.01–1.08)</td>
<td>1.06 (1.02–1.09)</td>
<td></td>
</tr>
<tr>
<td>Time-dependent 130–135.9</td>
<td>1.34 (1.27–1.41)</td>
<td>1.28 (1.23–1.32)</td>
<td>1.30 (1.26–1.34)</td>
<td>1.27 (1.23–1.32)</td>
<td>1.17 (1.13–1.21)</td>
<td></td>
</tr>
<tr>
<td>Baseline &gt;145</td>
<td>1.09 (0.94–1.27)</td>
<td>1.18 (1.08–1.29)</td>
<td>1.17 (1.08–1.27)</td>
<td>1.12 (1.02–1.22)</td>
<td>1.02 (0.93–1.11)</td>
<td></td>
</tr>
<tr>
<td>Time-dependent &gt;145</td>
<td>1.40 (1.20–1.64)</td>
<td>1.40 (1.28–1.53)</td>
<td>1.37 (1.27–1.49)</td>
<td>1.30 (1.19–1.42)</td>
<td>1.20 (1.10–1.31)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios are estimated from Cox models that included both baseline and time-dependent serum sodium categories and were adjusted for age, gender, race, geographic location, diabetes mellitus, atherosclerotic cardiovascular disease, congestive heart failure, liver disease, malignancy, depression, the Charlson comorbidity index, systolic blood pressure, estimated glomerular filtration rate, serum albumin, alkaline phosphatase, aspartate and alanine aminotransferase, total bilirubin, blood hemoglobin, glucose, and white blood cell count. Baseline serum sodium categories were established on the basis of measurements in the first 3 months of cohort participation for all models and were kept constant throughout follow-up. Time-dependent serum sodium categories were established with the use of repetitive quarterly serum sodium levels measured throughout follow-up.
recent study in hospitalized patients in whom the authors could link fatalities associated with severe hyponatremia (<120 mEq/L) to more severe underlying disease processes rather than the hyponatremia itself. Nevertheless, observational studies cannot completely overcome the problem of residual confounding, which can be better addressed by randomized controlled trials. One such large trial in patients that examined the effects of the vasopressin V2-receptor antagonist tolvaptan on mortality in patients with CHF did not detect a significant benefit on mortality, but more interventional studies are needed to determine whether other patient populations, other treatment regimens, or patients with different severities of hyponatremia might show different outcomes.

Our study is notable for its very large sample size and event numbers and the fact that it is representative of the entire geographic United States. Our study also has a number of limitations that should be considered when the results are interpreted. Our study population consisted mostly of male patients; hence, the results may not apply to female patients. We used data obtained during the course of clinical practice, and therefore selection bias is possible. However, the key laboratory variables used for cohort definition (serum creatinine and sodium) are part of routine panels that are measured in most patients receiving healthcare, and therefore it is unlikely that a significant proportion of actively enrolled veterans would have been excluded. We defined CKD using the Chronic Kidney Disease Epidemiology Collaboration equation because it is more accurate than other estimating equations (such as the Modification of Diet in Renal Disease equation) in patients with normal and mildly decreased GFR. The Chronic Kidney Disease Epidemiology Collaboration equation was, however, meant to be used with serum creatinine measured by the isotope dilution mass spectrometry–traceable method, which was not ubiquitous at the time when our cohort was defined (2005–2006), and hence the accuracy of the staging of CKD in our cohort is unclear. The associations between serum sodium and mortality did not change, however, if we used the Modification of Diet in Renal Disease equation to estimate GFR in our cohort participants (data not shown). We did not collect information about hospitalizations, and therefore we cannot determine whether the mortality associated with hyponatremia or hypernatremia occurred in the context of hospitalizations. We adjusted our analyses for a significant number of potential confounders, but we cannot rule out the presence of residual confounding. We used diagnostic codes to define comorbid conditions that could act as confounders in the association of serum sodium with mortality, which may have resulted in underestimation of their prevalence. By including laboratory variables reflecting abnormal liver function and/or structure, we were able to alleviate this concern as far as the confounding imparted by liver disease, but we did not have similar data to assess the presence and/or severity of the other relevant comorbid conditions. We had relatively few patients with extremely high or extremely low serum sodium levels, and therefore our ability to characterize outcomes associated with very severe degrees of hyponatremia and hypernatremia may be limited.

Conclusions

Both hyponatremia and hypernatremia are associated with increased all-cause mortality in patients with non–dialysis-dependent CKD. This association is independent of comorbid conditions and severity of kidney disease. Abnormal serum sodium levels can be used as predictors of outcomes in this patient population and can be considered treatment targets that need to be tested in clinical trials.

Acknowledgments

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Disclosures

Dr Kalantar-Zadeh has received honoraria from Otsuka Pharmaceuticals. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

We examined associations of serum sodium levels with all-cause mortality in 655 493 US veterans with chronic kidney disease, 15% of whom suffered from congestive heart failure. During a median follow-up of 5.5 years, 169 158 patients (26%) had at least 1 episode of hyponatremia, and 45 666 (7%) had at least 1 episode of hypernatremia. Both hyponatremia and hypernatremia were associated with significantly higher short-term mortality, independent of comorbidities such as congestive heart failure or liver disease. Severity of kidney disease did not affect the association of hyponatremia with mortality, but patients with more advanced chronic kidney disease appeared to tolerate hypernatremia relatively better. These observations extend the findings of earlier studies regarding the association of hyponatremia and hypernatremia with increased mortality to a patient population with chronic kidney disease, which is known to suffer from a high burden of comorbidities and a very high cardiovascular mortality rate. Even though the results of this study cannot prove that hyponatremia and hypernatremia are causes of higher mortality, they emphasize the important predictive value of serum sodium levels in patients with chronic kidney disease and establish this patient population as a potential target for future clinical trials testing interventions to correct abnormal serum sodium levels.