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LOW SERUM SODIUM LEVELS AT HOSPITAL ADMISSION: OUTCOMES AMONG 2.3 MILLION HOSPITALIZED PATIENTS

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BY

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ABSTRACT

Background: Hyponatremia is the most common electrolyte disorder among hospitalized patients. Controversies still exist over the relationship between hyponatremia and outcomes of hospitalized patients.

Methods: To analyze the association of low serum sodium levels at hospital admission with in-hospital mortality and patient disposition and to compare the distribution of the risk of death associated with hyponatremia across the lifespan of hospitalized patients, we conducted an observational study of 2.3 million patients using data extracted from the Cerner Health Facts database between 2000 and 2014. Logistic regression models were used in the analyses.

Results: 14.4% of hospitalized patients had serum sodium levels [Na] <135 mEq/L. In adjusted multinomial logistic regression analysis, we found that the risk of in-hospital mortality significantly increases for [Na] levels < 135 or ≥143 to ≤145 mEq/L compared to the reference interval of 140 to <143 mEq/L. We observed similar trends for the relationship between [Na] levels and discharge to hospice or to a nursing facility. We demonstrated that younger age groups (18 to

<45, 45 to <65) had a higher risk of in-hospital mortality compared to older age groups (65 to <75, ≥75) for [Na] levels <130 mEq/L or 143 to ≤145 mEq/L.

Conclusions: Hyponatremia is common among hospitalized patients and is independently associated with in-hospital mortality, discharge to hospice or to a nursing facility. The risk of death and other outcomes was more evident for [Na] <135 mEq/L. The mortality associated with low [Na] was significantly higher in younger versus older patients.

Keywords: Hyponatremia; Hospitalization; Outcomes; In-hospital mortality; Discharge disposition; Age

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CHAPTER 1

INTRODUCTION

Hyponatremia is the most frequent electrolyte disorder among hospitalized patients (1, 2). It is associated with poor outcomes such as increased mortality, prolonged length of stay in the hospital, and increased healthcare costs (3-11). In a retrospective study by Nzerue et al that included 5994 hospitalized patients with hyponatremia between 1997 and 2001, for the 168 patients with severe hyponatremia defined as serum sodium [Na] levels < 115 mEq/L, the mortality rate was 20%. They also found that severe hyponatremia was significantly associated with in-hospital mortality (3). In another retrospective study by Clayton et al conducted over a period of six months, 108 hospitalized patients with hyponatremia defined as serum [Na] levels ≤ 125 mEq/L, the in-hospital mortality rate was also 20% (4). Moreover, in a prospective case control study by Gill et al performed over a six-month period that included 104 hospitalized patients with severe hyponatremia (<125 mEq/L) and 104 randomly chosen patients with normonatremia (>135 mEq/L), the mortality rate was 27% in the severe hyponatremia group compared to 9% in the normonatremia group. They found that severe hyponatremia in hospitalized patients is associated with significantly increased mortality and prolonged length of stay in the hospital (5). Another retrospective cohort study by Zilberberg et al that included 198,281 hospitalized from 39 US hospitals between 2004 and 2005, hyponatremia defined as sodium <135 mEq/L was independently associated with increased in-hospital mortality, increased need for ICU admission, increased length of stay in the hospital, and

increased hospital costs compared to those without hyponatremia (6). In a meta-analysis by Corona et al, that included 46 studies, hyponatremia was significantly associated with prolonged length of stay in the hospital and increased risk of readmission after hospitalization. They also showed that hyponatremia contributed to approximately $3,000 higher in hospital costs compared to patients without hyponatremia (10) In another study by Amin et al, hyponatremia was associated with an 8.2% increase in the total hospital admission costs and a 15% increase in the 30 day hospital readmission rates (11).

Mechanism of the Association Between Hyponatremia and Mortality:

Different mechanisms have been proposed to explain the association between hyponatremia and mortality (12, 13). These mechanisms explain whether hyponatremia is a direct cause of mortality or the underlying severe disease is responsible for the mortality while hyponatremia is only a complication of this severe disease. The first mechanism suggests that acute hyponatremia, if untreated appropriately, will cause severe brain edema, encephalopathy, and brain herniation, which leads to death. Although is it very critical to recognize and treat patients with acute hyponatremia, this mechanism does not fully explain the relation between hyponatremia and mortality. The second mechanism suggests that hyponatremia is only a sign of underlying serious medical conditions. The high mortality rates in patients with advanced heart failure or cirrhosis who have hyponatremia can be explained by this mechanism. In the third mechanism, it is postulated that hyponatremia has an additive effect on the increase in mortality.

Comorbid conditions can cause increased mortality alone and the development of hyponatremia. Hyponatremia on the other hand, can further increase the risk of mortality independent of the underlying disease. This mechanism can be justified by the fact that multiple studies found an independent association between hyponatremia and the risk of in-hospital mortality even after adjusting for potential confounding factors including the different comorbid conditions.

Defining the Exact Level of Hyponatremia That is Associated With Poor Outcomes:

Hyponatremia is conventionally defined as having a serum [Na] <135 mEq/L. However, despite the wide recognition of this definition of hyponatremia, different cutoff points have been used by the various groups who have investigated the outcomes of hyponatremia in hospitalized patients (3, 5-9, 14, 15). Hence, there are large variations in the prevalence of hyponatremia that range from 5.5% to 38% (6-9, 14). Few studies have demonstrated harm associated with mild hyponatremia (130-134mEq/L) (7) or even a low-normal range of conventional normonatremia (<138 mEq/L) (8, 9). This has led some investigators to argue that the current definition of hyponatremia should be reevaluated (8). For example, in a prospective cohort study by Waikar et al that included 98,411 hospitalized patients at two teaching hospitals between 2000 and 2003, hyponatremia defined as serum [Na] <135 mEq/L was present in 14.5 % of patients at hospital admission (7). The risk of mortality was evident in cases of mild hyponatremia (130-134 mEq/L). Moreover, in a retrospective study Wald et

al that included 53,236 hospitalizations between 2000-2007, a serum sodium [Na] value <138 mEq/L, which is considered in the normal range, was independently associated with increased mortality in hospitalized patients, prolonged length of stay in the hospital, and discharge to a short or long term care facility (8). However, in this one-center study, the authors emphasized the need for multiple center studies to confirm these findings (8). Furthermore, in a retrospective study by Balling et al that included 2960 hospitalized patients between 1998-1999, hyponatremia, defined as a serum sodium [Na] below 137 mEq/L, was associated with greater mortality (27.5% versus 17.7%) and longer hospital stay compared to patients with normonatremia (Na ≥ 137 mEq/L) (9). However, in this one center study, they did not adjust for glucose levels in the analysis, and this may have resulted in overestimation of the prevalence of hyponatremia (9).

There are also conflicting reports regarding whether mortality continues to increase as hyponatremia worsens (8, 16, 17). In the study by Wald et al, the mortality due to hyponatremia continued to increase with the decrease in serum [Na] levels (8). However, in a retrospective study by Chawla et al, that included 45,693 hospitalized patients from a single community teaching hospital between 1996 and 2007, the in-hospital mortality increased as serum sodium fell from 134 to 120 mEq/L (16). However, for serum sodium levels below 120 mEq/L, the trend is reversed, and the mortality rate progressively decreased. Moreover, in the study by Holland-bill et al that included 279,508 hospitalized patients from the Danish National Patient Registry (DNPR) between 2006 and 2011 (17), the risk

of mortality increased as the serum [Na] decreased, but when [Na] values dropped to <132 mEq/L, there was no further increase in mortality. Despite that, they were able to demonstrate that the mortality risk increased with worsening hyponatremia when they performed a stratified analysis in patients with a primary diagnosis of cancer, liver disease, respiratory disease, and sepsis.

Age and Hyponatremia:

Hyponatremia is very common in the elderly patient population. Studies have shown that hyponatremia affects 11% of elderly people living in the community (18) and 18% of the elderly living in nursing facilities (19). Elderly patients have a higher propensity to develop hyponatremia due to several mechanisms. For example, aging may lead to impairment in the concentration capacity of the kidneys, and results in slower water excretion. Moreover, elderly patients commonly use several medications that are known to cause hyponatremia such as thiazide diuretics. Furthermore, elderly patients have a high prevalence of medical conditions that predispose them to the development of hyponatremia such as chronic congestive heart failure, chronic kidney disease, pneumonia, neurological disease (stroke), and malignancy (20, 21).

Although some studies have shown an increase in mortality in older patients (>65 years) with hyponatremia (22-24), others showed that hyponatremia was not associated with mortality compared to normonatremic patients in this elderly age group (25, 26) and one study surprisingly showed that mortality was more

prevalent in hospitalizations involving patients younger than 65 years compared to patients older than 65 years (8).

Hyponatremia and Other Comorbidities:

In addition to hyponatremia being associated with poor outcomes in general hospitalized patients, it is also prevalent in patients with different comorbidities and predisposes them to increased risk to poor outcomes. For example, it occurs in approximately 20% of patients with heart failure (27), 40% to 60% of patients with liver cirrhosis (28), and 35% of patients with syndrome of inappropriate antidiuretic hormone (SIADH) (29). In patients admitted to the hospital with acute heart failure, hyponatremia at hospital admission was an independent predictor for all-cause mortality and cardiovascular mortality (30). Moreover, in liver cirrhosis, hyponatremia is significantly associated with increased morbidity and mortality and affects survival post liver-transplant (31). Hence, the poor outcomes may be more pronounced in some comorbidities than in others.

Reasons for Conducting the Study:

Most of the studies addressing the relationship between hyponatremia and selected outcomes of hospitalized patients were single-center studies and did not include a large diverse population of hospitalized patients. Others used the ICD-9 codes for the diagnosis of hyponatremia and did not have the laboratory values of serum sodium levels, so they were not able to differentiate the impact of hyponatremia among patients with varying sodium concentrations (11). Lastly,

little is known about the association of hyponatremia with discharge disposition—specifically, discharge to hospice and nursing facility.

To address this gap in our knowledge regarding the cutoff points of hyponatremia associated with poor outcomes of hospitalized patients and the distribution of the risk of death associated with hyponatremia across the lifespan of these patients, we analyzed data on patients hospitalized between January 2000 and November 2014 derived from the Cerner Health Facts database.

CHAPTER 2

MATERIALS AND METHODS

Study Design, Data Source and Population Selection:

We conducted an observational study of patients hospitalized between January 2000 and November 2014 using the Cerner Health Facts database. Health Facts is a national database that includes de-identified electronic health records (EHR) information from over 600 hospitals and clinics in the United States. The study was reviewed and approved by the University of New Mexico Institutional Review Board (15-531; October 27, 2015). We included the index hospital admission defined by the first inpatient encounter of any patient during the study period who met the following inclusion criteria: 1) age ≥ 18 years, and 2) first serum sodium [Na] levels drawn during 24 hours before admission. The second inclusion criterion was chosen to reduce the possibility that the [Na] levels were affected by any treatments or iatrogenic causes after hospital admission.

Information was gathered regarding patients' demographics, co-morbidities, causes for admission, laboratory studies and disposition status at hospital discharge. The co-morbidities were identified using the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes, while the laboratory tests were identified using Logical Observation Identifiers Names and Codes (LOINC).The Deyo-Charlson Co-morbidity Index (Deyo-CCI) was also calculated (32). Deyo-CCI a widely used co-morbidity index adapted from the Charlson co-morbidity index for administrative databases. The index

uses ICD-9 codes to identify 17 co-morbidities which are assigned a score of 1, 2, 3, or 6. These scores are summed to yield the comorbidity score.

Since hyperglycemia is a hyperosmotic state affecting [Na] levels, we corrected the [Na] levels by adding 1.6 mEq/L for each 100 mg/dL above 100 mg/dL of the concomitantly measured serum glucose levels (33). After searching the literature for cases of extreme hyponatremia or extreme hypernatremia (34-37), we decided to exclude patients with [Na] values <90 or >201 mEq/L (Figure 1). We further excluded patients with [Na] > 145 mEq/L and those with missing gender, race and outcomes values. The final cohort available for analysis included 2,284,912 patients (Figure 1). Our primary outcomes were in-hospital mortality (n=63,359) and discharge disposition of hospitalized patients. The discharge dispositions included discharge to hospice (n=32,335), discharge to home (n=1,739,780), discharge to nursing facility (n=274,755), discharge to short or long term care hospital (n=91,703), rehabilitation (n=58,259), and left against medical advice (n=24,721). Discharge to hospice, discharge to nursing facility, and discharge to home were the main outcomes for discharge disposition.

Statistical Analyses:

We performed descriptive statistical analyses of the study cohort. Continuous variables were summarized as means and standard deviations (SD) and were compared using the student's t test. Categorical variables were summarized as percentages and were compared using the chi-square test.

To evaluate which patient characteristics are associated with increased risk of developing hyponatremia, we fitted a logistic regression model of the relation between hyponatremia (<135 mEq/L vs ≥135 to ≤145 mEq/L) and the different patient characteristics of interest including age, gender, race and selected comorbidities (hypertension, myocardial infarction, coronary artery disease, heart failure, diabetes mellitus (DM), peripheral vascular disease, chronic kidney disease (CKD), end stage renal disease (ESRD), cirrhosis, chronic pulmonary disease, chronic obstructive pulmonary disease (COPD), rheumatologic disease, cerebrovascular disease, dementia, peptic ulcer disease, adrenal insufficiency, hypothyroidism, depression, acquired immunodeficiency syndrome (AIDS), hemiplegia, metastatic cancer, lung cancer, malignancy, pneumonia, sepsis, syndrome of inappropriate antidiuretic hormone (SIADH), and urinary tract infections (UTI). We adjusted for all these selected comorbidities in our analyses as appropriate. In these analyses, Age was categorized into four different groups: ≥18 to <45, ≥45 to <65, ≥65 to <75, and ≥75 years old. We had 461,511 (20.20%) patients in the ≥18 to <45 group, 740,035 (32.40%) in the ≥45 to <65 group, 404,848 (17.70%) in the ≥65 to <75 group, and 678,518 (29.70%) in the ≥75 group.

We were interested in evaluating broader associations between [Na] and outcomes. We therefore examined associations between quantitatively measured [Na] and our study outcomes in two ways. First, in searching the literature, we realized that the serum [Na] levels may have a nonlinear relation with the different outcomes. Thus, to assess the flexible relation between the [Na] levels

and the different outcomes, we modeled this relationship using restricted cubic splines method with five knots. These knots corresponded to the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the cohort's [Na], and their values were 132, 136, 138, 140, and 143 mEq/L, respectively. Second, for simplicity in interpretation, we categorized the [Na] levels into the following eight groups: 1: < 120; 2: ≥ 120 to < 125; 3: ≥ 125 to < 130; 4: ≥ 130 to < 135; 5: ≥ 135 to < 138; 6: ≥ 138 to < 140; 7: ≥ 143 to ≤ 145 mEq/L and we considered 0: ≥ 140 to < 143 mEq/L as the reference group. Since we did not have a very large number of patients with serum sodium levels <135 mEq/L, we decided to categorize the serum sodium levels into 5 mEq/L intervals, as in other previous studies. However, since we had a very large number of patients with serum sodium levels ≥ 135 mEq/L, we let the restricted cubic spline knots guide us in this categorization. We used 138, 140 and 143 mEq/L to generate the categories. This led us to have an approximately equal number of patients in the 135 to < 138, 138 to < 140, and 140 to < 143 mEq/L categories (approximately 600,000 patients) (Table 3). Further, since our aim was to test the cutoff points of hyponatremia, we decided to use 140 to <143 mEq/L as the reference group.

Since we were studying multiple nominal outcomes, performing a binary analysis that reduces the 7 levels of outcomes down to two would potentially lead to loss of information. Therefore, we decided to perform multinomial logistic regression models as appropriate. These multinomial models allowed us to assess associations of each outcome while accounting for the competing risks of the others. In these models, we used "discharge to home" as the reference outcome.

We used the restricted cubic spline terms in these models to generate predicted probabilities across the continuum of [Na], and subsequently used these predictions in order to visualize the patterns of the associations between [Na] and the study outcomes (Figure 2). We used our defined [Na] categories in these models to examine effects of the different intervals of hyponatremia and normonatremia on our categorical outcomes (in-hospital mortality and patients' disposition), both with or without accounting for the following potential confounding covariates: age, gender, race, and the selected comorbidities (specified above).

To further examine if age has a differential effect on the relation between [Na] levels and the different outcomes, we first assessed this by using the restricted cubic splines method in age stratified multinomial logistic regression models to visualize the trends in the estimated probabilities (Figure 5, 6, 7, and 8). After that, we modeled the interaction between each previously defined age group and the aforementioned [Na] categories using multinomial logistic regression models adjusting for age, gender, race and the selected comorbidities. We also did a sensitivity analysis by performing all the aforementioned analyses while adjusting for the Deyo-CCI instead of the selected comorbidities. The scores in the Deyo-CCI ranged from 0 to 17. However, the number of patients that had a score of 12, 13, 14, 15, 16, or 17 was not very large, so we decided to group them into one category. Therefore, we had 12 categories of the Deyo-CCI to adjust for.

Subgroup Analysis:

To compare in-hospital mortality in different patient comorbidities, we modeled the interaction between each comorbidity of interest and the presence or absence of hyponatremia (<135 mEq/L) using logistic regression analysis. The covariate of the model were the selected comorbidities specified earlier.

All the analyses were performed using Stata version 14.1(StataCorp LP, College Station, TX).

CHAPTER 3

RESULTS

We found 2,698,978 patients who met our inclusion criteria (Figure 1). From this cohort 210,526 patients lacking a concomitant serum glucose determination were excluded from the study cohort. Our initial cohort of patients included 2,488,437 patients (Figure 1). The prevalence of hyponatremia (Na <135 mEq/L) at hospital admission was 14.4% (357,418) (Table 1). The prevalence was 14.7% (365,698) without adjusting for concomitant glucose. We noticed that after adjusting for the concomitant glucose, only 2.3% (8,280) of patients who were initially classified as having hyponatremia (365,698) were reclassified as normonatremic or hypernatremic.

Those patients with hyponatremia (<135 mEq/L) were older than patients with normonatremia (135-145 mEq/L), 64.1±18.1 vs. 60.8 ±19.1 years old ($p<0.001$). Patients with hyponatremia had a higher overall Deyo-CCI score compared with normonatremic patients 1.72±2.25 vs. 1.29±1.81, respectively, ($p<0.001$). Other pertinent patient characteristics are summarized in Table 1.

After adjusting for age, gender, race and the selected comorbidities, hyponatremia increased with increasing age. The odds ratios (ORs) [95 % confidence interval, CI] of having hyponatremia for ages ≥45 to <65, ≥65 to <75 and ≥75 were 1.21 [1.20-1.23], 1.35 [1.33-1.37] and 1.56 [1.54-1.58], respectively, compared to the reference age group ≥18 to <45 years old (Table 2).

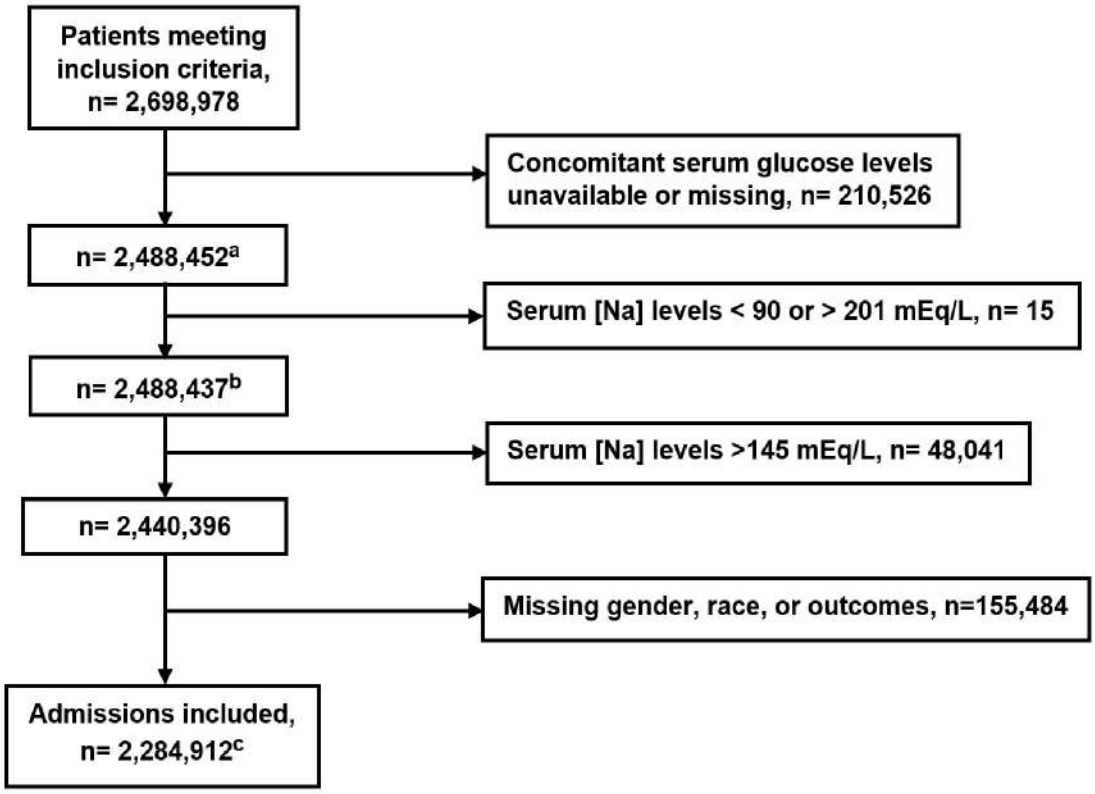

Figure 1. Flow Chart of the Sample Selection Process.

[a]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.

[b]This number was used to calculate the prevalence of hyponatremia (Na < 135 mEq/L) at hospital admission.

[c]The final cohort available for analysis.

Table 1. Characteristics of Hospitalized Patients With or Without Hyponatremia

Patient Characteristics	All Cohort[a] n= 2,488,437	Normonatremia and Hyponatremia patients[a] (n=2,440,396)	
		Presence of Hyponatremia (<135 mEq/L), n= 357,418	Absence of Hyponatremia (≥135 to ≤145 mEq/L), n=2,082,978
Age, mean (SD), y	61.5 (19)	64.1 (18.1)	60.8 (19.1)
Gender, %			
Females	54.29	53.98	54.34
Males	45.69	46.01	45.64
N/A	0.02	0.01	0.02
Race, %			
Caucasians	74.46	78.28	73.97
African Americans	17.35	13.48	17.84
Hispanic	2.16	1.93	2.20
Native Americans	0.39	0.50	0.37
Pacific Islanders	0.06	0.07	0.06
Asians	0.98	1.05	0.96
Others	2.31	2.12	2.34
N/A	2.29	2.56	2.24
Deyo-CCI, mean (SD)	1.36 (1.89)	1.72 (2.25)	1.29 (1.81)
Deyo-CCI categories, %			
0	42.52	36.85	43.61
1	25.35	24.88	25.41
2	14.68	15.45	14.52
≥3	17.45	22.82	16.45

N/A = not available; Deyo-CCI = Deyo Charlson Comorbidity Index.

Table 1. Characteristics of Hospitalized Patients With or Without Hyponatremia (continued).

Patient Characteristics	All Cohort[a] n= 2,488,437	Normonatremia and Hyponatremia patients[a] (n=2,440,396)	
		Presence of Hyponatremia (<135 mEq/L), n= 357,418	Absence of Hyponatremia (≥135 to ≤145 mEq/L), n=2,082,978
Comorbidities, %			
Hypertension	37.85	38.26	37.84
Myocardial Infarction	7.93	7.36	8.01
Coronary Artery Disease	20.82	19.74	21.05
Heart Failure	14.07	15.38	13.72
Diabetes Mellitus	21.96	24.97	21.40
Peripheral Vascular Disease	3.76	4.12	3.68
Chronic Kidney Disease	7.60	7.64	7.49
End Stage Renal Disease	2.42	3.34	2.28
Liver disease	2.44	4.73	2.04
Chronic Pulmonary disease	19.86	21.06	19.67
COPD	5.18	5.79	5.08
Adrenal Insufficiency	0.34	0.51	0.30
Hypothyroidism	9.32	10.52	9.12
Cerebrovascular disease	7.94	6.02	8.13
Hemiplegia/paraplegia	1.30	0.98	1.33
Rheumatologic disease	1.68	1.97	1.64
Depression	8.57	7.46	8.77
Dementia	3.5	2.57	3.42
AIDS	0.69	1.02	0.63
Malignancy[b]	7.84	11.39	7.26
Lung Cancer	2.07	3.85	1.77
Reasons for Hospitalization, %			
Pneumonia	4.81	6.20	4.55
Sepsis	2.46	3.58	2.16
SIADH	0.22	1.37	0.03
Urinary Tract Infection	6.62	7.91	6.23

COPD = Chronic Obstructive Pulmonary Disease; AIDS = Acquired Immunodeficiency syndrome; SIADH = Syndrome of Inappropriate Antidiuretic Hormone.

[a]Serum sodium levels corrected by adding 1.6 mEq/L for each 100 mg/dL above 100 mg/dL of the concomitantly measured serum glucose levels. These number are before excluding the patients with missing gender, race, or outcomes.

[b]Except lung cancer

Table 2. Factors Associated With Hyponatremia (<135 mEq/L)

	Multivariate Logistic Regression	
Variables Included in the Model	Adjusted* OR (95% CI)	P value
Age (Ref: Age 18 to <45) 45 to <65 65 to <75 ≥75	 1.21 (1.20-1.23) 1.35 (1.33-1.37) 1.56 (1.54-1.58)	 <0.001 <0.001 <0.001
Comorbidities		
DM (Ref: No DM)	1.25 (1.24-1.26)	<0.001
ESRD (Ref: No ESRD)	1.50 (1.47-1.53)	<0.001
Chronic Liver Disease (Ref: No Chronic Liver Disease	1.34 (1.28-1.39)	<0.001
Cirrhosis (Ref: No Cirrhosis)	2.67 (2.61-2.73)	<0.001
Adrenal Insufficiency (Ref: No Adrenal Insufficiency)	1.44 (1.37-1.52)	<0.001
AIDS (Ref: No AIDS)	1.98 (1.90-2.05)	<0.001
Lung Cancer (Ref: No Lung Cancer)	1.47 (1.44-1.51)	<0.001
Pneumonia (Ref: No Pneumonia)	1.33 (1.31-1.35)	<0.001
Sepsis (Ref: No Sepsis)	1.59 (1.57-1.62)	<0.001
SIADH (Ref: No SIADH)	40.91 (37.68-44.41)	<0.001
UTI (Ref: No UTI)	1.30 (1.29-1.31)	<0.001

OR=Odds Ratio; Ref=Reference; DM=Diabetes Milletus; ESRD=End Stage Renal Disease; AIDS= Acquired Immunodeficiency syndrome; SIADH = Syndrome of Inappropriate Antidiuretic Hormone; UTI=Urinary Tract Infection.

* Adjusted for age, gender, race and the selected comorbidities.

Furthermore, patients with DM, ESRD, chronic liver disease, cirrhosis, adrenal insufficiency, AIDS, lung cancer, pneumonia, sepsis, SIADH, and UTI were associated with a higher likelihood of developing hyponatremia (Table 2)

Low Serum Sodium Levels and the Outcomes:

The percentages of overall in-hospital mortality, discharge to hospice and discharge to nursing facility were higher in the hyponatremia group than in the normonatremia group (4.61%, 2.53% and 14.42% vs 2.46%, 1.22 % and 11.61%, respectively), whereas discharge to home was higher in the normonatremia group than in the hyponatremia group (64.82% vs 55.53%).

The crude probability of in-hospital mortality corresponding to the different serum [Na] levels was lowest at serum [Na] levels between 135 and 143 mEq/L and continued to increase above or below this range (Figure 2). The probability of discharge to hospice demonstrated a similar pattern, though less profound. The estimated probabilities of discharge to nursing facility also demonstrated a similar pattern but started to decrease at serum [Na] levels below 115mEq/L. We observed the opposite for discharge to home, such that the probability of this outcome increased up to serum [Na] levels between 135 and 143mEq/L, then decreased above this range (Figure 2).

For the serum [Na] categories we specified, the crude in-hospital mortality increased as [Na] decreased or increased relative to the 138 to <140 mEq/L interval (Table 3). This was also true for discharge to hospice and discharge to

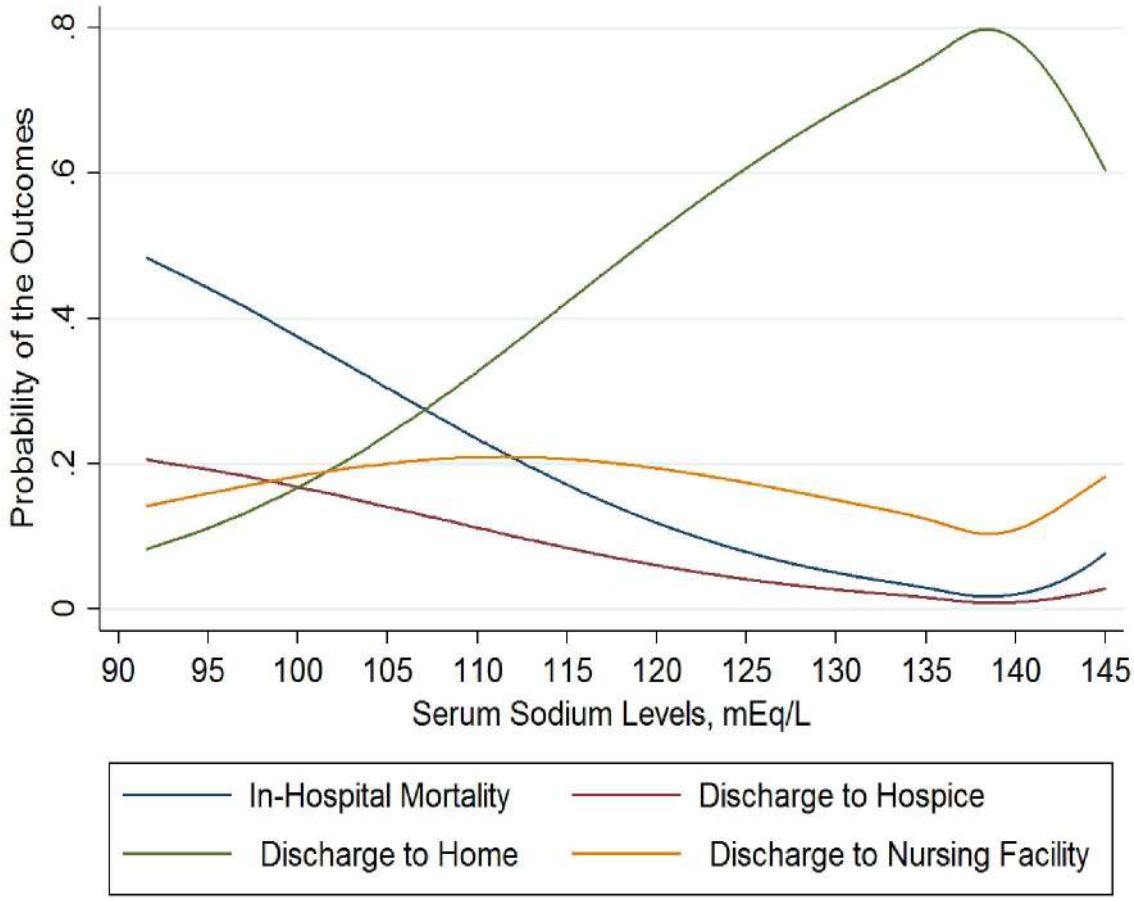

Figure 2. Restricted cubic splines of the crude estimated probability of in-hospital mortality, discharge to hospice, discharge to home, and discharge to nursing facility as a function of serum sodium levels at hospital admission. These estimated probabilities were derived from a multinomial logistic 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 3. Relationship between Serum Sodium levels at Hospital Admission and In-Hospital Mortality, Discharge to Hospice or to Nursing Facility

Serum [Na] levels[a] at Hospital Admission (mEq/L), n= 2,284,912		In-Hospital Mortality (n=63,359)		Discharge to Hospice (n=32,335)		Discharge to Nursing Facility (n=274,755)	
		In-Hospital Mortality, n (%)	Adjusted[b] Relative Risk Ratio (95% CI)	Discharge to Hospice, n (%)	Adjusted[b] Relative Risk Ratio (95% CI)	Discharge to Nursing Facility, n (%)	Adjusted[b] Relative Risk Ratio (95% CI)
Absence of Hyponatremia (≥135 to ≤145 mEq/L), n=1,950,594	143 to ≤ 145 (n=134,979)	7,242 (5.4%)[c]	2.15 (2.08-2.22)	2,981(2.2%)	1.91 (1.82-2.00)	22,085 (16.4%)	1.36 (1.33-1.38)
	140 to < 143 (n=602,058)	15,112 (2.5%)	1 (reference)	7,082 (1.2%)	1 (reference)	71,770 (11.9%)	1 (reference)
	138 to < 140 (n=601,610)	11,637 (1.9%)	0.78 (0.76-0.80)	5,997 (1%)	0.86 (0.83-0.89)	63,865 (10.6%)	0.97 (0.96-0.99)
	135 to < 138 (n=611,947)	13,953 (2.3%)	0.90 (0.88-0.92)	7,809 (1.3%)	1.06 (1.03-1.10)	68,836 (11.2%)	1.08 (1.07-1.10)
Presence of Hyponatremia (<135 mEq/L), n=334,318	130 to < 135 (n=280,970)	11,475 (4.1%)	1.45 (1.41-1.49)	6,369 (2.3%)	1.64 (1.58-1.70)	39,416 (14.0%)	1.26 (1.24-1.28)
	125 to < 130 (n=41,953)	2,941 (7.0%)	2.43 (2.32-2.54)	1,579 (3.8%)	2.56 (2.41-2.72)	7,038 (16.8%)	1.35 (1.31-1.39)
	120 to < 125 (n=8,982)	739 (8.2%)	3.12 (2.87-3.40)	408 (4.5%)	3.25 (2.91-3.63)	1,385 (15.4%)	1.21 (1.14-1.29)
	< 120 (n=2,413)	260 (10.8%)	4.85 (4.20-5.60)	110 (4.6%)	3.71 (3.01-4.56)	360 (14.9%)	1.32 (1.16-1.49)

CI = confidence interval.

[a]Serum sodium 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 relative risk ratios were derived from a multinomial logistic regression model adjusted for age, gender, race, and the selected comorbidities (p<0.001 for all). Discharge to home is the referent outcome (n=1,739,780).

[c]The percentages represent the percentage of each outcome within each serum sodium category.

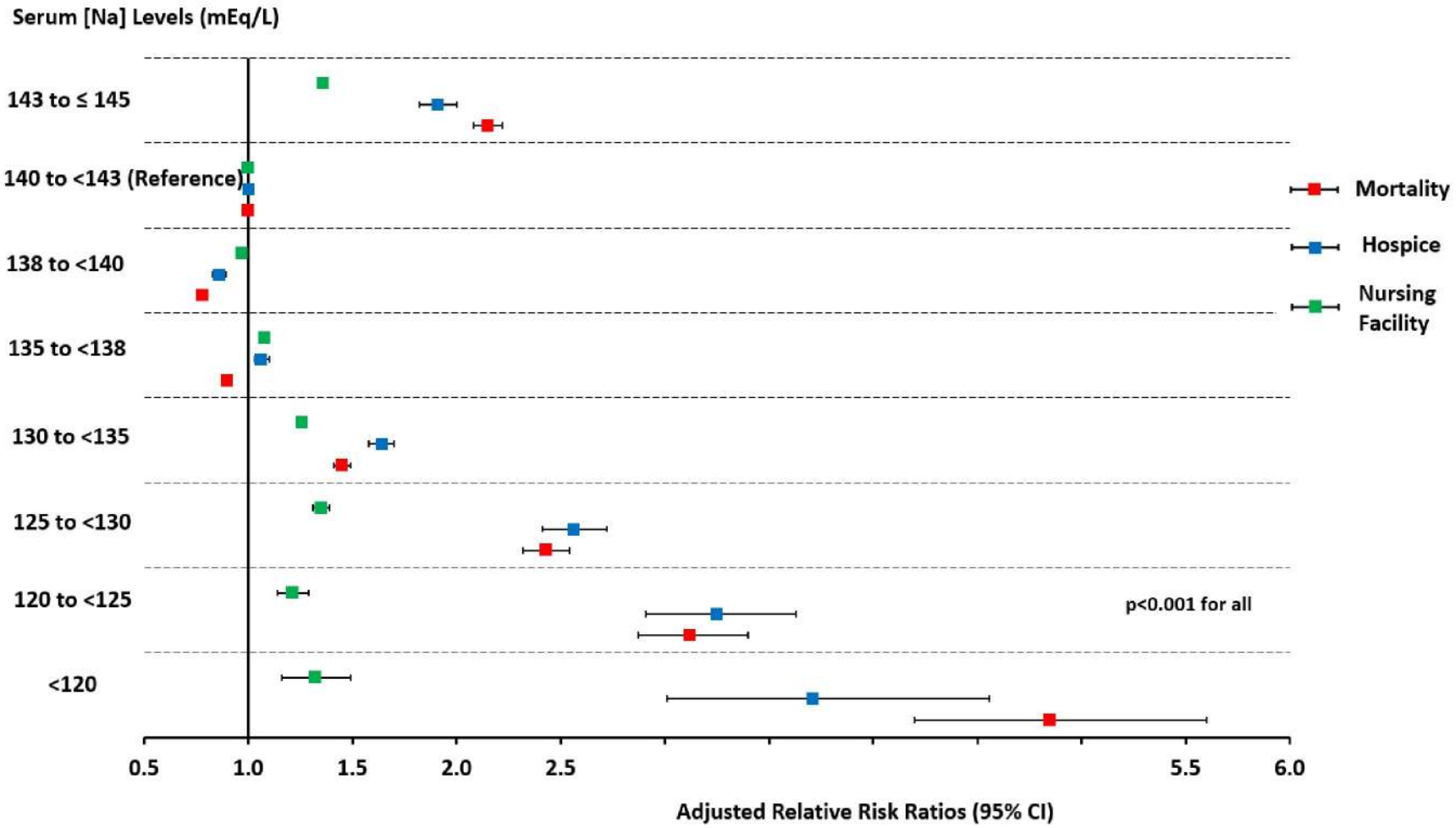

Figure 3. Forest plot of the relative risk ratios (95% CI) for in-hospital mortality, discharge to hospice, or discharge to nursing facility associated with different intervals of serum sodium levels (mEq/L) at hospital admission. The relative risk ratios were derived from multinomial logistic regression models adjusted for age, gender, race, and the selected comorbidities. Discharge to home and serum sodium levels of (140 to <143 mEq/L) served as referent. 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. CI = confidence interval.

nursing facility. However, the percentage of discharge to nursing facility decreased for the [Na] intervals 120 to <125 mEq/L and <120mEq/L (Table 3).

In the adjusted multinomial logistic regression analyses, we found that the likelihood of in-hospital mortality increased for [Na] levels <135 mEq/L or ≥ 143 to ≤145 mEq/L compared to the reference interval of 140 to <143 mEq/L ($p<0.001$) (Table 3, Figure 3). After adjusting for age, gender, race and the selected comorbidities, patients with [Na] levels of <120, 120 to <125, 125 to <130, 130 to <135, 135 to <138, 138 to <140 and 143 to ≤145 mEq/L compared with 140 to<143 mEq/L had in-hospital mortality relative risk ratios (RRRs) [95% CI] of 4.85 [4.20-5.60], 3.12 [2.87-3.40], 2.43 [2.32-2.54], 1.45 [1.41-1.49], 0.90 [0.88-0.92], 0.78 [0.76-0.80] and 2.15 [2.08-2.22] respectively ($p<0.001$ for all) (Table 3, Figure 3). This strong association with in-hospital mortality continued to rise with the increase in the severity of hyponatremia. Patients with [Na] levels of 138 to <140 mEq/L had the lowest likelihood of in-hospital mortality. We observed similar trends for the relationship between [Na] levels and discharge to hospice or to a nursing facility (Table 3, Figure 3). We obtained very similar results after adjusting for the Deyo-CCI instead of the selected comorbidities (Table 4, Figure 4).

Age and the Outcomes:

Using the method of restricted cubic splines, we observed that for low serum [Na], the in-hospital mortality was higher for younger age groups compared to older age groups. However, for [Na] levels within the normal range, the

Table 4. Relationship between Serum Sodium levels at Hospital Admission and In-Hospital Mortality, Discharge to Hospice or to Nursing Facility (Adjusting for the Deyo-CCI)

Serum [Na] levels[a] at Hospital Admission (mEq/L), n= 2,284,912		In-Hospital Mortality (n=63,359)	Discharge to Hospice (n=32,335)	Discharge to Nursing Facility (n=274,755)
		Adjusted[b] Relative Risk Ratio (95% CI)	Adjusted[b] Relative Risk Ratio (95% CI)	Adjusted[b] Relative Risk Ratio (95% CI)
Absence of Hyponatremia (≥135 to ≤145 mEq/L), n=1,950,594	143 to ≤ 145 (n=134,979)	2.30 (2.23-2.36)	2.00 (1.91-2.09)	1.43 (1.40-1.46)
	140 to < 143 (n=602,058)	1 (reference)	1 (reference)	1 (reference)
	138 to < 140 (n=601,610)	0.78 (0.76-0.79)	0.85 (0.82-0.88)	0.94 (0.93-0.96)
	135 to < 138 (n=611,947)	0.91 (0.89-0.93)	1.04 (1.01-1.08)	1.04 (1.02-1.05)
Presence of Hyponatremia (<135 mEq/L), n=334,318	130 to < 135 (n=280,970)	1.53 (1.50-1.57)	1.65 (1.59-1.70)	1.21 (1.19-1.23)
	125 to < 130 (n=41,953)	2.63 (2.52-2.74)	2.66 (2.51-2.82)	1.35 (1.31-1.39)
	120 to < 125 (n=8,982)	3.17 (2.93-3.44)	3.28 (2.95-3.66)	1.25 (1.18-1.33)
	< 120 (n=2,413)	4.72 (4.11-5.41)	3.79 (3.09-4.64)	1.40 (1.24-1.58)

CI = confidence interval; Deyo-CCI= Deyo-Charlson Comorbidity Index.

[a]Serum sodium 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 relative risk ratios were derived from a multinomial logistic regression model adjusted for age, gender, race, and the Deyo-CCI ($p<0.001$ for all). Discharge to home is the referent outcome (n=1,739,780).

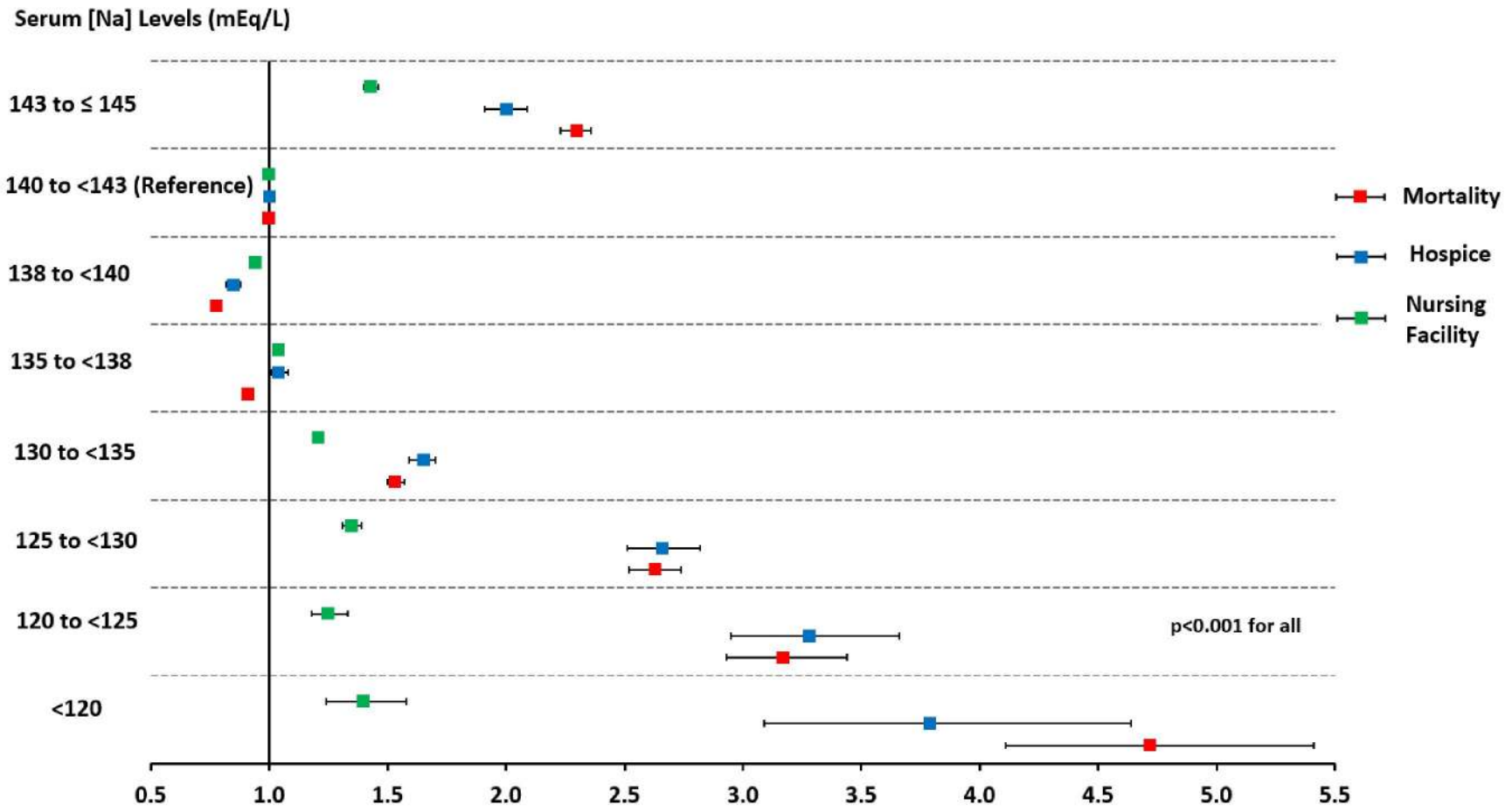

Figure 4. Forest plot of the relative risk ratios (95% CI) for in-hospital mortality, discharge to hospice, or discharge to nursing facility associated with different intervals of serum sodium levels (mEq/L) at hospital admission. The relative risk ratios were derived from multinomial logistic regression models adjusted for age, gender, race, and Deyo-CCI. Discharge to home and serum sodium levels of (140 to <143 mEq/L) served as referent. 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. CI = confidence interval; Deyo-CCI = Deyo Charlson Comorbidity Index.

in-hospital mortality was higher for older age groups compared to younger age groups (Figure 5). Older age groups had a higher probability of discharge to hospice at normal serum [Na] than younger age groups. However, as serum [Na] decreased, the probability of discharge to hospice for the youngest (18 to <45) and oldest (≥75) age groups, was lower than that for the middle age groups (age 45 to <65 and 65 to <75) (Figure 6).

For discharge to nursing facility, older age groups had higher estimated probabilities compared to younger age groups for all [Na] levels (Figure 7). For discharge to home, for normal [Na] levels, the probability for discharge to home was higher in the younger age groups compared to older age groups. However, as the serum [Na] levels decreased, discharge to home was higher in the older age groups compared to the younger age groups (Figure 8).

We obtained similar findings after modeling the interaction of each age group with the different [Na] categories and after adjusting for age, gender, race and the selected comorbidities (Figure 9, Table 5). We compared the relative risk ratios (RRRs) for in-hospital mortality associated with the [Na] categories between the different age groupings from the model that included the age by [Na] interation (Figure 9, Table 5) using linear combinations of coefficients estimation (Table 6). We noted that for [Na] <130 mEq/L and ≥143 to ≤145 mEq/L, the relative risk ratios (RRRs) for in-hospital mortality were significantly greater for each age group compared to the consecutive older age group, except for ages ≥65 to <75 and ≥ 75 in the [Na] category of <120 mEq/L, ≥18 to <45 and 45 to <65 in the [Na] category of 120 to <125 mEq/L, and ≥65 to

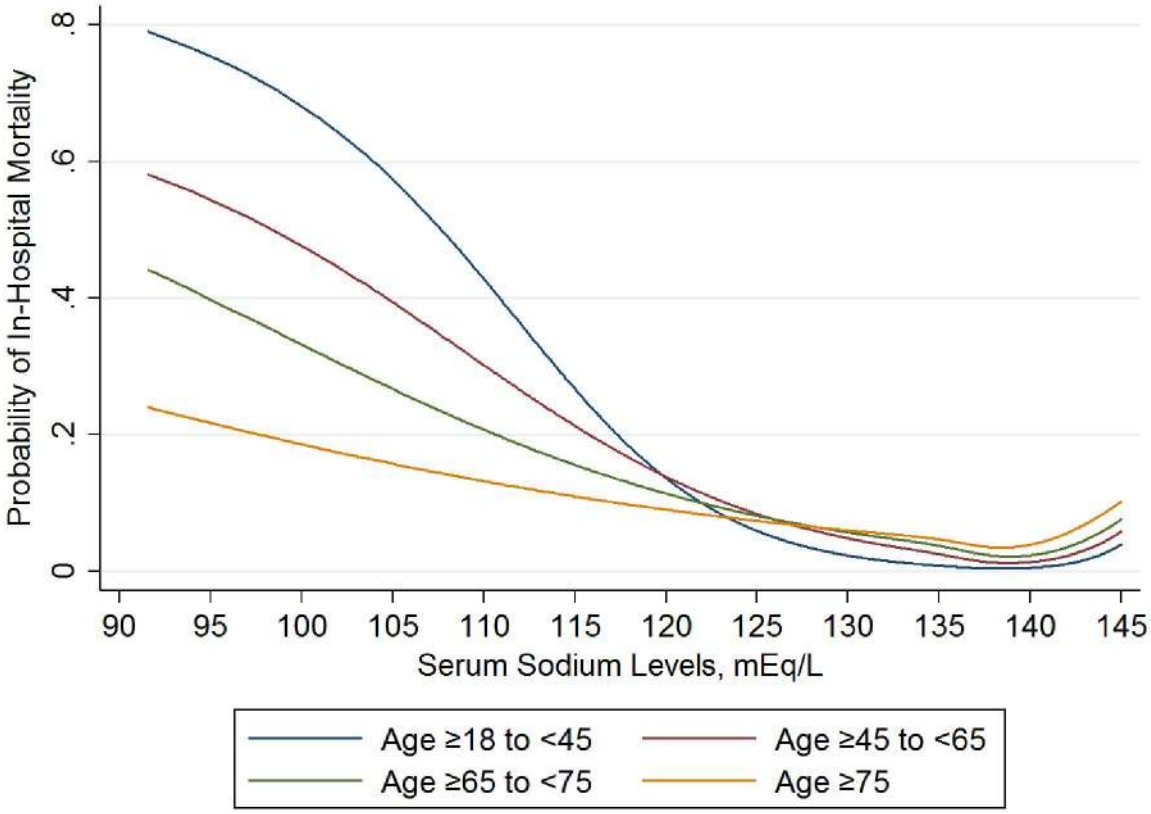

Figure 5. Restricted cubic splines of the estimated probability of in-hospital mortality as a function of serum sodium levels for different age groups. These estimated probabilities were derived from a multinomial logistic regression models stratifies by age.

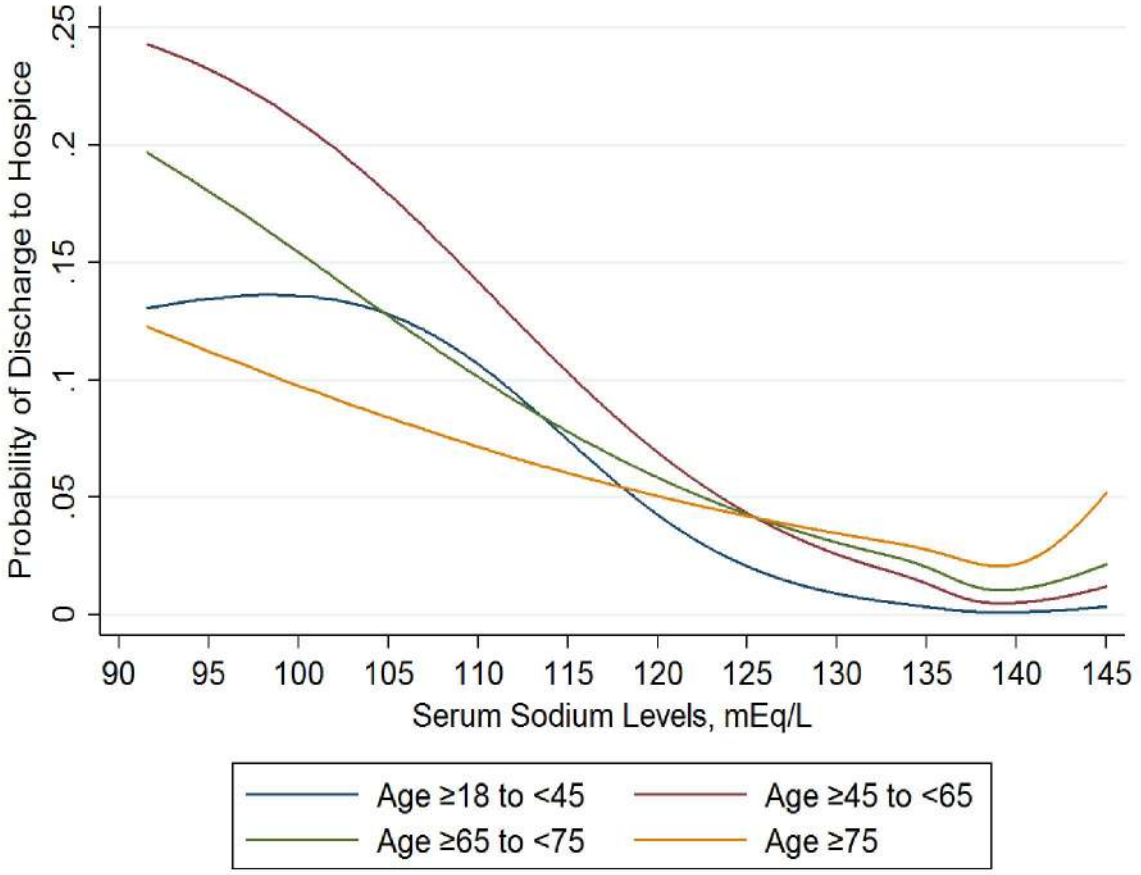

Figure 6. Restricted cubic splines of the estimated probability of discharge to hospice as a function of serum sodium levels for different age groups. These estimated probabilities were derived from a multinomial logistic regression models stratifies by age.

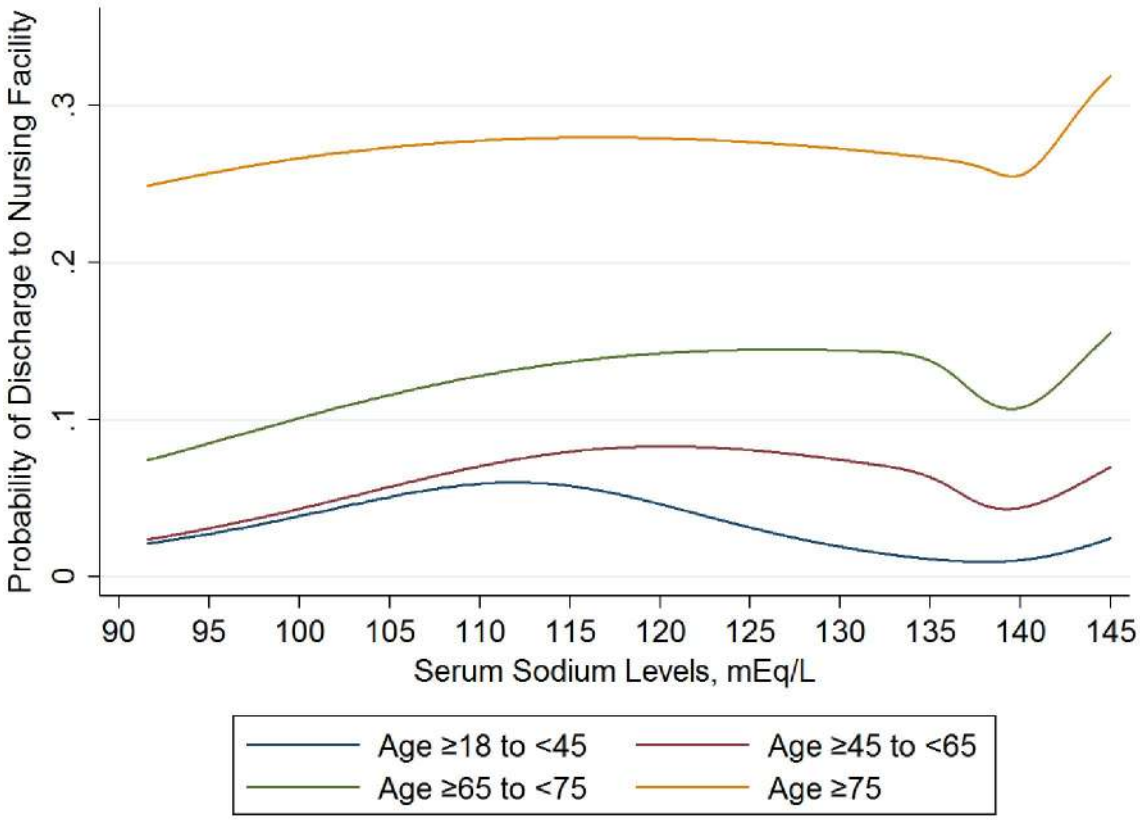

Figure 7. Restricted cubic splines of the estimated probability of discharge to nursing facility as a function of serum sodium levels for different age groups. These estimated probabilities were derived from a multinomial logistic regression models stratifies by age.

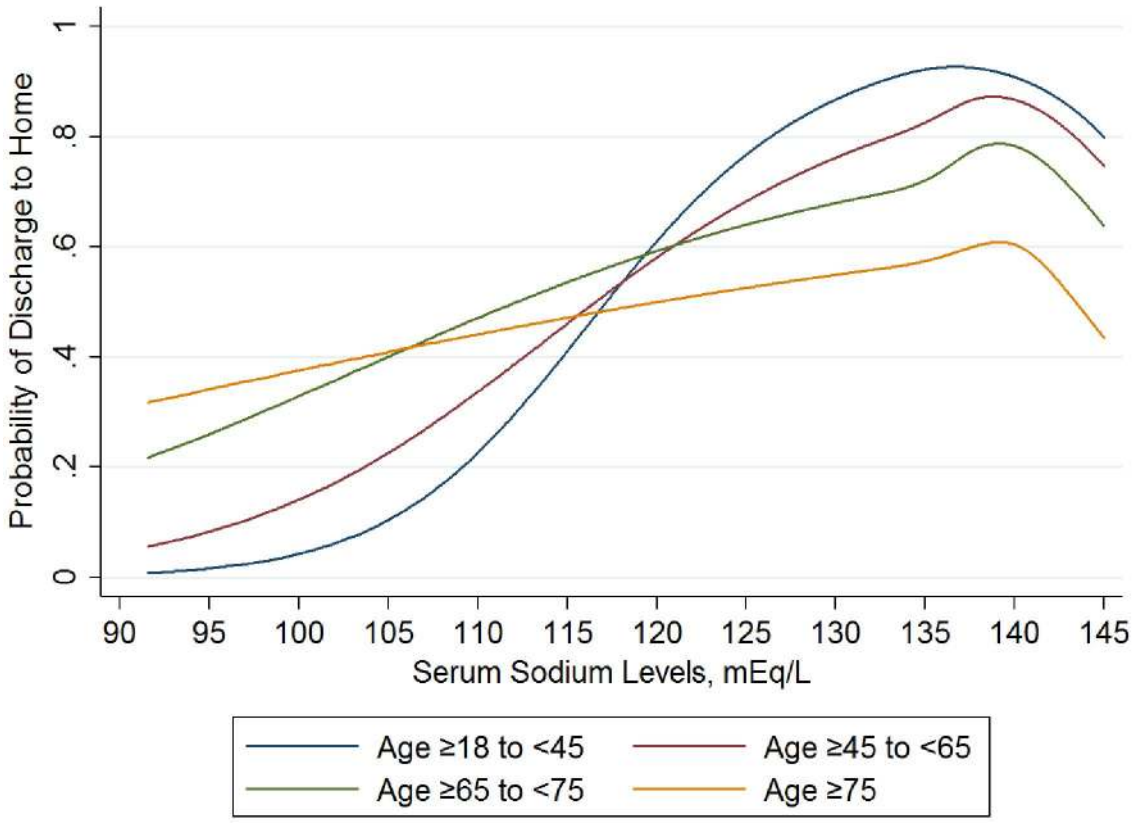

Figure 8. Restricted cubic splines of the estimated probability of discharge to home as a function of serum sodium levels for different age groups. These estimated probabilities were derived from a multinomial logistic regression models stratifies by age.

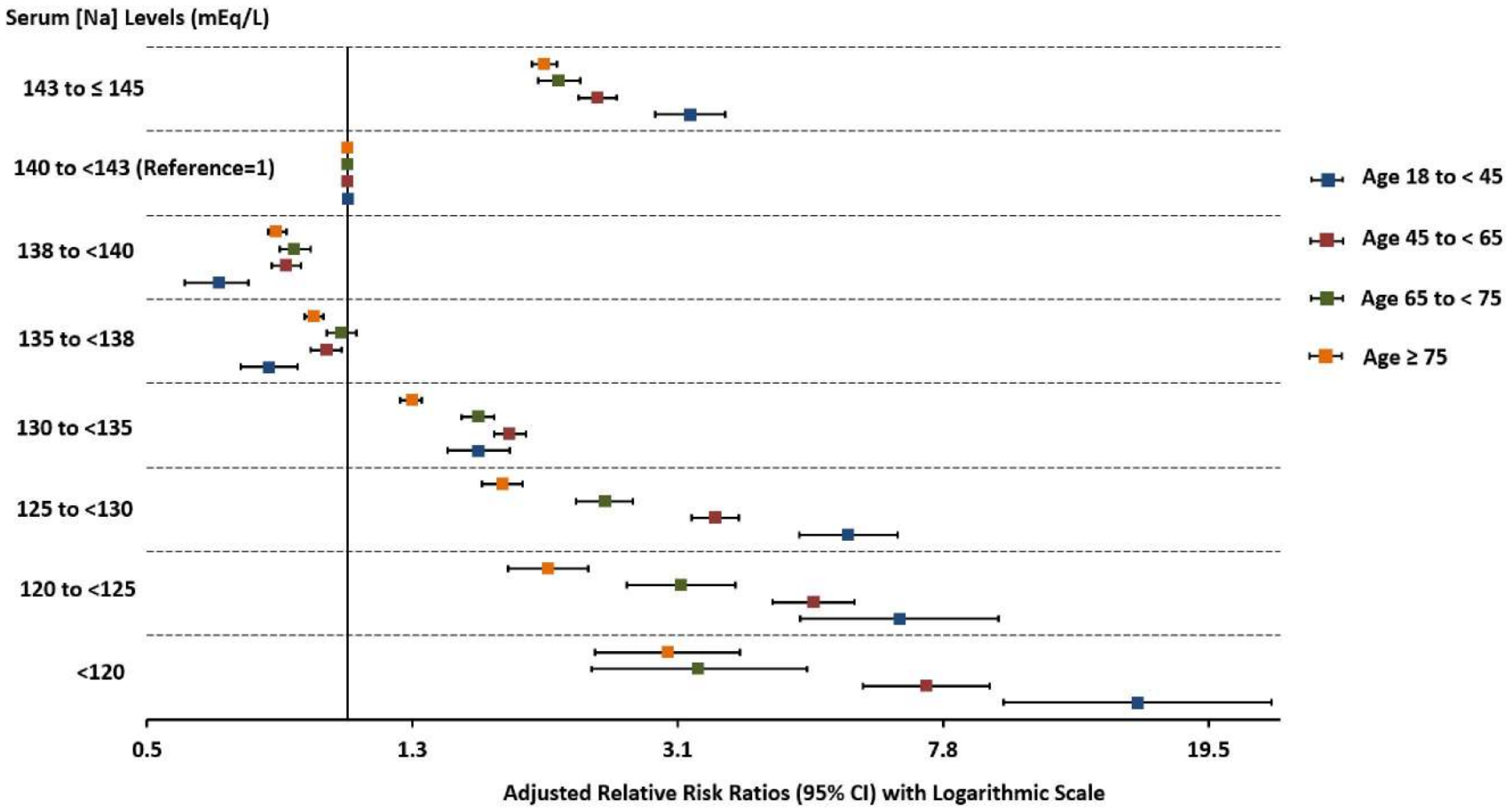

Figure 9. Forest plot of the relative risk ratios (95% CI) for in-hospital mortality associated with different intervals of serum sodium levels (mEq/L) at hospital admission for the different age groups. The relative risk ratios were derived from multinomial logistic regression models adjusted for age, gender, race, and the selected comorbidities. Serum sodium levels of (140 to <143 mEq/L) served as referent and each age group served as its own referent. 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. CI = confidence interval. p<0.001 for all except for age 65 to <75 in the 135 to <138 mEq/L category (p=0.43).

Table 5. In-hospital Mortality Associated With Different Intervals of Serum [Na] levels for the Different Age Groups.

Final Cohort, n= 2,284,912	Serum Sodium Categories, mEq/L							
Age groups	< 120 (n=2,413)	120 to <125 (n=8,982)	125 to < 130 (n=41,953)	130 to < 135 (n=280,970)	135 to < 138 (n=611,947)	138 to < 140 (n=601,610)	140 to < 143 (n=602,058)	143 to ≤ 145 (n=134,979)
Age 18 to <45 (n=461,511)	n=209	n=657	n=3,675	n=47,147	n=142,670	n=134,810	n=112,739	n=19,604
Mortality, n (%)	27 (12.9%)[a]	43 (6.5%)	208 (5.7%)	622 (1.3%)	794 (0.6%)	591 (0.4%)	758 (0.7%)	431 (2.2%)
Adjusted RRR[b] (95% CI)	15.3 (9.6-24.3)	6.7 (4.8-9.5)	5.6 (4.7-6.7)	1.6 (1.4-1.7)	0.76 (0.69-0.84)	0.64 (0.57-0.71)	1 (Reference)	3.3 (2.9-3.7)
Age 45 to <65 (n=740,035)	n=905	n=2,989	n=12,811	n=89,157	n=199,810	n=200,104	n=194,784	n=39,475
Mortality, n (%)	116 (12.8%)	281 (9.4 %)	965 (7.5%)	3,256 (3.6%)	3,402 (1.7%)	2,717 (1.4%)	3,135 (1.6%)	1,517 (3.8%)
Adjusted RRR (95% CI)	7.4 (5.9-9.2)	5.0 (4.3-5.7)	3.5 (3.3-3.8)	1.7 (1.7-1.8)	0.93 (0.88-0.97)	0.81 (0.77-0.85)	1 (Reference)	2.4 (2.2-2.5)
Age 65 to <75 (n=404,848)	n=433	n=1,719	n=8,468	n=52,649	n=104,535	n=103,702	n=108,698	n=24,644
Mortality, n (%)	36 (8.3%)	148 (8.6%)	612 (7.2%)	2,546 (4.8%)	3,009 (2.9%)	2,449 (2.4%)	2,949 (2.7%)	1,313 (5.3%)
Adjusted RRR (95% CI)	3.4 (2.3-4.9)	3.1 (2.6-3.8)	2.4 (2.2-2.7)	1.6 (1.5-1.7)	0.98 (0.93-1.03)[c]	0.83 (0.79-0.88)	1 (Reference)	2.1 (1.9-2.2)
Age ≥75 (n=678,518)	n=866	n=3,617	n=16,999	n=92,017	n=164,932	n=162,994	n=185,837	n=51,256
Mortality, n (%)	81 (9.3%)	267 (7.4%)	1,156 (6.8%)	5,051 (5.5%)	6,748 (4.1%)	5,880 (3.6%)	8,270 (4.4%)	3,981 (7.8%)
Adjusted RRR (95% CI)	3.0 (2.3-3.9)	2.0 (1.7-2.3)	1.7 (1.6-1.8)	1.2 (1.2-1.3)	0.89 (0.86-0.92)	0.78 (0.76-0.81)	1 (Reference)	2.0 (1.9-2.0)
Total mortality, n (%)	260 (10.8%)	739 (8.2%)	2,941 (7.0%)	11,475 (4.0%)	13,953 (2.3%)	11,637 (1.9%)	15,112 (2.5%)	7,242 (5.4%)

[a]The percentages and the relative risk ratios RRR of in-hospital mortality are within(for) each age group with the respective serum [Na] category.

[b]The relative risk ratios (RRRs) are derived from a multinomial logistic regression model adjusted for age, gender, race, and the selected comorbidities.

CI=Confidence interval. p<0.001 for all except: [c] p=0.45.

Table 6. Comparisons of the Relative Risk Ratios of In-Hospital Mortality Associated With the Different Serum Sodium Interval for the Different Age Groups.

Age groups comparisons	<120 mEq/L		120 to <125 mEq/L		125 to<130 mEq/L		130 to <135 mEq/L		135 to <138 mEq/L		138 to <140 mEq/L		143 to ≤145 mEq/L	
	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value	RRR (95% CI)	P value
Age0-Age1	2.07(1.24 -3.46)	0.005	1.34(0.93 -1.95)	0.12	1.58(1.31 -1.91)	<0.001	0.89(0.79 -1.01)	0.07	0.82(0.73 -0.91)	<0.001	0.79(0.70 -0.89)	<0.001	1.38(1.20 -1.58)	<0.001
Age1- Age2	2.19(1.43 -3.37)	<0.001	1.58(1.25 -2.00)	<0.001	1.46(1.29 -1.66)	<0.001	1.11(1.03 -1.20)	0.005	0.95(0.88 -1.02)	0.19	0.97(0.90 -1.05)	0.45	1.14(1.04 -1.26)	0.007
Age 2-Age3	1.11(0.71 -1.74)	0.64	1.58(1.25 -2.00)	<0.001	1.42(1.26 -1.60)	<0.001	1.26(1.18 -1.35)	<0.001	1.10(1.03 -1.17)	0.005	1.06(0.99 -1.13)	0.07	1.05(0.97 -1.14)	0.24
Age0-Age2	4.55(2.51 -8.24)	<0.001	2.13(1.44 -3.14)	<0.001	2.32(1.91 -2.82)	<0.001	1.00(0.88 -1.13)	0.96	0.78(0.69 -0.87)	<0.001	0.77(0.68 -0.87)	<0.001	1.57(1.36 -1.81)	<0.001
Age0-Age3	5.07(3.00 -8.58	<0.001	3.36(2.33 -4.87)	<0.001	3.30(2.75 -3.96)	<0.001	1.26(1.12 -1.41)	<0.001	0.85(0.76 -0.95)	0.003	0.81(0.73 -0.91)	<0.001	1.65(1.45 -1.88)	<0.001
Age1-Age3	2.44(1.75 -3.40)	<0.001	2.50(2.06 -3.04)	<0.001	2.08(1.87 -2.31)	<0.001	1.41(1.32 -1.50)	<0.001	1.04(0.98 -1.11)	0.18	1.03(0.97 -1.10)	0.35	1.20(1.11 -1.30)	<0.001

RRR=Relative Risk Ratio;

Age0=Age (≥18 to <45); Age1=Age (≥45 to <65); Age2=Age (≥65 to <75); Age3=Age ≥75.

<75 and ≥ 75 in the [Na] category of 143 to ≤145 mEq/L. The difference was not statistically significant. However, for 135 to <138 and 138 to <140 mEq/L [Na] categories, the relative risk ratios (RRRs) for in-hospital mortality were significantly lower in the 18 to <45 age groups compared to all other older age groups. We obtained similar finding after adjusting for Deyo-CCI instead of the comorbidities (data not shown).

In-Hospital Mortality in Other Patient Subgroups

We compared in-hospital mortality among the different patient's subgroups with or without hyponatremia. We found that patients with HIV, depression, chronic kidney disease, coronary artery disease, metastatic cancer and any malignancy (except lung cancer) had a higher likelihood of in-hospital mortality compared to patients with the same comorbidities but without hyponatremia (Figure 10).

Although we opted to use the 1.6 correction factor, repeating the analysis without any adjustments for concomitant glucose or after adding 2.4 mEq/L (38) resulted in similar conclusions (data not shown).

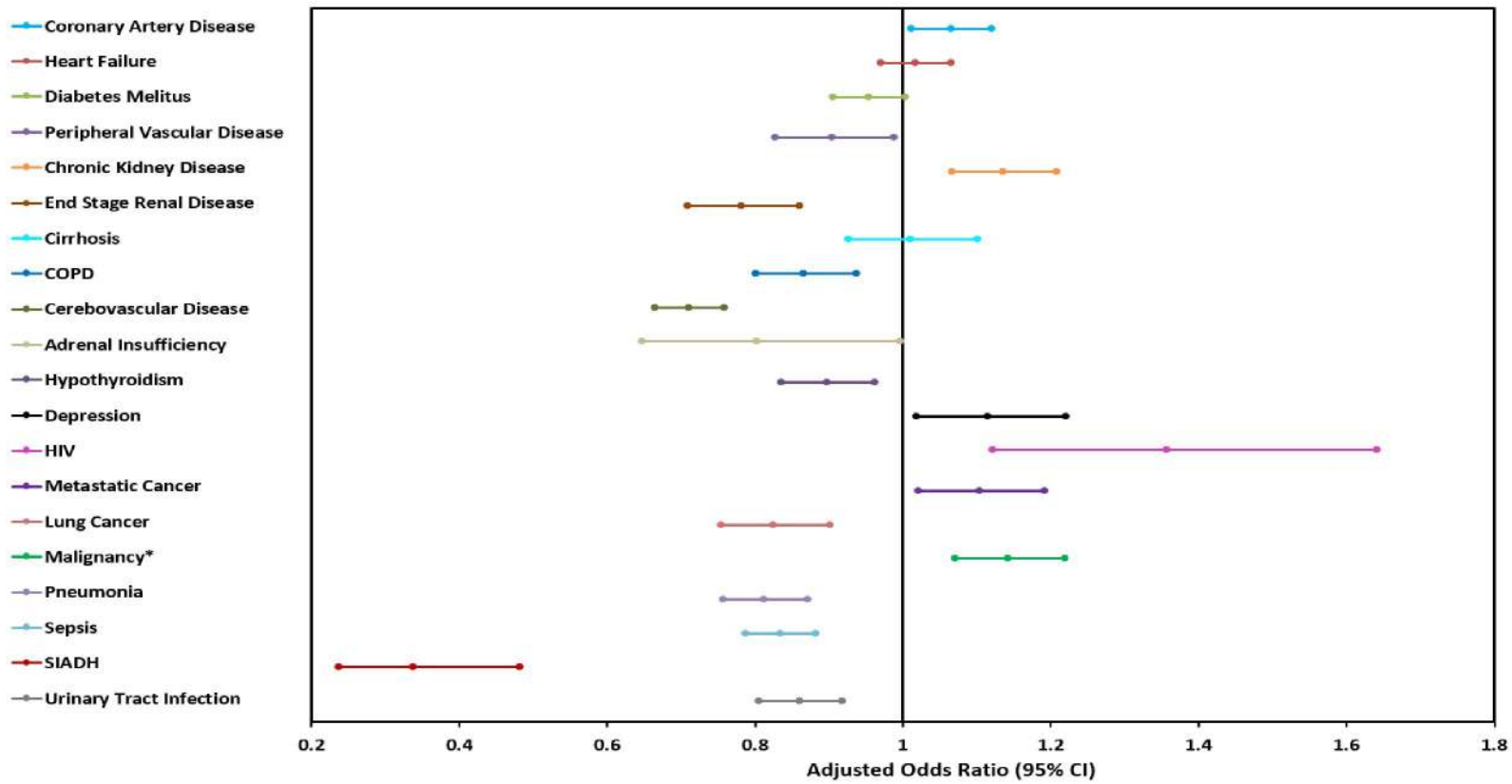

Figure 10. Forest plot of the odds ratios (95% CI) for the comparison of in-hospital mortality in different subgroups of patients with versus without serum sodium levels of <135 mEq/L. The odds ratios were derived from logistic regression models adjusted for age, gender, race, and the selected comorbidities of the patients. The *P* values for interaction between serum sodium levels <135 mEq/L and the different subgroup mentioned above are as follows: Coronary artery disease 0.02, heart failure 0.47, diabetes mellitus 0.07, peripheral vascular disease 0.03, chronic kidney disease <0.001, end stage renal disease <0.001, cirrhosis 0.81, COPD <0.001, cerebrovascular disease <0.001, adrenal insufficiency 0.05, hypothyroidism 0.003, depression 0.02, HIV 0.002, metastatic cancer 0.01, lung cancer <0.001, malignancy <0.001, pneumonia <0.001, sepsis <0.001, SIADH <0.001, and urinary tract infection <0.001.

* Any malignancy except lung cancer

COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; SIADH=syndrome of inappropriate antidiuretic hormone secretion.

CHAPTER 4

DISCUSSION

In this observational study using a large multicenter database, we were able to demonstrate using the cutoff point of <135 mEq/L that the prevalence of hyponatremia was common at hospital admission (14.4%). We showed that having [Na] levels < 135 mEq/L or ≥ 143 to ≤145 mEq/L is an independent risk factor for in-hospital mortality and increased discharge to hospice or to a nursing facility. Moreover, we found that younger patients admitted with [Na] levels <130 mEq/L or ≥143 to ≤ 145 mEq/L had a higher risk of in-hospital mortality compared to older patients.

In general, our results corroborate those of several other investigators. For example, Waikar et al (7) reported that the prevalence of hyponatremia at hospital admission in two teaching hospitals with 98,411 patients was 14.5 % and in another study by Holland-bill et al (17), which included 279,508 hospitalized patients, using the same cutoff point of <135 mEq/L the prevalence was 15 %. In another study by Wald et al, which included 53,236 adult hospitalizations, the prevalence of hyponatremia at hospital admission was higher (38%) (8). However, using the same cutoff point used by Wald et al (<138 mEq/L) yielded a very similar prevalence (40.56%).

Our results are in accordance to previous studies showing that hyponatremia is an independent risk factor for in-hospital mortality (7, 8, 17). Moreover, we documented an independent association between hyponatremia and the

increased risk of discharge to hospice or to a nursing facility. Furthermore, we demonstrated that the in-hospital mortality continues to worsen with the increase in the severity of hyponatremia, a conclusion that was also reached by Wald et al (8). However, this conclusion is at odds with the findings of Holland-bill et al (17). In that study the risk of mortality increased as the [Na] levels decreased; however, when [Na] values dropped to <132 mEq/L there was no further increase in mortality. Also our results are in disagreement with the findings of study by Chawla et al that included 45,693 hospitalized patients from a single hospital between 1996 and 2007. In this study, the in-hospital mortality increased as [Na] decreased from 134 to 120 mEq/L (16). However, there was an opposite pattern for [Na] below 120 mEq/L were the mortality rate decreased progressively.

Although in the present study the risk of in-hospital mortality was the lowest in the 138 to <140 mEq/L group, the in-hospital mortality for the 135 to < 138 mEq/L group was still low compared to the other [Na] categories. Our results support the traditional lower cutoff point of normonatremia of 135 mEq/L. Realizing that the risk of in-hospital mortality intensified for values ≥ 143 to ≤145 mEq/L, we support the proposition expressed by Wald et al that the traditional higher cutoff point of normonatremia (≤145 mEq/L) needs to be reevaluated. Based on our own findings reported herein, we advocate the use of < 143 mEq/L as a higher cutoff point for normonatremia.

We demonstrated that the likelihood of in-hospital mortality associated with [Na] levels varied between the various age groups. Younger age groups (≥18 to <45 years and ≥45 to <65 years) had higher likelihood of in-hospital mortality

compared to older age groups (≥65 to <75 years, ≥75 years) for [Na] levels <130 mEq/L or ≥143 to ≤ 145 mEq/L. It is the contention of some investigators that elderly patients have a high risk of mortality at hospital admission (22-24). However, other investigators do not agree with this position (25, 26). In a retrospective study by Ganguli and colleagues that included 608 elderly participants aged >65 years in a home-based primary care program, it was found that hyponatremia was independently associated with falls, fractures, hospitalizations but not mortality (26). In a case control study by Ahamed et al, including patients aged ≥ 65 years old admitted to the hospital during a 6 months period, hyponatremia was independently associated with admission-associated falls and increased length of hospital stay but was not associated with increased risk of mortality (25). Moreover, Wald et al (8) compared the mortality rates of patients younger than 65 years old versus patients who were at least 65 years old and found that the in-hospital mortality rate was higher in younger patients compared to older patients.

The differential association between hyponatremia and mortality in the different age groups has several plausible explanations. It is well known that chronic hyponatremia (>48 hours) is very common in elderly population: chronic hyponatremia is present in 11.3 % of elderly people living in the community (18) and 18% of the elderly residing in nursing home facilities (19). In chronic hyponatremia, adaptation mechanisms in the brain render patients less prone to the development of brain herniation. Moreover, the possibility of developing osmotic demyelination after the correction of chronic hyponatremia is rare and

less likely if the hyponatremia is corrected slowly (39). The other possible explanation is the difference in the ratio of the brain size to the cranial vault between elderly patients and younger patients. The high ratio of the size of the brain to the cranial vault in children has been postulated to play and important role in impeding brain adaptation mechanisms and leading to the observed increased mortality for those with hyponatremia (40). Hence, it is believed that the decrease in brain volume due to brain atrophy in the elderly plays a protective role against the sequelae of hyponatremic encephalopathy (41). In contrast, younger patients probably suffer from acute hyponatremia which develops over the course of few hours and most probably die from cerebral edema and brain herniation (39). Due to the inhibitory effects of estrogen on the brain adaptation to hyponatremia, menstruating women have 25 times higher risk of death or permanent neurological damage from hyponatremic encephalopathy than postmenopausal women (41). Furthermore, younger patients are more likely to engage in risky behaviors such as ecstasy use (42) and marathon running (43) that are linked to fatal complications of hyponatremia.

Our study has several strengths. The size of our study allowed us to robustly investigate the association between the different levels of hyponatremia and selected outcomes of hospitalized patients even with very low levels of hyponatremia. For example, for patients with serum sodium levels < 120 mEq/L the number of deaths was 260 out of 2413, which, to our knowledge, is higher than that found in any other published report. Our cohort included a diverse

patient population from many hospitals in the United States, hence our results are generalizable to the US population.

Our study had several limitations. First, inherent in our study was the use of ICD-9 codes to identify patients' comorbidities, which is prone to billing and coding errors. However, the Health Facts data undergo extensive review before being added to the database. Second, we based our interpretation of the relationship between in-hospital mortality due to hyponatremia and age on the assumption that chronic hyponatremia is common in older patients and acute hyponatremia is common in younger patients. We did not have the [Na] data in the outpatient setting which is very important to distinguish chronic from acute hyponatremia. Third, we also did not have the information about the use of the outpatient medications that predispose to the development of hyponatremia. Including the data about these medications would enhance the information provided in our study. Moreover, confirming that the elderly patients in our study are in fact taking the medications that are known to cause chronic hyponatremia will make us more comfortable in stating our assumption that chronic hyponatremia was more common in these patients. Nevertheless, we believe that accounting for the real causes of hyponatremia or determining the exact mechanism for the association between hyponatremia and in-hospital mortality should not distract us from the important finding in our study that hyponatremia, regardless of the cause, is independently associated with increased in-hospital mortality. Finally, 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 (RCT) to overcome this limitation may not be feasible.

CONCLUSIONS

Hyponatremia is common among hospitalized patients and regardless of the cause, it contributes significantly to the morbidity and mortality of hospitalized patients. It is an independent risk factor for increased in-hospital mortality and increased discharge to hospice or to nursing facility. Moreover, younger patients admitted with hyponatremia had a higher risk of in-hospital mortality compared to older patients. Our study underscores the need for more alertness to the [Na] levels in the outpatient setting and emphasizes the need for providing equal attention and care to all patients presenting to hospital with hyponatremia. Our next step would be to test whether the optimal correction of hyponatremia would improve the outcomes of hospitalized patients.

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