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Hypernatremia in Hospitalized Patients: A Large Population-Based Study

Soraya Arzhan,[1] *Maria-Eleni Roumelioti*,[1] *Igor Litvinovich*,[1] *Cristian G. Bologa*,[2] *Orrin B. Myers*,[3] *and Mark L. Unruh*[1,4]

Key Points

- Hypernatremia has been studied less than hyponatremia and may serve as an important predictor of outcomes among hospitalized patients.
- This work addresses a key gap regarding outcomes of hypernatremia by assessing the relationship of hypernatremia to outcomes by eGFR or age groups.
- Hypernatremia was significantly associated with in-hospital mortality and discharge to a hospice or nursing facility.

Abstract

Background Hypernatremia is a frequently encountered electrolyte disorder in hospitalized patients. Controversies still exist over the relationship between hypernatremia and its outcomes in hospitalized patients. This study examines the relationship of hypernatremia to outcomes among hospitalized patients and the extent to which this relationship varies by kidney function and age.

Methods We conducted an observational study to investigate the association between hypernatremia, eGFR, and age at hospital admission and in-hospital mortality, and discharge dispositions. We analyzed the data of 1.9 million patients extracted from the Cerner Health Facts databases (2000–2018). Adjusted multinomial regression models were used to estimate the relationship of hypernatremia to outcomes of hospitalized patients.

Results Of all hospitalized patients, 3% had serum sodium (Na) >145 mEq/L at hospital admission. Incidence of in-hospital mortality was 12% and 2% in hyper- and normonatremic patients, respectively. The risk of all outcomes increased significantly for Na >155 mEq/L compared with the reference interval of Na=135–145 mEq/L. Odds ratios (95% confidence intervals) for in-hospital mortality and discharge to a hospice or nursing facility were 34.41 (30.59–38.71), 21.14 (17.53–25.5), and 12.21 (10.95–13.61), respectively (all $P<0.001$). In adjusted models, we found that the association between Na and disposition was modified by eGFR ($P<0.001$) and by age ($P<0.001$). Sensitivity analyses were performed using the eGFR equation without race as a covariate, and the inferences did not substantially change. In all hypernatremic groups, patients aged 76–89 and ≥90 had higher odds of in-hospital mortality compared with younger patients (all $P<0.001$).

Conclusions Hypernatremia was significantly associated with in-hospital mortality and discharge to a hospice or nursing facility. The risk of in-hospital mortality and other outcomes was highest among those with Na >155 mEq/L. This work demonstrates that hypernatremia is an important factor related to discharge disposition and supports the need to study whether protocolized treatment of hypernatremia improves outcomes.

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Introduction

Compared with hyponatremia, hypernatremia among hospitalized patients is a less prevalent electrolyte disorder (1–3) and its outcomes have been less studied (1). The prevalence of hypernatremia among hospitalized patients has been reported as being between 1% and 4% (1,2,4–7).

Although some studies have shown an increase in mortality in older patients with hypernatremia (8–10), others have not demonstrated this association (1,11). There have also been limitations in selecting the clinical setting, such as inpatient or outpatient (1,9,12), which has led to variations in the prevalence of hypernatremia (13–15). Additionally, little is known about

[1]Division of Nephrology, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico
[2]Division of Translational Informatics, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico
[3]Department of Family and Community Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico
[4]Medicine Service, Division of Nephrology, Raymond G. Murphy VA Medical Center, Albuquerque, New Mexico

Correspondence: Prof. Mark L. Unruh, Department of Internal Medicine, University of New Mexico School of Medicine, 1 University of New Mexico, MSC 10 5550, Albuquerque, NM 87131. Email: mlunruh@salud.unm.edu

the association between hypernatremia and discharge dispositions—specifically, discharge to a hospice or nursing facility in hospitalized patients (1). These discharge dispositions are key patient-centered outcomes. Moreover, most of the studies addressing the relationship between hypernatremia and selected outcomes of hospitalized patients were single-center studies and did not use a large diverse sample.

Impairment in kidney function and aging are predisposing factors for hypernatremia. Substantial knowledge gaps remain regarding prognostic implications of hypernatremia in hospitalized patients considering different levels of eGFR (16,17). Some studies have demonstrated that advanced CKD and lower eGFR have an apparent protective effect on hypernatremia-related mortality (18). However, controversies still exist over the outcomes of hypernatremia (17,18). The lack of population-based evidence supports the need to evaluate the relationship of hypernatremia to outcomes among hospitalized patients with various levels of kidney function.

To address the knowledge gaps regarding hypernatremia and its correlation with poor outcomes in hospitalized patients, we analyzed data on hospitalized patients from the Cerner Health Facts national database. Furthermore, we investigated the relationship between age and eGFR with outcomes among hospitalized patients.

Materials and Methods

We conducted an observational retrospective cohort study of patients hospitalized between 2000 and 2018 using the Cerner Health Facts database. The Institutional Review Board of the University of New Mexico approved this study protocol (no. 19-429). The requirement for informed consent was waived. This study was conducted in accordance with the principles of the Declaration of Helsinki.

We defined the index hospital admission as the first inpatient encounter during the study period for patients who met the following inclusion criteria: (*1*) age ≥18 years, and (*2*) first serum sodium concentration (Na) drawn within 24 hours of admission. The second inclusion criterion reduced the likelihood of the Na being affected by various treatments or iatrogenic causes after hospital admission. All laboratory results in Table 1 were taken within 24 hours of admission. The missing rate for laboratory results is reported in Supplemental Table 1.

Patient demographics, comorbidities, causes of admission, laboratory studies, and disposition status at hospital discharge were collected. The comorbidities were identified using the International Classification of Diseases, 9th and 10th editions, Clinical Modification (ICD-9 and 10 CM) codes. Laboratory tests were identified using Logical Observation Identifiers Names and Codes (LOINC) (19). The Quan-Charlson Comorbidity Index (Quan-CCI)—a comorbidity index adapted from the Charlson comorbidity index for administrative databases—was also calculated (20).

We corrected the Na by adding 1.6 mEq/L for each 100 mg/dl above 100 mg/dl of the concomitantly measured serum glucose levels (21–23). To calculate eGFR, we applied the CKD-EPI Equation (24). The primary outcomes were determined as in-hospital mortality, discharge disposition of hospitalized patients (hospice, nursing facility, or home), and length of stay. We further excluded patients with Na <135 mEq/L, those with missing eGFR and Na values, and those with discharge dispositions other than home, a hospice, or a nursing facility.

Statistical Analyses

Categorical variables were expressed as percentages, and subgroups were compared using chi-squared tests. Continuous variables were summarized as mean±SD or as medians and interquartile ranges if distributions were skewed. Patient characteristics in normonatremic (Na 135–145 mEq/L) and different hypernatremic (Na >145 mEq/L) groups (mild, moderate, severe) were compared using the Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables.

Interrelated associations between Na levels and multiple disposition outcomes were evaluated using multinomial logistic regression model analysis while accounting for the competing risks of in-hospital mortality and other dispositions. Discharge to home was used as the reference outcome. For a descriptive, graphical analysis, we used restricted cubic splines in the model to estimate probabilities for in-hospital mortality and discharge to a hospice or nursing facility across the continuous range of Na. For our primary analyses, we discretized Na into four categories: normonatremia: Na 135–145 mEq/L (reference category); mild hypernatremia: Na >145–150 mEq/L; moderate hypernatremia: Na >150–155 mEq/L; and severe hypernatremia: Na >155 mEq/L. Analysis models without and with covariates were fitted for age, sex, race/ethnicity, CKD, and Quan-CCI.

Potential effect modification of the relationship between eGFR and outcomes by Na was assessed by adding Na category×eGFR category interactions to models. We categorized eGFR levels into five different groups: eGFR ≥90 ml/min per 1.73 m^2 (reference category), eGFR 60–89 ml/min per 1.73 m^2, eGFR 30–59 ml/min per 1.73 m^2, eGFR 15–29 ml/min per 1.73 m^2, and eGFR <15 ml/min per 1.73 m^2. Sensitivity of eGFR models to race was assessed by removing race from the model.

Potential effect modification of the relationship between age and outcomes by Na was assessed by adding Na category × age category interactions to models. To evaluate interrelated associations between age and outcome of Na, we categorized age into five different groups: 18–45, 46–65 (reference category), 66–75, 76–89, and ≥90 years old. Custom linear contrasts were used to obtain odds ratios (OR) by subgroup. Sensitivity analysis of results to patient comorbidities was conducted by replacing selected covariates with Quan-CCI. Predicted values from models were obtained to visualize relationships between Na and outcomes.

Finally, we assessed the relationships between Na levels and length of hospitalization (days) among those who were discharged to home. The distribution was right skewed, so log-transformed days were used in linear models of length of stay adjusted for CKD and the Quan-CCI, taking an approach that follows our multinomial logistic regression analyses. We report regression coefficients from the models to summarize the magnitude of the effect on log-transformed days. Moreover, we tested for the differential effect of age and eGFR on these associations. All statistical analyses were performed using R v3.4 (The R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Characteristics of hospitalized patients with hyper- or normonatremia

Patient Characteristics	All Cohort, *N*=1,963,020 (100%)	Normonatremia, *N*=1,902,406 (97%)	Hypernatremia, *N*=60,614 (3%)	Standardized Mean Difference
Age, yr	58.2 (±19.2)	57.9 (±19.2)	65.5 (±18.7)	0.4
BMI, kg/m^2	29.6 (±8.1)	29.6 (±8.1)	27.8 (±8.1)	0.23
Systolic BP, mm Hg	137.8 (±26)	137.8 (±25.9)	136.7 (±29.7)	0.04
Diastolic BP, mm Hg	78 (±15.8)	78 (±15.8)	76.6 (±17.6)	0.08
eGFR, ml/min per 1.73 m^2	81.2 (±30.2)	81.7 (±30)	65.9 (±32.2)	0.51
eGFR, ml/min per 1.73 m^2				0.51
<15	40,865 (2)	37,957 (2)	2908 (5)	
15–29	76,993 (4)	70,607 (4)	6386 (11)	
30–59	359,665 (18)	341,726 (18)	17,939 (30)	
60–89	668,029 (34)	649,686 (34)	18,343 (30)	
≥90	817,468 (42)	802,430 (42)	15,038 (25)	
Sex				
Women	1,036,709 (53)	1,005,506 (53)	31,203 (52)	0.03
Race				0.17
White	1,508,639 (77)	1,465,674 (77)	42,965 (71)	
Black	283,213 (14)	271,349 (14)	11,864 (20)	
Native American	18,502 (0.9)	17,412 (0.9)	1090 (2)	
Asian	31,399 (2)	30,342 (2)	1057 (2)	
Hispanic	35202 (2)	34,173 (2)	1029 (2)	
Pacific Islander	3277 (0.2)	3232 (0.2)	45 (0.1)	
Other	82,788 (4)	80,224 (4)	2564 (4)	
Quan-CCI categories				0.29
0	716,464 (37)	699,932 (37)	16,532 (27)	
1–2 (mild)	477,687 (24)	462,726 (24)	14,961 (25)	
3–4 (moderate)	219,075 (11)	209,590 (11)	9485 (16)	
≥5 (severe)	196,545 (10)	186,407 (10)	10,138 (17)	
Unknown	353,249 (18)	343,751 (18)	9498 (16)	
Quan-CCI	1.8 (±2.3)	1.7±2.3	2.4±2.7	0.28
Comorbidities				
Hypertension	648,371 (33)	627,375 (33)	20,996 (35)	0.07
Heart failure	167,581 (9)	158,554 (8)	9027 (15)	0.22
Diabetes mellitus	336,193 (17)	321,721 (17)	14,472 (24)	0.18
Peripheral vascular disease	50,629 (3)	48,794 (3)	1835 (3)	0.03
Ischemic heart disease	339,847 (17)	326,996 (17)	12,851 (21)	0.1
CKD	113,837 (6)	107,513 (6)	6324 (10)	0.19
ESKD	21,559 (1)	20,763 (1)	796 (1)	0.02
COPD	275,385 (14)	265,806 (14)	9579 (16)	0.04
Adrenal hyperactivity	750 (0)	704 (0)	46 (0.1)	0.02
Hyperthyroidism	6475 (0.3)	6219 (0.3)	256 (0.4)	0.02
Hypothyroidism	110,031 (6)	106,415 (6)	3616 (6)	0.01
Liver disease	52,958 (3)	50,561 (3)	2397 (4)	0.07
Depression	156,180 (8)	150,750 (8)	5430 (9)	0.03
Dementia	29,178 (2)	26,180 (1)	2998 (5)	0.22
Hypercoagulopathy	5226 (0.3)	5108 (0.3)	118 (0.2)	0.02
Leading diagnosis				
Head trauma	30,341 (2)	28,591 (2)	1750 (3)	0.1
Ischemic stroke	50,237 (3)	48,243 (3)	1994 (3)	0.04
Hemorrhagic stroke	8872 (0.5)	8,293 (0.4)	579 (1)	0.07
Obstetrics/gynecologic conditions	59,733 (3)	59,528 (3)	205 (0.3)	0.24
Pneumonia	113,544 (6)	107,142 (6)	6402 (11)	0.19
Sepsis	76,692 (4)	70,196 (4)	6496 (11)	0.3
Central diabetes insipidus	716 (0)	568 (0)	148 (0.2)	0.06
Nephrogenic diabetes insipidus	120 (0)	81 (0)	39 (0.1)	0.04
Urinary tract infection	117,440 (6)	109,994 (6)	7446 (12)	0.24
Laboratory tests				
Serum albumin, g/dl	3.8 (±0.6)	3.7 (±0.6)	3.6 (±0.7)	0.24
Serum creatinine, mg/dl	1.1 (±1)	1.1 (±1)	1.4 (±1.2)	0.28
Serum potassium, mEq/L	4 (±0.6)	4 (±0.5)	4.1 (±0.7)	0.08
Glucose, mg/dl	134.8 (±73.3)	133.5 (±70.5)	172.7 (±124.4)	0.39
Hemoglobin A1C	7 (±2.1)	7 (±2.1)	7.4 (±2.4)	0.15
CO_2, meq/L	25.3 (±3.9)	25.3 (±3.8)	24.8 (±5.7)	0.12

Table 1. (Continued)

Patient Characteristics	All Cohort, N=1,963,020 (100%)	Normonatremia, N=1,902,406 (97%)	Hypernatremia, N=60,614 (3%)	Standardized Mean Difference
O_2 saturation, %	96.3 (±6.3)	96.3 (±6.2)	95.5 (±8)	0.11
Calcium, mg/dl	9.1 (±0.6)	9.1 (±0.6)	9.1 (±0.9)	0.06
Phosphorus, mg/dl	3.5 (±1.2)	3.5 (±1.1)	3.8 (±1.7)	0.2
Magnesium, mmol/L	2 (±0.4)	2 (±0.4)	2.1 (±0.5)	0.29
Chloride, mmol/L	103.6 (±4.3)	103.5 (±4.1)	108.2 (±5.9)	0.93
Serum osmolality, mOsm/L	299 (±27.5)	295.8 (±24.9)	326.9 (±32.3)	1.08
Anion gap, mmol/L	10.8 (±4.1)	10.7 (±4)	13.6 (±5.6)	0.61
Intact PTH, pg/ml	195.8 (±299.7)	195.8 (±299.4)	196.6 (±305.5)	0.003
Ferritin, ng/ml	228.5 (±359.6)	226.1 (±357.5)	293.4 (±404.8)	0.18
Iron saturation, %	21.9 (±22.3)	21.9 (±22.3)	21.8 (±20.9)	0.003
Hemoglobin, g/dl	13 (±2.2)	13 (±2.2)	12.8 (±2.5)	0.09
WBC, $>10^3$/ml	10 (±4.7)	10 (±4.6)	11.2 (±6)	0.22
Platelet count	233.4 (±83.8)	233.7 (±83.5)	225.9 (±92.4)	0.09
Serum uric acid, mmol/L	96.6 (±37.1)	95.9 (±36.3)	115.3 (±49.5)	0.45
BUN, mmol/L	18.8 (±13.7)	18.5 (±13.2)	28.7 (±22.7)	0.55
AST, IU/L	43 (±94.3)	42.4 (±92.2)	62.7 (±142.7)	0.17
ALT, IU/L	39.7 (±81.8)	39.3 (±80.8)	50 (±107.6)	0.11
Total bilirubin, μmol/L	0.7 (±0.9)	0.7 (±0.9)	0.7 (±0.8)	0.04
Serum total protein, mg/dl	6.9 (±0.8)	6.9 (±0.8)	6.8 (±1)	0.12

Data shown as mean (±SD) or n (%). Normonatremia: serum sodium (Na) 135–145 mEq/L; hypernatremia: Na>145 mEq/L. Na levels corrected by adding 1.6 mEq/L for each 100 mg/dL above 100 mg/dL of the concomitantly measured serum glucose levels. BMI, body mass index; Quan-CCI, Quan-Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; PTH, parathyroid hormone; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Results

A total of 3,896,382 patients met our inclusion criteria. The final cohort included 1,963,020 patients (Figure 1), of whom 60,614 (3%) had hypernatremia (Na >145 mEq/L) at hospital admission.

Hypernatremic patients had significantly lower eGFR and were older compared with normonatremic patients (both P<0.001). Patient characteristics are summarized in Table 1. We found statistically significant differences (P<0.001) for the comparison between hypernatremic and normonatremic patients for all patient characteristics. We also reported standardized mean differences. Some of the laboratory data in Table 1 had a high missing rate. Supplemental Table 1 details the missing rate. One reason for such a large percentage of missing laboratory values could be the time frame of blood test drawing (within 24 hours of admission). We did not include the laboratory tests taken after 24 hours of admission.

Frequencies of outcomes by hypernatremia status, eGFR category, and age group are summarized in Supplemental Table 2. The incidence of in-hospital mortality was 12% among hypernatremic patients compared with 2% in normonatremic patients. The relative frequencies of discharge to a hospice in hypernatremic and normonatremic patients were 2% and 0.7%, respectively. The relative frequencies of discharge to a nursing facility in hypernatremic and normonatremic patients were 26% and 11%, respectively.

Serum Sodium and the Outcomes

The crude probability of in-hospital mortality corresponding to Na was lowest between 135 and 145 mEq/L and continued to increase above this range (Figure 2). The probability of discharge to a hospice demonstrated a similar pattern, albeit less profound. The estimated probability of discharge to a nursing facility at lower Na levels appeared to show an up-trending pattern but started to decrease at Na above 155 mEq/L. The probability of discharge to home increased to an Na between 135 and 145 mEq/L, then decreased above this range, and again started to increase slightly above 155 mEq/L. Discharge to a hospice showed a slight increase at Na above 150 mEq/L and then remained steady (Figure 2).

For the Na categories, in the adjusted multinomial logistic regression analysis, we found that the OR for in-hospital mortality significantly increased as Na increased relative to normonatremia interval (P<0.001). We observed similar trends for discharge to a hospice or nursing facility (Table 2).

There was a significant association between Na categories and length of hospitalization (P<0.001). These overall relationships are shown in Table 4. For those discharged to their homes, median length of stay was 2.94 days. Length of stay was shortest for normonatremia.

eGFR and the Outcomes

The main test for interaction between eGFR levels and Na categories demonstrated a significant association between these two factors and in-hospital mortality (P<0.001). Generally, crude ORs of in-hospital mortality increased as Na increased relative to the 135–145 mEq/L interval and as eGFR decreased below 90 ml/min per 1.73 m^2. This was also true for discharge to a hospice or nursing facility (Figure 3, Table 2).

The adjusted model showed that the ORs of in-hospital mortality significantly increased as Na rose above 145 mEq/L and eGFR decreased below 90 ml/min per 1.73 m^2

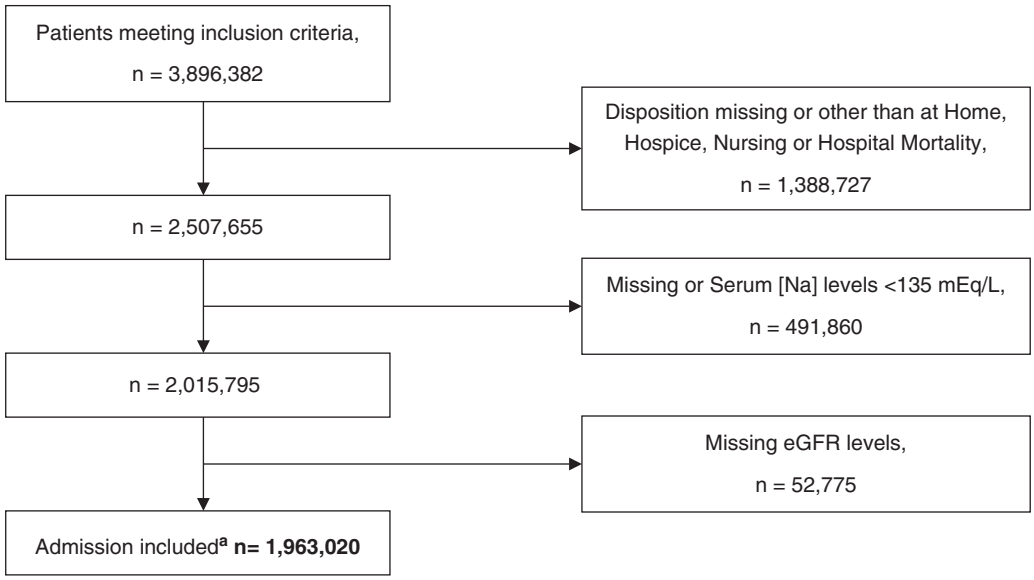

Figure 1. | **Flow chart of the sample selection process.** [a]The final cohort available for analysis. Serum sodium levels were corrected by adding 1.6 mEq/L for each 100 mg/dl above 100 mg/dl of the concomitantly measured serum glucose levels.

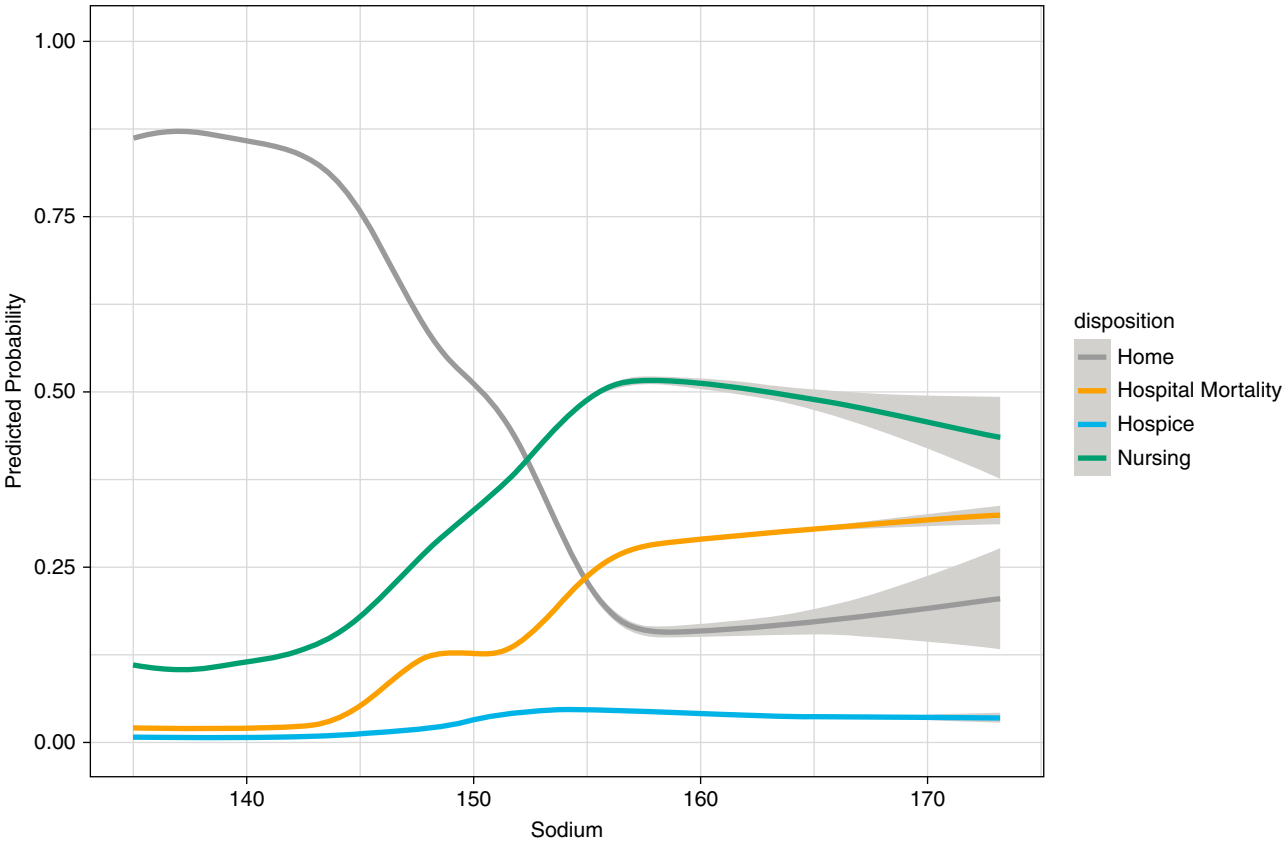

Figure 2. | **Restricted cubic splines of the crude probability of in-hospital mortality, discharge to a hospice, discharge to home, and discharge to a nursing facility as a function of serum sodium levels at hospital admission.** These estimated probabilities were derived from a multinomial logistic regression model. Serum sodium levels were corrected by adding 1.6 mEq/L for each 100 mg/dl above 100 mg/dl of the concomitantly measured serum glucose levels.

Table 2. Relationships between serum sodium levels stratified by eGFR levels and outcomes

Natremia Status[a] at Hospital Admission	In-Hospital Mortality Adjusted[b] Odds Ratio (95% Confidence Interval)	Discharge to a Hospice Adjusted[b] Odds Ratio (95% Confidence Interval)	Discharge to a Nursing Facility Adjusted[b] Odds Ratio (95% Confidence Interval)
Normonatremia	1	1	1
Hypernatremia			
Mild	4.8 (4.6 to 4.9)	2.1 (1.9 to 2.3)	2.1 (2 to 2.1)
Moderate	22.6 (20.9 to 24.4)	10.41 (9 to 12)	6.97 (6.5 to 7.5)
Severe	34.4 (30.6 to 38.7)	21.1 (17.5 to 25.5)	12.2 (11 to 13.6)
eGFR level, ml/min per 1.73 m^2			
Normonatremia			
<15	5.4 (5.1 to 5.6)	0.8 (0.7 to 0.9)	1.4 (1.3 to 1.4)
15–29	5.5 (5.3 to 5.8)	1 (0.9 to 1.1)	1.4 (1.3 to 1.4)
30–59	2.3 (2.2 to 2.4)	0.5 (0.5 to 0.5)	1 (1 to 1)
60–89	1.5 (1.4 to 1.5)	0.6 (0.5 to 0.6)	0.9 (0.9 to 1)
≥90	1	1	1
Mild hypernatremia			
<15	14 (12.4 to 16)	0.1 (0.1 to 0.3)	2.7 (1.9 to 2.4)
15–29	19.2 (17.6 to 21.1)	0.4 (0.3 to 0.5)	4 (3.7 to 4.3)
30–59	11.9 (11.2 to 12.7)	2 (1.7 to 2.1)	2.5 (2.4 to 2.6)
60–89	6 (5.5 to 6.4)	1.7 (1.5 to 1.9)	1.6 (1.6 to 1.7)
≥90	8.1 (7.4 to 8.7)	1.6 (1.3 to 2)	2.2 (2 to 2.3)
Moderate hypernatremia			
<15	54.6 (42.5 to 70.2)	0.17 (0 to 1.9)	6.6 (5.2 to 8.4)
15–29	69.3 (55.8 to 86)	3.91 (2.3 to 6.6)	16.5 (13.6 to 20.1)
30–59	22 (19 to 25.4)	5 (3.9 to 6.4)	5.4 (4.8 to 6.1)
60–89	36.6 (30.6 to 43.9)	36.4 (29.5 to 44.8)	11.6 (10 to 13.5)
≥90	15.5 (12.5 to 19.3)	0 (NA)	4 (3.3 to 4.8)
Severe hypernatremia			
<15	656.5 (328.7 to 1311.1)	4.2 (0.5 to 34.2)	124.3 (62.8 to 246.6)
15–29	849 (67.2 to 107.2)	9.1 (6.1 to 13.7)	10.7 (8.5 to 13.4)
30–59	89.6 (73.4 to 109.3)	12.2 (8.5 to 17.4)	15.2 (12.6 to 18.4)
60–89	300.5 (215.1 to 419.9)	52.2 (32.2 to 84.7)	33.6 (23.9 to 47.3)
≥90	30 (19.9 to 45.4)	34.6 (19.6 to 61)	10 (7 to 14.2)

Normonatremia: Na >135–145 mEq/L; hypernatremia: Na >145 mEq/L (mild hypernatremia: Na >145–150 mEq/L; moderate hypernatremia: Na >150–155 mEq/L; severe hypernatremia: Na >155 mEq/L). Na, serum sodium level; OR, odds ratio.
[a]Na levels corrected by adding 1.6 mEq/L for each 100 mg/dl above 100 mg/dl of the concomitantly measured serum glucose levels.
[b]The adjusted ORs were derived from a multinomial logistic regression model adjusted for age, sex, race, CKD, and the Quan-CCI (all $P<0.001$).

compared with the reference Na interval and eGFR >90 ml/min per 1.73 m^2 ($P<0.001$). Different trends were observed for each Na category (Table 2, Figure 3).

In the unadjusted model, discharge to a hospice showed the same trend as for in-hospital mortality. The highest ORs in normonatremia and mild hypernatremia were observed with an eGFR of 15–29 and in moderate and severe hypernatremia with an eGFR <15 ml/min per 1.73 m^2. In all Na categories, the lowest ORs of discharge to a hospice were observed with an eGFR ≥90 ml/min per 1.73 m^2 (Figure 3). Adjusted model showed different patterns in each Na category (Figure 3, Table 2).

With regard to discharge to a nursing facility, the unadjusted model showed that in normonatremia and mild and moderate hypernatremia, the highest ORs were observed with an eGFR of 15–29 ml/min per 1.73 m^2, whereas the lowest ORs were observed with an eGFR ≥90 ml/min per 1.73 m^2 (Figure 3).

Length of stay showed an up-trending pattern as function of eGFR in all Na categories, with the two exceptions of patients with an eGFR of 60–89 ml/min per 1.73 m^2in normonatremia and mild hypernatremia, who had the shortest length of stay. For moderate and severe hypernatremia, the shortest length of stay was observed for eGFRs ≥90 ml/min per 1.73 m^2. The longest length of stay was observed for those with an eGFR <15 ml/min per 1.73 m^2 in all Na categories (Figure 4, Table 4).

The sensitivity analysis was performed using the eGFR equation without race as a covariate. The inferences did not substantially change after removing race from our eGFR model (Figure 5).

Age and the Outcomes

In all Na categories, we found a significant association between age and outcomes (all $P<0.001$). The crude results showed that older age groups had higher ORs of in-hospital mortality and discharge to a hospice or nursing facility in all Na categories (Figure 6). In the adjusted model, in each Na category, the relationship between age

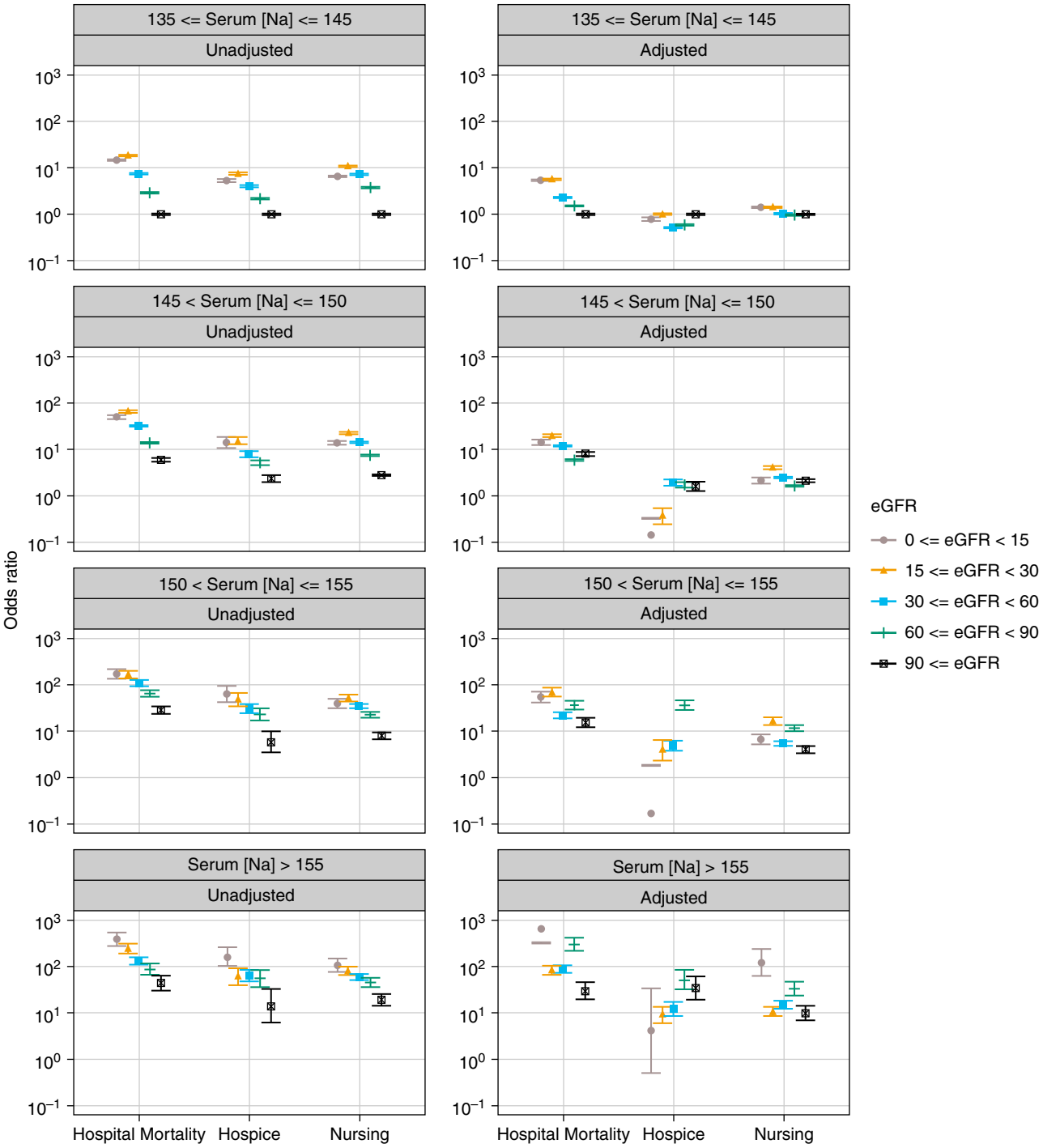

Figure 3. | Plot of odds ratios (95% CI) for in-hospital mortality and discharge to a hospice or nursing facility associated with different intervals of serum sodium levels (mEq/L) at hospital admission stratified by eGFR levels. The odds rations were derived from multinomial logistic regression models adjusted for age, sex, race, and the selected comorbidities and reasons for hospitalization. Discharge to home and serum sodium levels of 135–145 mEq/L served as the reference. Serum sodium levels were corrected by adding 1.6 mEq/L for each 100 mg/dl increase above 100 mg/dl of the concomitantly measured serum glucose levels. Error bars indicated 95% CI. 95% CI, 95% confidence interval.

group and outcomes was largely similar to those in the crude models, with an increased risk of mortality and discharge to a hospice or nursing facility with older age (Figure 6, Table 3).

Across all Na categories, older age was associated with greater length of stay (Figure 4, Table 4).

Discussion

In this cohort study composed from a data warehouse for a large number of hospitals, we found that 3% of hospitalized patients had hypernatremia (Na >145 mEq/L). We demonstrated that in-hospital mortality was associated with higher levels of hypernatremia. The observation that

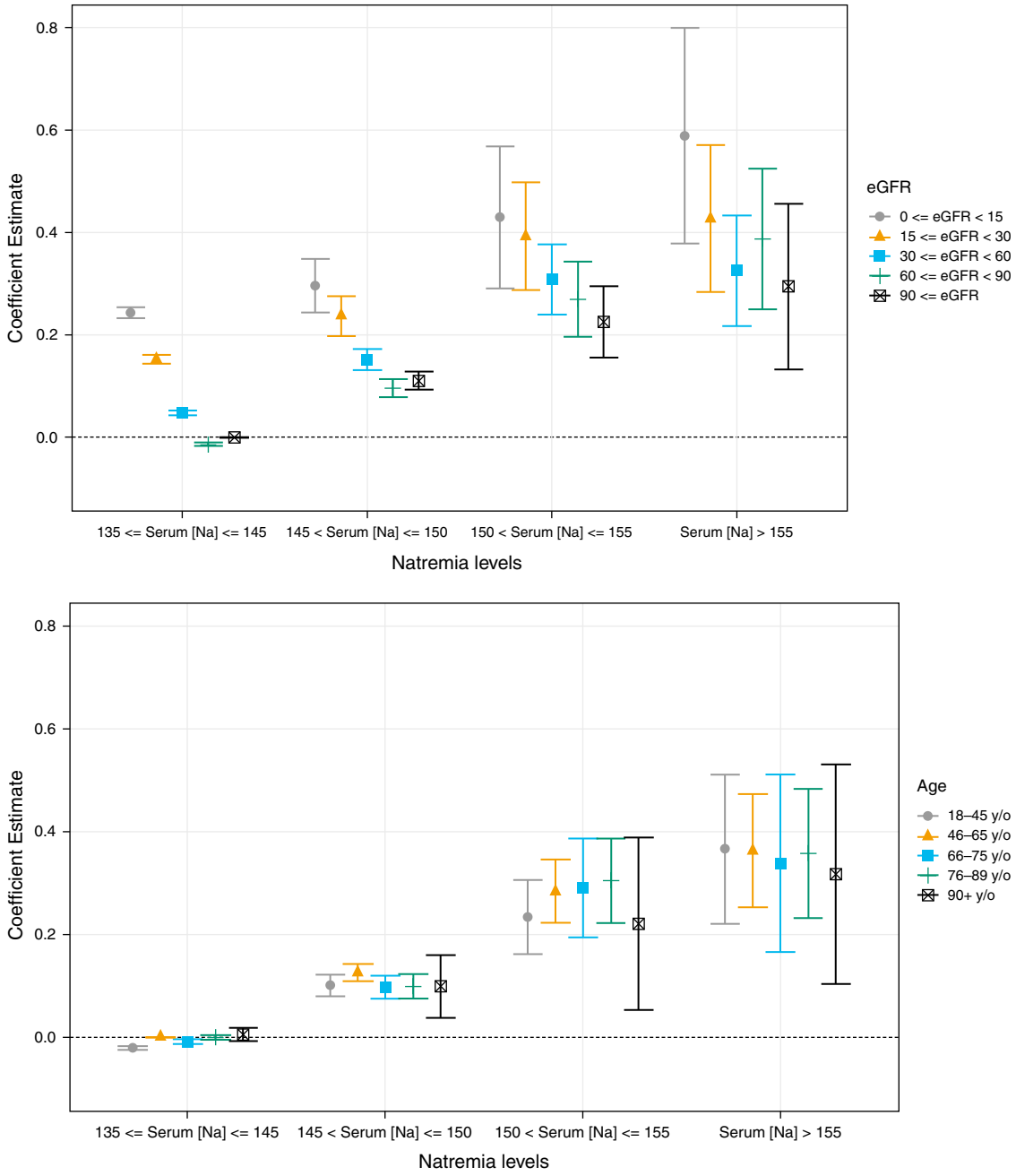

Figure 4. | **Plot of relationships between serum sodium levels at hospital admission and length of hospitalization among those discharged to home stratified by eGFR/age.**

hypernatremia was associated with a higher mortality rate (12%) was found to be independent of observed chronic disease. We also noticed a significant association between hypernatremia and increased odds of discharge to a hospice or nursing facility.

This report confirms previous observations relating hypernatremia to mortality in a large and diverse sample and hospitalized patients and extends previous research by examining discharge disposition. Tsipotis *et al.* (1) conducted a cohort study of 19,072 unselected hospitalized adults to investigate the crude relationship between clinical outcomes and community-acquired hypernatremia, defined as Na >142 mEq/L, demonstrating a relationship between hypernatremia and mortality among these patients. In addition, Tsipotis *et al.*'s study revealed a decrement in ORs of in-hospital mortality for Na >157 mEq/L in both the unadjusted and adjusted models (1). Our findings in terms of increment of in-hospital mortality along with the increase in the severity of hypernatremia are similar to the findings by Jin Jung *et al.* (3), who studied 79,998 patients, including 180 patients with hypernatremia, admitted to an urban tertiary care hospital in Korea. However, our conclusion is in contrast with the findings of Bataille *et al.* (25), who did not find a statistical relationship between the level of hypernatremia and mortality. In

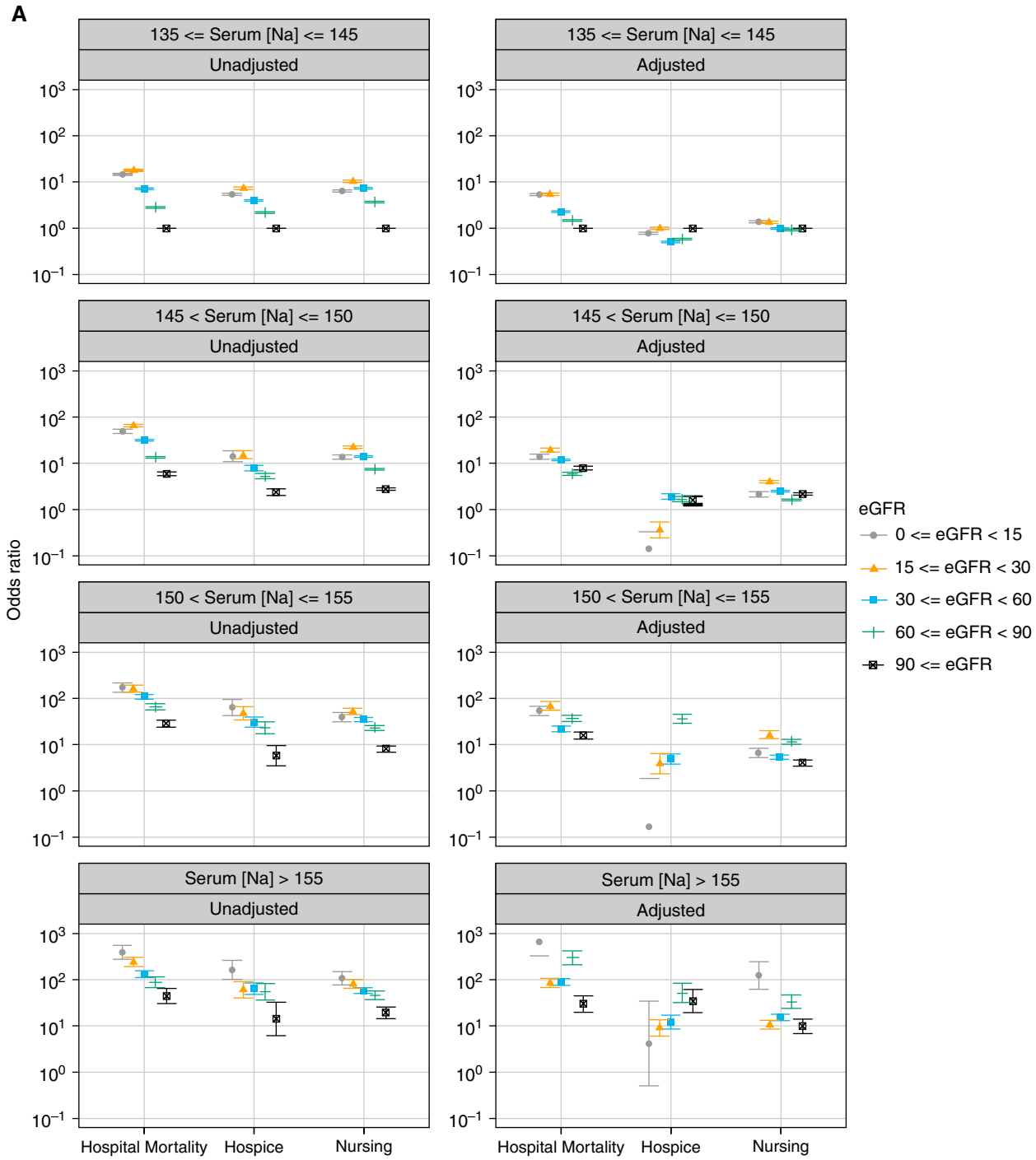

Figure 5. | **Plot of the relative risk ratios (95% CI) for in-hospital mortality and discharge to a hospice or nursing facility associated with different intervals of serum sodium levels (mEq/L) at hospital admission stratified by eGFR levels with developing race/ethnicity in the model.** (A) Before removing race from model. (B) After removing race from model. The sensitivity analyses were performed using the eGFR equation without a race covariate.

line with our results, previous studies by Hu *et al.* (13,26) in China and Funk *et al.* (14) in Austria demonstrated that there are independent associations between hypernatremia and the risk of in-hospital mortality, even after adjusting for potential confounding factors.

The results of this report revealed that eGFR was significantly lower in hypernatremic patients compared with normonatremic patients. With regard to the different levels of hypernatremia stratified by eGFR levels, the general pattern showed that by increasing Na and decreasing eGFR level, the risk of outcomes increased. Tsipotis *et al.* (1) showed that the highest ORs of in-hospital mortality in patients with hypernatremia on admission belonged to eGFR 30–59 ml/min per 1.73 m^2. Han *et al.* (27) investigated

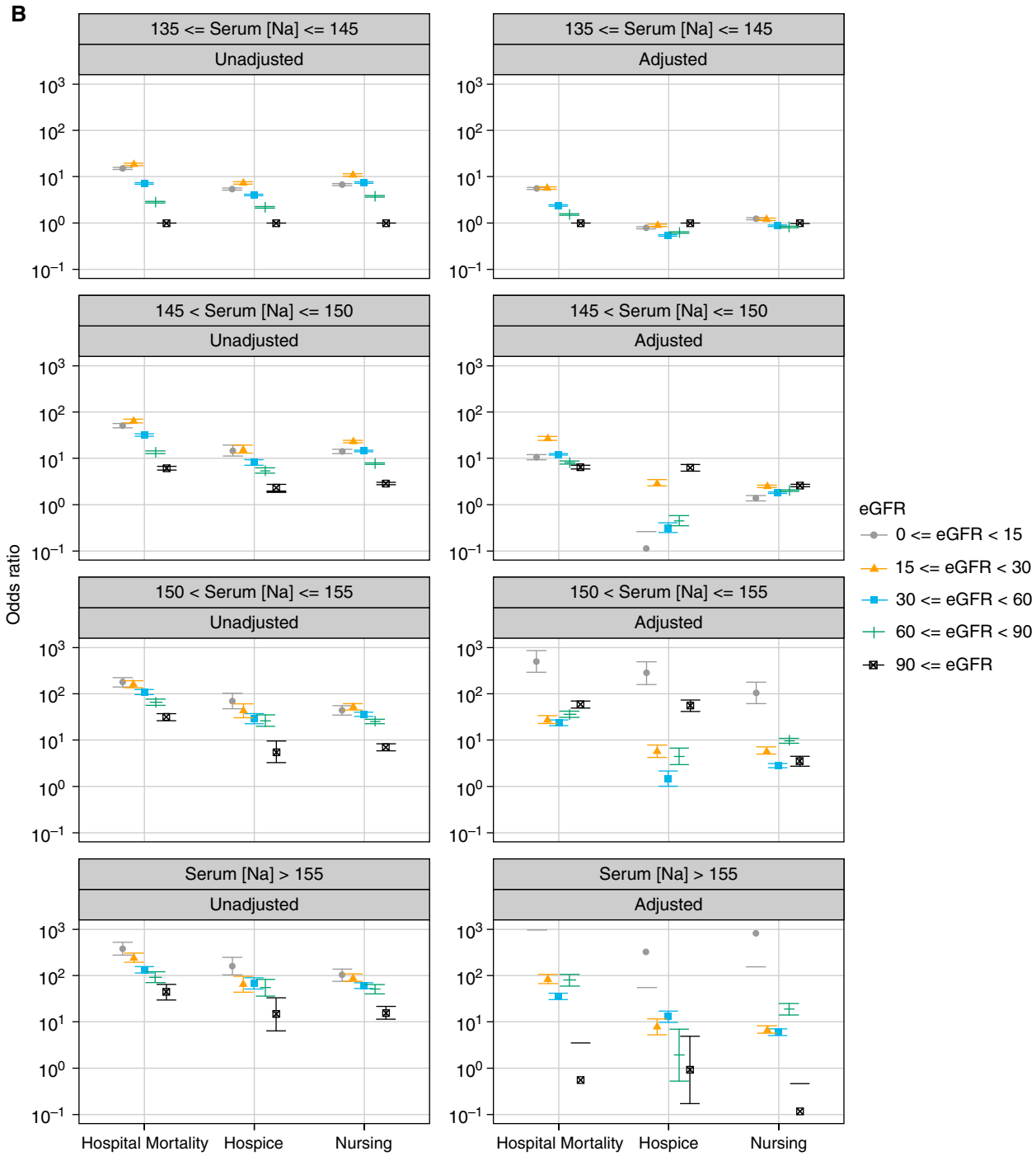

Figure 5. | (*Continued*)

associations between Na and CKD and observed that hypernatremia in patients with CKD in the outpatient setting were short- and long-term risk factors for mortality. Chiu *et al*. (28) reported no significant association with hypernatremia and mortality in an outpatient population with CKD. Sun *et al*. also found that the stage of CKD did not appear to affect the mortality associated with hypernatremia (29). In contrast, Kovesdy *et al*. (18) demonstrated that more advanced CKD displayed a relatively lower mortality associated with hypernatremia compared with patients with less severe stages of CKD. These differences can result from the nature of our inpatient population, who suffer from more acute conditions.

Patients with hypernatremia were older than normonatremic patients (65.51±18.70 years and 57.93±19.18 years, respectively; $P<0.001$). The results of our analyses generally revealed an up-trending pattern of ORs for all outcomes in higher Na and older age groups. In accordance

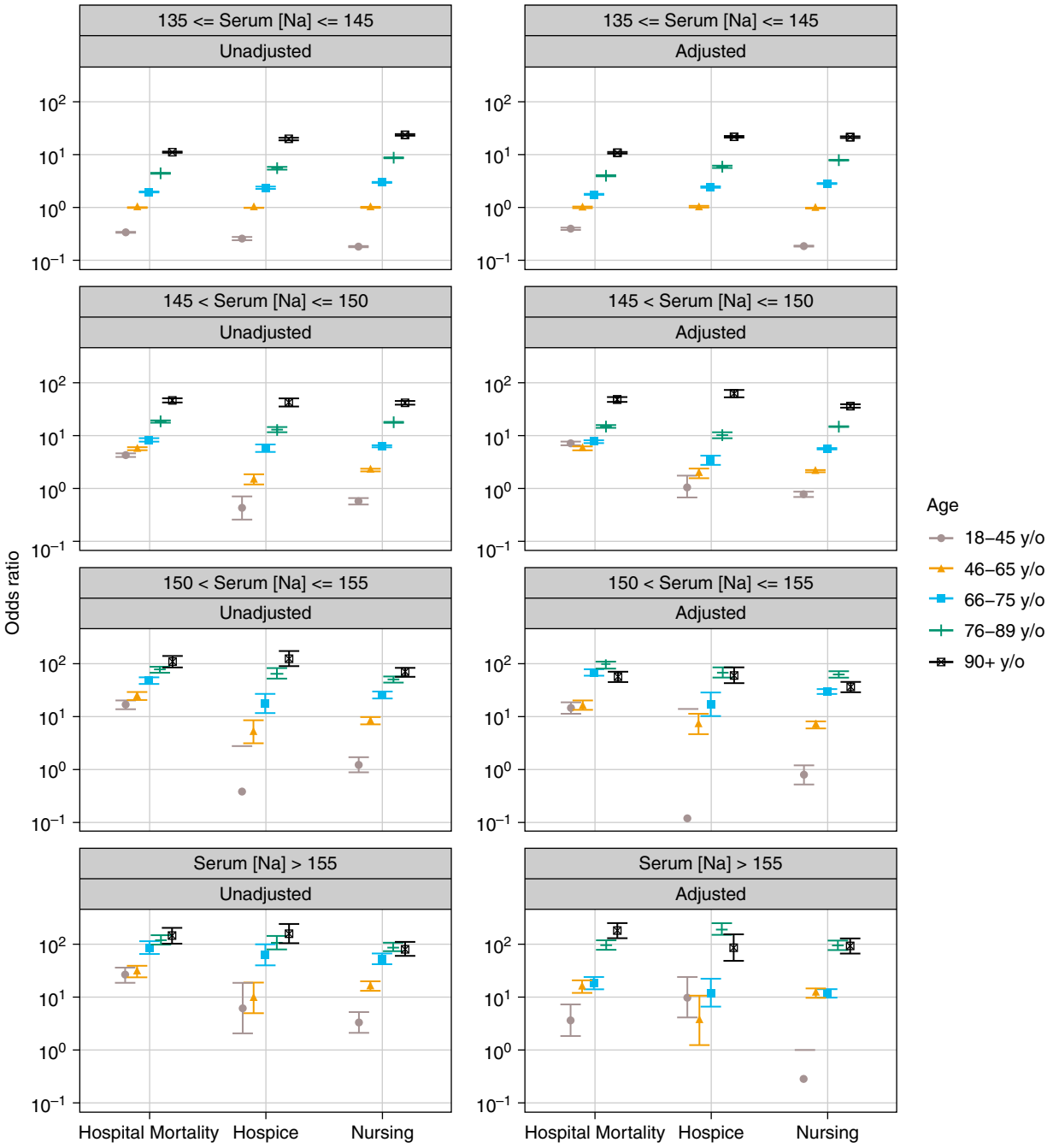

Figure 6. | **Plot of the relative risk ratios (95% CI) for in-hospital mortality and discharge to a hospice or nursing facility associated with different intervals of serum sodium levels (mEq/L) at hospital admission stratified by age groups**.

with other studies (30–32), our study demonstrated that the odds of in-hospital mortality in all Na groups increased with aging. This can be attributed to the fact that elderly patients with hypernatremia present with fewer symptoms of hypernatremia compared with younger patients. A delay in diagnosis and treatment of hypernatremia can carry higher rates of mortality and poorer outcomes. Moreover, age-related impairment in organ function, decreased thirst drive, impaired urinary concentrating ability, reduced total body water, chronic illnesses, and disabilities predispose older adults to dehydration and hypernatremia (30). Our results also demonstrated that older patients with higher Na had greater ORs of discharge to a nursing facility.

Our study has several strengths. First, to the best of our knowledge, the association between hypernatremia and its outcomes (*i.e.*, in-hospital mortality and discharge dispositions) has not been studied systematically at a large population level. Additionally, our study addressed a key gap in knowledge because we investigated the relationship between different levels of hypernatremia and selected outcomes through stratifying by eGFR level and age group in a large diverse population. Our study also has some

Table 3. Relationships between serum sodium levels, stratified by age, and outcomes

Natremia Status[a] at Hospital Admission	Age Group, yr	In-Hospital Mortality Adjusted[b] Odds Ratio (95% Confidence Interval)	Discharge to a Hospice Adjusted[b] Odds Ratio (95% Confidence Interval)	Discharge to a Nursing Facility Adjusted[b] Odds Ratio (95% Confidence Interval)
Normonatremia	18–45	0.4 (0.4 to 0.4)	0 (N/A)	0.2 (0.2 to 0.2)
	46–65	1	1	1
	66–75	1.8 (1.76 to 1.9)	2.4 (2.3 to 2.6)	2.9 (2.8 to 2.9)
	76–89	4 (3.9 to 4.1)	5.9 (5.6 to 6.3)	8.1 (8 to 8.2)
	≥90	11 (10.6 to 11.5)	21.8 (20.5 to 23.3)	21.7 (21.2 to 22.1)
Mild hypernatremia	18–45	7.1 (6.5 to 7.8)	1.1 (0.7 to 1.7)	0.8 (0.7 to 0.9)
	46–65	5.7 (5.4 to 6.1)	2 (1.6 to 2.4)	2.1 (2 to 2.2)
	66–75	7.7 (7.2 to 8.3)	3.4 (2.8 to 4.2)	5.7 (5.4 to 6)
	76–89	14.9 (14.1 to 15.8)	10.3 (9 to 11.7)	15 (14.4 to 15.5)
	≥90	48.3 (43.5 to 53.6)	62.8 (53.7 to 73.4)	36.2 (33.3 to 39.3)
Moderate hypernatremia	18–45	14.8 (12 to 18.2)	0.1 (0 to 14.1)	0.8 (0.5 to 1.2)
	46–65	16.1 (13.8 to 18.8)	7.2 (4.7 to 11.2)	7 (6.1 to 8)
	66–75	66.7 (55.8 to 79.8)	16.9 (10.1 to 28.4)	29.5 (25.1 to 34.7)
	76–89	96.2 (83.3 to 111.1)	68.3 (53.4 to 87.4)	61.3 (54.1 to 69.5)
	≥90	57.3 (45.7 to 71.7)	59.3 (41.7 to 84.5)	36.5 (30.3 to 43.9)
Severe hypernatremia	18–45	3.7 (1.9 to 7.3)	10.2 (4.2 to 24.6)	0.3 (0.1 to 1)
	46–65	16.2 (12.3 to 21.4)	3.7 (1.3 to 10.8)	12.7 (9.9 to 14.9)
	66–75	18.5 (14.2 to 24.2)	12.3 (6.8 to 22.3)	11.7 (9.7 to 14.7)
	76–89	98.4 (79.4 to 122)	194.8 (150 to 252.9)	99.6 (83.1 to 119.3)
	≥90	181.7 (130.6 to 252.7)	87.5 (49.1 to 156.1)	94 (69.4 to 127.3)

Normonatremia: Na >135–145 mEq/L; hypernatremia: Na >145 mEq/L (mild hypernatremia: Na >145–150 mEq/L; moderate hypernatremia: Na >150–155 mEq/L; severe hypernatremia: Na >155 mEq/L). CI, confidence interval; Na, serum sodium level; OR, odds ratio.

[a]Na levels corrected by adding 1.6 mEq/L for each 100 mg/dl above 100 mg/dl of the concomitantly measured serum glucose levels.

[b]The adjusted ORs were derived from a multinomial logistic regression model adjusted for age, sex, race, CKD, and the Quan-CCI (all $P<0.001$).

limitations. First, we were unable to include a disease severity scoring modality such as the Acute Physiology and Chronic Health Evaluation or Sequential Organ Failure Assessment. However, this study included the identification of the comorbidities and reason for hospitalization using ICD-9 and -10 codes to account for the presence of medical conditions, and we were able to adjust for the Quan-CCI, which has been widely used to predict survival of hospitalized patients and predicts in-hospital mortality in critically ill patients well (20). Second, we did not have information about outpatient medication that might predispose them to hypernatremia. Because of the observational nature of our study, we cannot preclude the possibility of residual confounding and cannot draw any causal interpretations from our results. However, conducting large randomized controlled trails to overcome this limitation may not be easily practicable. Furthermore, we did not account for AKI in this report, and this is a limitation. However, the aim of our study was to investigate the relationships between hypernatremia and outcomes considering the level of kidney function (based on eGFR). Nevertheless, these limitations should not undermine the importance of the finding that hypernatremia, regardless of the cause, is significantly associated with increased in-hospital mortality.

Hypernatremia is relatively common among hospitalized patients, and regardless of the cause, it is significantly related to mortality and discharge to a nursing facility or hospice. Our study underscores the need for more awareness about hypernatremia and emphasizes the need for addressing water depletion among patients presenting to hospital with hypernatremia. We found that all levels of hypernatremia independently increased the odds of in-hospital mortality and discharge to a hospice or nursing facility. The prognosis for hypernatremic patients may improve if hypernatremia is corrected properly and in a timely manner. Further studies are needed to evaluate and develop the best treatment and management of hypernatremia in order to decrease the rate of adverse outcomes considering the level of kidney function and age. Duration of hypernatremia and its effect on poor outcomes is another issue that merits further study.

Disclosures

M.L. Unruh reports consultancy for Cara Therapeutics to chair of Data Monitoring Committee; a consulting agreement between Cara and the University of New Mexico; research funding from Dialysis Clinic, Inc.; and honoraria from the American Society of Nephrology, NKF, and the Renal Research Institute related to lectures. M.-E. Roumelioti reports participating in Dialysis Clinic, Inc., quality meetings and receiving financial support. All remaining authors have nothing to disclose.

Table 4. Relationships between serum sodium levels at hospital admission and length of hospitalization among those discharged to home (stratified by eGFR/age)

Natremia Status[a] at Hospital Admission	Length of Stay among those Discharged to Home (*N*=1,664,500)	
	Median, Interquartile Range	Coefficient and 95% Confidence Interval
Normonatremia	2.9 (1.9–4.6)	Reference
Hypernatremia		
Mild	3.3 (2.1–5.4)	0.1 (0.1 to 0.1)
Moderate	4.1 (2.7–7.0)	0.3 (0.2 to 0.3)
Severe	4.7 (3–7.7)	0.4 (0.3 to 0.4)
eGFR level, ml/min per 1.73 m^2		
Normonatremia		
<15	4 (2.6–6.5)	0.2 (0.2 to 0.3)
15–29	3.5 (2.2–5.6)	0.1 (0.1 to 0.1)
30–59	3 (2–4.9)	0.05 (0.04 to 0.05)
60–89	2.9 (1.9–4.4)	−0.01 (-0.02 to 0.01)
≥90	2.9 (1.9–4.4)	Reference
Mild hypernatremia		
<15	4.3 (2.8–6.9)	0.3 (0.2 to 0.3)
15–29	4 (2.6–6.1)	0.2 (0.2 to 0.3)
30–59	3.4 (2.2–5.6)	0.1 (0.1 to 0.2)
60–89	3.2 (2.2–5.2)	0.1 (0.1 to 0.1)
≥90	3.2 (2–5.3)	0.1 (0.1 to 0.1)
Moderate hypernatremia		
<15	5.4 (3.7–9.1)	0.4 (0.3 to 0.6)
15–29	5 (3.3–7.7)	0.4 (0.3 to 0.5)
30–59	4.2 (2.8–7.0)	0.3 (0.2 to 0.4)
60–89	4 (2.5–6.9)	0.3 (0.2 to 0.3)
≥90	3.8 (2.2–6.3)	0.2 (0.2 to 0.3)
Severe hypernatremia		
<15	7 (4.9–12.4)	0.6 (0.4 to 0.8)
15–29	5 (3.7–7.5)	0.4 (0.3 to 0.6)
30–59	4.3 (2.9–6.9)	0.3 (0.2 to 0.4)
60–89	4.5 (3–8.5)	0.4 (0.3 to 0.5)
≥90	4 (2.7–6.8)	0.3 (0.1 to 0.5)
Age group, yr		
Normonatremia		
18–45	2.9 (1.9–4.4)	0 (N/A)
46–65	3 (1.9–4.7)	Reference
66–75	3 (1.9–4.7)	−0 (N/A)
76–89	3 (2–4.7)	0 (N/A)[b]
≥90	3 (2–4.6)	0 (N/A)[c]
Mild hypernatremia		
18–45	3.1 (2–5.3)	0.1 (0.9 to 0.1)
46–65	3.4 (2.1–5.7)	0.1 (0.1 to 0.1)
66–75	3.3 (2.1–5.4)	0.1 (0.1 to 0.1)
76–89	3.3 (2.1–5.3)	0.1 (0.1 to 0.1)
≥90	3.3 (2.1–5.2)	0.1 (0 to 0.2)
Moderate hypernatremia		
18–45	3.8 (2.4–6.1)	0.2 (0.2 to 0.3)
46–65	4.2 (2.7–7.2)	0.3 (0.2 to 0.3)
66–75	4.4 (2.5–7.9)	0.3 (0.2 to 0.4)
76–89	4.7 (3–6.9)	0.3 (0.2 to 0.4)
≥90	3.9 (2.8–6.1)	0.2 (0.1 to 0.4)[d]
Severe hypernatremia		
18–45	4.3 (3.2–7.8)	0.4 (0.2 to 0.5)
46–65	4.7 (2.8–7.9)	0.4 (0.2 to 0.5)
66–75	4.4 (2.9–7.8)	0.3 (0.8 to 0.5)
76–89	4.8 (3.4–7.1)	0.4 (0.2 to 0.5)
≥90	5.8 (3–6.7)	0.3 (0.1 to 0.5)

Normonatremia: Na >135–145 mEq/L; hypernatremia: Na >145 mEq/L (mild hypernatremia: Na >145–150 mEq/L; moderate hypernatremia: Na >150–155 mEq/L; severe hypernatremia: Na >155 mEq/L). IQR, interquartile range.
[a]Na levels corrected by adding 1.6 mEq/L for each 100 mg/dl above 100 mg/dl of the concomitantly measured serum glucose levels.
P<0.01 for all categories, except [b]*P*=0.87, [c]*P*=0.43, and [d]*P*=0.01.

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Author Contributions

S. Arzhan was responsible for the investigation and project administration and wrote the original draft of the manuscript; S. Arzhan, C.G. Bologa, I. Litvinovich, and O.B. Myers were responsible for data curation; S. Arzhan, O.B. Myers, M.-E. Roumelioti, and M.L. Unruh were responsible for conceptualization; S. Arzhan and M.L. Unruh were responsible for funding acquisition, resources, and visualization; C.G. Bologa, I. Litvinovich, and O.B. Myers were responsible for software; C.G. Bologa, I. Litvinovich, O.B. Myers, M.-E. Roumelioti, and M.L. Unruh were responsible for validation; C.G. Bologa and O.B. Myers were responsible for the formal analysis; O.B. Myers and M.L. Unruh were responsible for supervision; and all authors were responsible for the methodology and reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at https://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000702022/-/DCSupplemental

Supplemental Table 1. Missing laboratory data profile.

Supplemental Table 2. Profile of hospitalized patients with and without hypernatremia.

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