

## ORIGINAL RESEARCH

# Association of Serum Sodium With Morbidity and Mortality in Hospitalized Patients Undergoing Major Orthopedic Surgery

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**BACKGROUND:** Dysnatremia may predispose to falls and fractures, and serum sodium may influence bone health. Little is known of the association of perioperative dysnatremia and clinical outcomes in those undergoing major orthopedic surgery.

**OBJECTIVE:** We examined the association of serum sodium (corrected for glucose) with morbidity and mortality in a sample of hospitalized patients undergoing major orthopedic procedures at 2 large academic medical centers.

**DESIGN:** Retrospective observational study.

**SETTING AND PARTICIPANTS:** Adult patients admitted to major academic teaching hospitals for a major orthopedic procedure from January 2006 to January 2011.

**METHODS:** The association of serum sodium with log-transformed hospital length of stay was assessed by fitting linear regression models. The association with 30-day mortality was assessed by fitting Cox proportional hazards models.

**RESULTS:** There were 16,206 unique admissions, of which 44.8% were male, with a mean age of 62.5 years.

Mean corrected serum sodium was  $138.5 \pm 2.9$  mmol/L; 1.2% had moderate/severe hyponatremia, 6.4% had mild hyponatremia, and 2.5% were hypernatremic. In adjusted models, compared with normonatremia, moderate/severe hyponatremia, mild hyponatremia, and hypernatremia were associated with a 1.6-, 1.4-, and 1.4-day-longer hospital stay, respectively, and greater risk of 30-day mortality (hazard ratio [HR]: 2.47, 95% confidence interval [CI]: 1.33-4.59 for moderate/severe hyponatremia; HR: 1.80, 95% CI: 1.21-2.66 for mild hyponatremia; and HR: 2.99, 95% CI: 1.79-4.98 for hypernatremia).

**CONCLUSION AND RELEVANCE:** Dysnatremia is relatively common in the hospitalized orthopedic population and associated with greater length of stay and 30-day mortality. Future studies should address potential mechanisms underlying these associations and whether correction of perioperative dysnatremia may improve patient outcomes. *Journal of Hospital Medicine* 2014;9:297-302. © 2014 Society of Hospital Medicine

Sodium is the predominant extracellular cation and a major determinant of serum osmolality. As such, the serum sodium (SNa) concentration in humans is closely maintained by sensitive homeostatic mechanisms. However, disorders of sodium homeostasis are relatively common in selected patient populations, resulting in hyponatremia (<135 mmol/L) or hypernatremia (>144 mmol/L).<sup>1,2</sup>

The presence of hyponatremia is independently associated with greater mortality in hospitalized individuals,<sup>3</sup> including patients with congestive heart failure<sup>4</sup> and cancer.<sup>5</sup> In prior subgroup analyses of patients with musculoskeletal disorders undergoing surgery, hyponatremia (<135 mmol/L) at the time of hospital admission was associated with a 2.31-fold

greater risk of death, compared with normonatremic individuals (135-144 mmol/L).<sup>3</sup> Hyponatremia is also associated with increased fracture risk<sup>6,7</sup> and disturbances of gait<sup>8</sup>; however, controversy remains as to whether this association is causal or simply a marker of comorbid disease. On the other hand, hypernatremia has been associated with greater risk of mortality in critically ill patients<sup>9</sup>; however, there is a relative paucity of data regarding clinical associations in the orthopedic population.

We aimed to examine the relationship of the perioperative SNa (corrected for glucose) with length of stay and 30-day mortality in patients undergoing major orthopedic surgery. We hypothesized that both hypo- and hypernatremia would be associated with greater length of stay and greater 30-day mortality.

## METHODS

### Study Population

Administrative and laboratory data were obtained from individuals admitted to 2 major hospitals in Boston, Massachusetts. Brigham and Women's Hospital is a 793-bed academic medical center; Massachusetts General Hospital is a 907-bed academic medical center. These hospitals provide care to an ethnically and socioeconomically diverse population within eastern

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**TABLE 1.** Characteristics of Study Sample and Comparisons Across Categories of Perioperative Corrected SNa\*

	Perioperative SNa (mmol/L)				P†
	≤130, n = 198	131–134, n = 1,036	135–143, n = 15,563	≥144, n = 409	
Age (y)	72.5 ± 14.9	66.8 ± 17.1	62.6 ± 16.5	65.1 ± 17.0	<0.001
Male (%)	32.3	45.5	45.2	37.2	<0.001
Black (%)	1.6	4.2	4.7	5.3	0.18
CHF (%)	13.1	9.2	4.5	6.6	<0.001
DM (%)	10.1	13.3	12.4	12.0	0.61
Cancer (%)	14.1	10.8	4.5	4.4	<0.001
COPD (%)	13.1	14.4	13.1	14.2	0.63
Hypothyroid (%)	12.1	11.0	10.5	10.3	0.84
Liver disease (%)	2.0	1.1	0.6	0.5	0.02
D-CI score					<0.001
0	43.4	48.0	61.5	60.6	
1–2	41.4	38.6	31.9	33.8	
≥3	15.2	13.4	6.6	6.6	
Glucose (mg/dL)	142 ± 100	136 ± 57	133 ± 42	147 ± 108	<0.001

NOTE: Continuous variables are expressed as means ± standard deviation.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; D-CI, Deyo modification of Charlson Comorbidity Index. DM, diabetes mellitus; SNa, serum sodium.

\*Corrected for simultaneous measurement of glucose.

†P value refers to global testing the null of no difference across categories of admission serum sodium, calculated by analyses of variance for continuous variables and  $\chi^2$  test for categorical variables.

Massachusetts and the surrounding region. The study was deemed exempt by the Partners Institutional Review Board.

The Research Patient Data Registry serves as a central data warehouse for over 1.8 million inpatients and outpatients; it contains information on patient demographics, diagnoses, procedures, medications, inpatient and outpatient encounters, and laboratory results. The database has been accessed previously for clinical studies.<sup>3,10</sup> Between January 1, 2006 and January 27, 2011, data from the index admission of adult individuals undergoing major orthopedic procedures were abstracted from the Research Patient Data Registry (n = 21,663). Those without availability of simultaneous measurements of SNa and glucose within 6 days of surgery (to minimize iatrogenic influences on SNa) were excluded (n = 4995), leaving 16,668 admissions available for analysis. Reasons for exclusion included a length of stay ≤1 day (n = 137) and/or age <18 years (n = 327). The final cohort consisted of 16,206 unique individuals.

The following data were retrieved: age, race, sex, length of stay, vital status (linked to the Social Security Death Index), International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes (up to 10 per patient), and inpatient sodium and glucose measurements. The Deyo modification of the Charlson Comorbidity Index (D-CI) was used to estimate comorbid disease status (sum of the weighted number of comorbid conditions based on 17 diagnostic categories identified from ICD-9-CM diagnosis codes).<sup>11</sup>

**Exposures and Outcomes**

The primary exposure of interest was the serum sodium concentration during hospitalization most

proximal to the day of surgery. All serum sodium measurements were corrected for concomitant serum glucose >100 mg/dL in the following manner: corrected sodium (SNa) = measured sodium + (measured glucose-100/100)\*1.6.<sup>12</sup> SNa was then categorized into moderate/severe hyponatremia (≤130 mmol/L), mild hyponatremia (131–134 mmol/L), normonatremia (135–143 mmol/L), or hypernatremia (≥144 mmol/L). The primary outcomes of interest were hospital length of stay and 30-day mortality. Length of stay was log-transformed due to the highly right-skewed distribution. For mortality analyses, at-risk time was considered from the date of laboratory measurement of SNa until death or 30 days later, whichever came first.

**Statistical Analysis**

Continuous variables were examined graphically and recorded as means (± standard deviations); comparisons were made using t tests. Categorical variables were examined by frequency distribution, recorded as proportions, and comparisons were made using the  $\chi^2$  test.

The association between log-transformed length of stay and category of SNa was assessed by linear regression models; the association with all-cause mortality was assessed by fitting Cox proportional hazards models. Initially unadjusted models were fit. To explore the extent of confounding, case-mix adjusted models were fit as follows: model 1 was adjusted for age, race (black vs nonblack), sex (male vs female), and clinical center. Model 2 was adjusted for the same variables as model 1, in addition to the D-CI score (1, 2, or ≥3) and diagnosis of fracture; model 3 was adjusted for the same covariates as model 2 plus

**TABLE 2.** Association of Categories of Perioperative Corrected SNa With Log-Transformed LOS\*

	Difference (95% CI) in LOS in Days According to Category of Perioperative SNa <sup>†</sup>			
	≤130 mmol/L, n = 198	131–134 mmol/L, n = 1,036	135–143 mmol/L, n = 14,563	≥144 mmol/L, n = 409
Median LOS in days [IQR]	6 [4–9]	5 [4–8]	4 [3–6]	5 [4–7]
Unadjusted	2.2 (1.9–2.6) <i>P</i> < 0.001	1.8 (1.6–1.9) <i>P</i> < 0.001	REF	1.5 (1.3–1.7) <i>P</i> < 0.001
Model 1	2.2 (1.8–2.6) <i>P</i> < 0.001	1.7 (1.6–1.9) <i>P</i> < 0.001	REF	1.5 (1.3–1.7) <i>P</i> < 0.001
Model 2	1.7 (1.4–2.0) <i>P</i> < 0.001	1.4 (1.3–1.5) <i>P</i> < 0.001	REF	1.4 (1.2–1.5) <i>P</i> < 0.001
Model 3	1.6 (1.4–1.9) <i>P</i> < 0.001	1.4 (1.3–1.5) <i>P</i> < 0.001	REF	1.4 (1.2–1.5) <i>P</i> < 0.001
Fracture <sup>‡</sup>				
Present, n = 5,296	1.4 (1.1–1.9) <i>P</i> = 0.02	1.2 (1.0–1.4) <i>P</i> = 0.01	REF	1.7 (1.3–2.1) <i>P</i> < 0.001
Absent, n = 10,910	1.8 (1.5–2.2) <i>P</i> < 0.001	1.5 (1.4–1.7) <i>P</i> < 0.001	REF	1.2 (1.0–1.3) <i>P</i> = 0.02

NOTE: Model 1 adjusted for age, race, sex, and clinical center; model 2 adjusted for same variables as model 1 plus categories of the Deyo Charlson Comorbidity Index and diagnosis of fracture; model 3 adjusted for same as model 2 plus individual diagnostic codes for congestive heart failure, diabetes, cancer, and liver disease.

Abbreviations: CI, confidence interval; LOS, length of stay; SNa, serum sodium.

\*Corrected for simultaneous measurement of glucose.

<sup>†</sup>Exponentiation of the original  $\beta$  coefficients was performed to determine the LOS in days.

<sup>‡</sup>Effect estimates were obtained using model 3, without the inclusion of fracture as a covariate.

individual covariate terms for congestive heart failure (CHF), diabetes, cancer, and liver disease. To further assess for the presence of nonlinear relationships in mortality analyses, restricted and adjusted cubic splines were fit with knots corresponding to SNa values of 135, 137, 139, 141, and 143 mmol/L (approximately the 10th, 25th, 50th, 75th, and 90th percentiles). The linearity assumption for continuous variables was assessed by comparative model fit diagnostics using Akaike's information criterion. The proportionality assumption was assessed by Schoenfeld residual testing.

Subgroup analyses were performed according to the presence or absence of a diagnostic code for fracture. As the majority of patients had their SNa measured on the same day as surgery, sensitivity analyses were performed that restricted inclusion to those individuals with SNa measured within 60 days prior to admission.

Two-tailed *P* values < 0.05 were considered statistically significant. Analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC) and Stata 10MP (StataCorp, College Station, TX).

## RESULTS

### Baseline Characteristics

The primary cohort consisted of 16,206 individuals. Mean age was 62.5 years ( $\pm 16.6$ ), 44.8% were male, 4.6% were black, 4.9% had CHF, and 12.4% were diabetic. The mean SNa was  $138.5 \pm 2.9$  mmol/L; 1.2% had moderate/severe hyponatremia, 6.4% had mild hyponatremia, and 2.5% were hypernatremic. Those with lower SNa tended to be older, female, and more likely to have CHF, cancer, liver disease, and higher comorbidity scores than those with normonatremia (Table 1).

### Hospital Length of Stay

The median length of stay was 4 days (interquartile range, 3–6 days). The unadjusted length of stay was greater for those with hypo- and hypernatremia

compared with those who were normonatremic. In multivariable adjusted models this pattern persisted, with evidence for a J-shaped association for categories of SNa with greater length of stay (Table 2). In adjusted subgroup analyses, similar J-shaped patterns of association (model 3) were evident in those with and without a diagnosis of fracture.

In sensitivity analyses restricted to individuals with SNa available within 60 days prior to admission, the effect estimates for the relationships between categories of hyponatremia and length of stay were qualitatively unchanged (see Supporting Information, Table A, in the online version of this article).

### 30-Day Mortality

Overall, patients contributed 1325 years of at-risk time, during which 208 deaths were recorded within 30 days of orthopedic surgery. In both unadjusted and case-mix adjusted models, there was evidence for the presence of a J-shaped association for categories of SNa with greater 30-day mortality (Table 3). Restricted cubic spline analyses provided additional evidence for the presence of a nonlinear relationship, with hypo- and hypernatremia being associated with greater 30-day mortality (Figure 1). In adjusted subgroup analyses, mild hyponatremia and hypernatremia remained associated with greater mortality in those with fracture, whereas only moderate/severe hyponatremia remained associated with greater mortality in those without a diagnosis of fracture.

In sensitivity analyses, when restricted to individuals with SNa available within 60 days prior to admission, the effect estimates for the relationships between categories of hyponatremia and length of stay were qualitatively unchanged (see Supporting Information, Table B, in the online version of this article).

## DISCUSSION

In this study of hospitalized patients undergoing major orthopedic procedures, we report that abnormal

**TABLE 3.** Association of Categories of Perioperative Corrected SNa With 30-Day Mortality\*

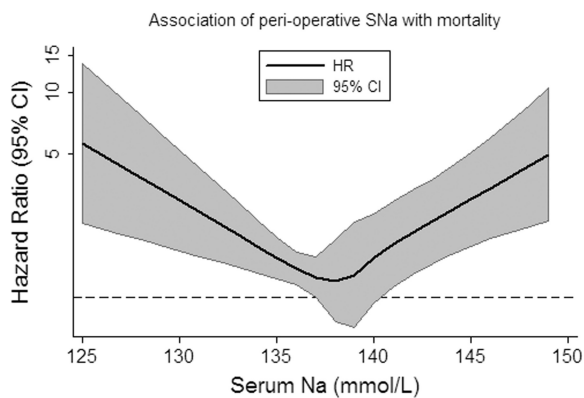
	Hazard Ratio (95% CI) for 30-Day Mortality According to Category of Perioperative SNa			
	<130 mmol/L, n = 198	131–134 mmol/L, n = 1,036	135–143 mmol/L, n = 14,563	≥144 mmol/L, n = 409
Unadjusted	5.73 (3.11-10.6)	3.48 (2.40-5.04)	REF	4.90 (3.03-7.91)
Model 1	3.49 (1.88-6.49)	2.36 (1.60-3.50)	REF	3.83 (2.31-6.35)
Model 2	2.89 (1.56-5.35)	1.96 (1.33-2.90)	REF	3.14 (1.88-5.21)
Model 3	2.47 (1.33-4.59)	1.80 (1.21-2.66)	REF	2.99 (1.79-4.98)
Fracture <sup>†</sup>				
Present, n = 5,296	1.94 (0.84-4.47)	1.83 (1.13-2.97)	REF	3.12 (1.72-5.66)
Absent, n = 10,910	3.85 (1.53-9.68)	1.58 (0.80-3.14)	REF	2.73 (0.98-7.62)

NOTE: Model 1 adjusted for age, race, and sex; model 2 adjusted for same variables as model 1 plus categories of the Deyo Charlson comorbidity index and diagnosis of fracture; model 3 adjusted for same as model 2 plus individual diagnostic codes for congestive heart failure, diabetes, cancer, and liver disease. All models were stratified by clinical center.

Abbreviations: CI, confidence interval; SNa, serum sodium.

\*Corrected for simultaneous measurement of glucose.

<sup>†</sup>Effect estimates were obtained using model 3, without the inclusion of fracture as a covariate.



**FIG. 1.** Association of corrected serum sodium (SNa) with mortality, expressed as a restricted cubic spline with knots at 135, 137, 139, 141, and 143 mmol/L. The multivariable adjusted model (model 3) included covariate terms for age and race (black vs nonblack), sex (male vs female), categories of Deyo-Charlson Comorbidity Index, and individual codes for congestive heart failure, diabetes, cancer, liver disease, and fracture. The model was stratified by clinical center. Estimates are presented for glucose-corrected SNa values between 125 and 150 mmol/L. Abbreviations: CI, confidence interval; HR, hazard ratio.

preadmission and perioperative SNa during hospitalization are: (1) present in approximately 10% of patients, (2) associated with greater hospital length of stay, and (3) associated with greater 30-day mortality.

The incidence of perioperative hyponatremia (<135 mmol/L) in prior studies ranges from 9.1% to 26.5% in studies of patients over 65 years of age admitted to the hospital with large bone fractures.<sup>13,14</sup> In our study, the overall incidence of hyponatremia (SNa <135 mmol/L) was 7.6%. Of note, our sample included individuals aged ≥18 years and was not limited to individuals with fractures, which may partly explain why the incidence was lower than that previously reported.

Few studies have examined the association of perioperative hyponatremia with length of stay in the hospitalized orthopedic surgery population. We found that both hyponatremia and hypernatremia (corrected for glucose) were independently associated with

greater adjusted hospital length of stay, compared with normonatremic individuals. This has important implications for healthcare costs and resource utilization. However, it is unclear if dysnatremia is associated with other metrics of postoperative recovery that could delay discharge, or whether dysnatremia alone is responsible for the decision to delay discharge (despite other measures of recovery being deemed adequate).

Leung et al. recently examined the association of preoperative hyponatremia (<135 mmol/L, uncorrected and measured within 90 days of surgery) with 30-day mortality in 964,263 patients from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) dataset.<sup>15</sup> They found that preoperative hyponatremia was associated with 44% greater adjusted odds (odds ratio [OR]: 1.44, 95% CI: 1.38-1.50) of 30-day mortality in the whole cohort and with 56% greater adjusted odds (OR: 1.56, 95% CI: 1.22-1.99) in the subgroup of orthopedic patients. Waikar et al. also reported that hyponatremia is associated with greater in-hospital and long-term mortality in the subgroup of hospitalized patients who were admitted for musculoskeletal problems requiring surgery.<sup>3</sup> Our analyses support these findings and provide greater confidence by specifically focusing on patients admitted for major orthopedic surgery. We also expand the current knowledge base by correcting for serum glucose concentrations and by reporting associations of moderate/severe hyponatremia with adverse clinical outcomes.

The incidence of perioperative hypernatremia in our study was 2.5%, which compares to 1.0% to 2.6% in other studies of orthopedic patients.<sup>14,16</sup> Hypernatremia has previously been associated with greater mortality in hospitalized patients in the intensive care unit (ICU) setting at the time of admission,<sup>17</sup> during the ICU stay,<sup>9</sup> in older patients (>60 years),<sup>18</sup> and in those with decompensated liver disease.<sup>19</sup> More recently, Leung et al. performed further analyses using

data from the ACS NSQIP, reporting that preoperative hypernatremia (>144 mmol/L, uncorrected and measured within 90 days of surgery) is associated with 44% greater adjusted odds (OR: 1.44, 95% CI: 1.33-1.56) of 30-day mortality, but was not significantly associated with greater mortality in the orthopedic subgroup.<sup>20</sup> We extend the literature by examining glucose-corrected SNa and again by focusing specifically on those undergoing major orthopedic surgery, reporting an association of perioperative hypernatremia with greater length of stay and 30-day mortality. In our study, when we specifically examined the association of preoperative SNa values, we noted attenuation of the effect estimates and loss of statistical significance, confirming the subgroup findings of Leung et al.<sup>20</sup> The reasons for this are not clear, but may relate to the possibility that perioperative hypernatremia (as opposed to preoperative) is a stronger marker of concurrent illness severity and therefore more closely associates with adverse clinical outcomes.

As with most observational studies in this area, the question of whether dysnatremia is causative or merely a marker of comorbidity remains. In this regard, there are some unique points that deserve mention in this cohort of patients. Hyponatremia has previously been associated with several musculoskeletal abnormalities, including a greater risk of fracture,<sup>7,16,21</sup> which may contribute to the observed associations with greater morbidity and mortality. For example, Verbalis et al. reported that the induction and maintenance of hyponatremia by administration of 1-deamino-8-D-arginine vasopressin in rodent models is associated with reduced bone mineral density in excised rat femurs, which may predispose to greater fracture risk.<sup>22</sup> In humans, the same authors reported that hyponatremia (<135 mmol/L) was independently associated with greater odds of having osteoporosis at the femoral neck in individuals aged 50 years or older (OR: 2.87, 95% CI: 1.41-5.81), compared with normonatremic individuals (135-145 mmol/L).<sup>22</sup> On the other hand, Kinsella et al. found that hyponatremia (<135 mmol/L) associated with greater odds of having a fracture (OR: 2.25, 95% CI: 1.24-4.09), independent of the presence of osteoporosis as measured by hip and vertebral T-scores, suggesting an association between hyponatremia and fracture, independent of osteoporosis.<sup>6</sup> Other potential confounders of these associations may include gait disturbance and unsteadiness, which could contribute to greater fall and fracture risk.<sup>7,8,21</sup> Additional proposed mechanisms for the association of hyponatremia with adverse outcomes include the development of cerebral edema,<sup>23</sup> abnormal nerve conduction,<sup>24</sup> and predisposition to infection,<sup>25</sup> perhaps via altered immune functioning in the presence of hypo-osmolality. Unfortunately, due to data limitations, we were unable to investigate these hypotheses further in our present

study. In relation to hypernatremia, associations with impairment in neurologic,<sup>26</sup> myocardial,<sup>27</sup> and immune functioning have been reported previously, which may contribute to some of the excess risk associated with this condition.

There are several limitations of this study that deserve further mention. We used ICD-9 and diagnosis-related group codes to ascertain data on primary diagnoses and comorbid conditions, raising the possibility of some degree of misclassification of covariates in this study. We were unable to differentiate between elective versus urgent/emergent procedures. Given the large sample size and intrinsic data limitations, we were unable to ascertain the underlying causes of dysnatremia, or examine practice differences between the 2 institutions from which the sample was sourced. The majority of our sample had perioperative SNa measurements performed on the same day as their major orthopedic procedure. Although we were unable to confirm the timing of SNa measurements relative to the operation, it is not uncommon for elective cases to have initial hospitalization labs drawn in the recovery room, as opposed to preoperatively. In sensitivity analyses, we found similar patterns of association for hyponatremia with outcomes, but not for hypernatremia, when we examined the SNa measurement within 60 days prior to admission as the exposure of interest. Although these analyses were underpowered, they provide some modicum of reassurance that the observed associations of perioperative hyponatremia with adverse outcomes are robust. Whether perioperative dysnatremia, measured in the recovery room, has associations with clinical outcomes that are distinct from immediate preoperative dysnatremia requires further research. The possibility of residual confounding (eg, administration of fluids, medications, severity of illness) that was not captured by the D-CI index, functional status and infection remain important considerations. Finally, caution must be applied before generalizing our results from 2 large academic centers to the general hospitalized orthopedic population.

In conclusion, we report that dysnatremia on admission for patients requiring major orthopedic surgery is present in approximately 10% of patients and is associated with greater length of stay and all-cause mortality. Further research is required to assess whether dysnatremia is a mediator or marker for increased morbidity and mortality, and whether perioperative correction of hypo- or hypernatremia will improve clinical outcomes in these patients.

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## References

- Palevsky PM. Hyponatremia. *Semin Nephrol.* 1998;18(1):20–30.
- Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med.* 2006;119(7suppl 1):S30–S35.
- Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med.* 2009;122(9):857–865.
- Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA.* 2003;290(19):2581–2587.
- Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatremia in medical cancer patients: epidemiology, aetiology and differential diagnosis. *Support Care Cancer.* 2000;8(3):192–197.
- Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol.* 2010;5(2):275–280.
- Hoorn EJ, Rivadeneira F, van Meurs JB, et al. Mild hyponatremia as a risk factor for fractures: the Rotterdam Study. *J Bone Miner Res.* 2011;26(8):1822–1828.
- Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med.* 2006;119(1):71.e71–78.
- Lindner G, Funk GC, Lassnigg A, et al. Intensive care-acquired hyponatremia after major cardiothoracic surgery is associated with increased mortality. *Intensive Care Med.* 2010;36(10):1718–1723.
- Waikar SS, Wald R, Chertow GM, et al. Validity of international classification of diseases, ninth revision, clinical modification codes for acute renal failure. *J Am Soc Nephrol.* 2006;17(6):1688–1694.
- Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613–619.
- Katz MA. Hyperglycemia-induced hyponatremia—calculation of expected serum sodium depression. *N Engl J Med.* 1973;289(16):843–844.
- Sandhu HS, Gilles E, DeVita MV, Panagopoulos G, Michelis MF. Hyponatremia associated with large-bone fracture in elderly patients. *Int Urol Nephrol.* 2009;41(3):733–737.
- Beloosesky Y, Hershkovitz A, Solovey B, Salai M, Weiss A. Hip fracture post-operation dysnatremia and Na<sup>+</sup>-courses in different cognitive and functional patient groups. *Arch Gerontol Geriatr.* 2011;53(2):179–182.
- Leung AA, McAlister FA, Rogers SO Jr, Pazo V, Wright A, Bates DW. Preoperative hyponatremia and perioperative complications. *Arch Intern Med.* 2012;172(19):1474–1481.
- Lewis JR, Hassan SK, Wenn RT, Moran CG. Mortality and serum urea and electrolytes on admission for hip fracture patients. *Injury.* 2006;37(8):698–704.
- Lindner G, Funk GC, Schwarz C, et al. Hyponatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis.* 2007;50(6):952–957.
- Snyder NA, Feigal DW, Arief AI. Hyponatremia in elderly patients. A heterogeneous, morbid, and iatrogenic entity. *Ann Intern Med.* 1987;107(3):309–319.
- Warren SE, Mitas JA II, Swerdlin AH. Hyponatremia in hepatic failure. *JAMA.* 1980;243(12):1257–1260.
- Leung AA, McAlister FA, Finlayson SR, Bates DW. Preoperative hyponatremia predicts increased perioperative morbidity and mortality. *Am J Med.* 2013;126(10):877–886.
- Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. *QJM.* 2008;101(7):583–588.
- Verbalis JG, Barsony J, Sugimura Y, et al. Hyponatremia-induced osteoporosis. *J Bone Miner Res.* 2010;25(3):554–563.
- Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. *Am J Kidney Dis.* 2013;62(1):139–149.
- Aranyi Z, Kovacs T, Szirmai I, Vastagh I. Reversible nerve conduction slowing in hyponatremia. *J Neurol.* 2004;251(12):1532–1533.
- Jensen AG, Wachmann CH, Poulsen KB, et al. Risk factors for hospital-acquired Staphylococcus aureus bacteremia. *Arch Intern Med.* 1999;159(13):1437–1444.
- Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med.* 2000;342(20):1493–1499.
- Lenz K, Gossinger H, Laggner A, Druml W, Grimm G, Schneeweiss B. Influence of hypernatremic-hyperosmolar state on hemodynamics of patients with normal and depressed myocardial function. *Crit Care Med.* 1986;14(10):913–914.