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ORIGINAL RESEARCH

Evaluation of Incremental Healthcare Resource Burden and Readmission Rates Associated With Hospitalized Hyponatremic Patients in the US

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BACKGROUND: Hyponatremia is a prevalent electrolyte disorder in hospitalized patients indicative of greater morbidity and mortality. A large-scale retrospective analysis was conducted to evaluate the incremental burden of hospitalized hyponatremic (HN) versus non-HN patients in terms of hospital resource utilization, costs, and hospital readmissions in the real-world setting.

METHODS: HN patients (≥18 years) were selected from the Premier Hospital Database between January 1, 2007 and March 31, 2010 and matched to a non-HN control cohort using propensity score matching. Bivariate and multivariate statistics were employed to evaluate the differences in healthcare resource utilization, costs, and hospital readmissions between patient cohorts.

RESULTS: Among the matched patient cohorts, length of stay (LOS) (8.8 ± 10.3 vs 7.7 ± 8.5 days, $P < 0.001$), hospital admission costs ($15,281 ± $24,054 vs $13,439 ± $22,198, $P < 0.001$), intensive care unit (ICU) LOS (5.5 ± 7.9 vs 4.9 ± 7.1 days, $P < 0.001$), and ICU costs ($8525 ± $13,342 vs $7597 ± $12,695, $P < 0.001$) were greater for the HN versus non-HN cohort, as were hospital readmission rates 30 days postdischarge. Multivariate regressions further demonstrated that hyponatremia was associated with an increase of 10.9% for LOS, 8.2% for total hospitalization costs, 10.2% for ICU LOS, and 8.9% for ICU costs. Additionally, after multivariate adjustment, hyponatremia was associated with a 15.0% increased chance for hospital readmission 30 days postdischarge ($P < 0.0001$).

CONCLUSIONS: Hyponatremia is an independent predictor of increased hospitalization LOS and cost, ICU admission and cost, and 30-day hospital readmission, and therefore represents a potential target for intervention to reduce healthcare expenditures for a large population of hospitalized hyponatremic patients. *Journal of Hospital Medicine* 2012;7:634–639. © 2012 Society of Hospital Medicine

Hyponatremia is an electrolyte disorder most commonly defined as a serum sodium concentration <135 mEq/L.[1] Its exact definition can vary across studies, but typically ranges between <130 and <138 mEq/L.[2,3] Signs and symptoms of hyponatremia can include malaise, headache, disorientation, confusion, muscle weakness, and cramps. If severe, seizures, respiratory arrest, brainstem herniation, coma, and death may result.

The incidence of hyponatremia in the general hospitalized population has been reported to range between 1% and 6% when defined as <130–135 mEq/L,[4,5] and its occurrence increases with a more prolonged hospital stay to 13%.[6] A recent study reported that when hyponatremia was defined with a less stringent threshold of <138 mEq/L, the incidence at admission rose to 38%.[3] Hyponatremia is a comorbid condition of multiple diseases, occurring in approximately 20% of patients with heart failure,[7,8] and 40% to 57% of patients with advanced cirrhosis.[9,10] The syndrome of the inappropriate release of antidiuretic hormone (SIADH) is additionally a predominant cause of hyponatremia, with a prevalence reported as high as 35% in hospitalized patients.[11]

Hyponatremia is not only widespread, but also an independent predictor of mortality. In a retrospective cohort analysis, Waikar et al reported that in comparison to patients who were normonatremic, patients with serum sodium concentrations <135 mEq/L had a risk of in-hospital mortality as high as 47%, and that this risk doubled for patients with serum sodium concentrations between 125 and 129 mEq/L.[6] In the study by Wald et al, which defined hyponatremia as <138 mEq/L, the risk of in-hospital mortality was similar.[3] In both of these studies, even mild hyponatremia (130–137 mEq/L) was associated with increased risk of in-hospital mortality.[3,6]

The overall cost of hyponatremia is estimated to range between $1.6 and $3.6 billion for 2011.[12,13] Hospital readmissions are a significant contributor to total healthcare costs, with some being entirely avoidable with increased standards of care. The Centers for Medicare and Medicaid Services has begun to not only publicly report hospital readmission rates, but also penalize hospitals for early readmissions.[14]

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Strategies to reduce hospital readmissions are currently being integrated into healthcare reform policy.[14] In the present study, the incremental burden of hospitalized hyponatremic (HN) versus non-HN patients in terms of hospital resource utilization, costs, and early hospital readmission in the real-world was evaluated.

METHODS

Study Design

This study was a retrospective analysis that examined healthcare utilization and costs among HN patients using the Premier Hospital Database. The database contains over 310 million hospital encounters from more than 700 US hospitals, or 1 out of every 4 discharges in the US. The administrative data available included patient and provider demographics, diagnoses and procedures, as well as date-stamped billing records for all pharmacy, laboratory, imaging, procedures, and supplies.

Patient Selection and Matching

HN patients were eligible for study inclusion if they were a hospital inpatient discharged between January 1, 2007 and March 31, 2010, were >18 years of age at admission, and had either a primary or secondary diagnosis of hyponatremia or hyposmolality (defined as International Classification of Diseases, Ninth Revision (ICD-9-CM) code: 276.1x). Patients were excluded if they had been transferred from another acute care facility, transferred to another acute care or critical access facility, or left against medical advice. Labor and delivery patients (ICD-9-CM codes: 72.xx-74.xx, V22.x, V23.x, V27.x, and V28.x), and patients classified as observational were also excluded. A second cohort of non-hyponatremic patients was created using the same inclusion and exclusion criteria, with the exception that patients not have a primary or secondary diagnosis of hyponatremia or hyposmolality (defined as ICD-9-CM code: 276.1x).

The matching of hyponatremia (HN) and control (non-HN) cohorts was accomplished using a combination of exact and propensity score matching techniques. Patients were first exact matched on age, gender, Medicare Severity-Diagnosis Related Group (MS-DRG) assignment, and hospital geographic region. Propensity score matching was further utilized to create the final study cohorts for outcomes comparisons. Propensity score matching is commonly used in retrospective cohort studies to correct for sample selection bias due to observable differences between groups.[15,16] The propensity score was generated using logistic regression with the dependent variable as hyponatremia (yes vs no) and the following covariates: age, race, admission source, attending physician specialty, 3M All Patient Refined-Diagnosis Related Group (APR-DRG) Severity of Illness and Risk of Mortality index scores, Deyo-Charlson Comorbidity Index score, selected hyponatremia-related comorbidity conditions, and hospital size, region, and urban/rural designation. These covariates were initially selected by an expert panel of physicians, and backward selection was utilized in the logistic regression using the most parsimonious model.[17]

Following generation of the propensity scores, HN patients were matched to non-HN patients 1:1 using a nearest neighbor matching algorithm, including hospital identification and propensity score.[18] Inclusion of hospital identification in the matching sequence, as well as provider characteristics, especially hospital size, attending physician specialty, and geographic region in the propensity score, was used to control for potential clustering effects at the physician and hospital level.[19] During the propensity score matching process, likelihood-ratio test, Hosmer-Lemshow goodness of fit, and concordance c statistics were utilized to assess the fitness of the models.[20] The final propensity score model produced a concordance c statistic of 0.8.

Outcome Measures and Statistical Analyses

The following outcome measures were compared between the matched HN and non-HN patient cohorts: total and intensive care unit (ICU) hospitalization costs, total and ICU length of stay (LOS), ICU admission, and 30-day hospital readmission. Bivariate descriptive statistics were employed to test for significant differences in demographics, patient clinical characteristics, and unadjusted costs and healthcare resource utilization and readmission rates between patient cohorts. To detect statistically significant differences in continuous and categorical variables, respectively, *t* tests and chi-square tests were performed.

Multivariate analysis of outcome measures utilized generalized linear models. Due to the skewed nature of LOS and cost data, LOS was analyzed using multivariate negative binomial regression and cost was analyzed using multivariate gamma regression.[21] Binary outcomes (ICU admission and 30-day readmission) were analyzed using multivariate logistic regression. The analysis accounted for potential confounding factors by inclusion of the following covariates: age group, gender, race, admission source, and Deyo-Charlson Comorbidity Index score. These covariates were previously identified in the Wald et al hyponatremia study,[3] and were verified using likelihood-ratio, Hosmer-Lemshow goodness of fit, and concordance c statistics.

Subgroup Sensitivity Analysis

For the subgroup sensitivity analyses, patients were identified as having community-acquired pneumonia (CAP), congestive heart failure (CHF), urinary tract infection (UTI), or chronic obstructive pulmonary disease (COPD) based upon principal diagnosis codes. Patients were categorized according to these subgroup

TABLE 1. Baseline Demographics and Clinical and Hospital Characteristics for Matched Cohorts of Hyponatremic and Non-Hyponatremic Patients

	Hyponatremic Discharges N (%)	Non-Hyponatremic Discharges N (%)
Sample Discharges	558,815 (100.0%)	558,815 (100.0%)
Age median (IQR)	70.00 (57.0–81.0)	70.00 (57.0–81.0)
Gender		
Female	319,069 (57.1%)	319,069 (57.1%)
Male	239,746 (42.9%)	239,746 (42.9%)
Race		
American Indian	3,465 (0.6%)	3,448 (0.6%)
Asian/Pacific	10,065 (1.8%)	9,690 (1.7%)
Black	63,776 (11.4%)	66,233 (11.9%)
Hispanic	24,341 (4.4%)	24,426 (4.4%)
White	377,434 (67.5%)	376,639 (67.4%)
Other/unknown	79,734 (14.3%)	78,379 (14.0%)
Primary payer		
Medicare—traditional	310,312 (55.5%)	310,643 (55.6%)
Managed care	75,476 (13.5%)	78,184 (14.0%)
Medicare—managed care	45,439 (8.1%)	47,947 (8.6%)
Non-cap		
Medicaid	44,690 (8.0%)	43,767 (7.8%)
Other	82,898 (14.8%)	78,274 (14.0%)
Admission source		
Physician referral	5,022 (0.9%)	4,636 (0.8%)
Transfer from another nonacute health facility	18,031 (3.2%)	18,163 (3.3%)
Emergency room	417,556 (74.7%)	420,401 (75.2%)
Other/unknown	118,206 (21.2%)	115,615 (20.7%)
APR-DRG severity of illness		
1—Minor	14,257 (2.6%)	12,993 (2.3%)
2—Moderate	174,859 (31.3%)	179,356 (32.1%)
3—Major	263,814 (47.2%)	265,422 (47.5%)
4—Extreme	105,885 (19.0%)	101,044 (18.1%)
Attending physician specialty		
Internal Medicine	235,628 (42.1%)	240,875 (43.1%)
Hospitalist	88,250 (15.8%)	87,720 (15.7%)
Family Practice (FP)	73,346 (13.1%)	72,828 (13.0%)
Orthopedic Surgery (ORS)	23,595 (4.2%)	22,949 (4.1%)
Cardiovascular Diseases (CD)	19,521 (3.5%)	18,057 (3.2%)
Comorbidities		
Human immunodeficiency virus	3,971 (0.7%)	4,018 (0.7%)
Cancer/neoplasm/malignancy	107,851 (19.3%)	105,199 (18.8%)
Pulmonary disease	77,849 (13.9%)	77,184 (13.8%)
Cirrhosis/hepatic disease	23,038 (4.1%)	23,418 (4.2%)
SIADH	1,972 (0.4%)	1,278 (0.2%)
Subgroup populations		
Community-acquired pneumonia	26,291 (4.7%)	26,291 (4.7%)
Congestive heart failure	23,020 (4.1%)	23,020 (4.1%)
Urinary tract infection	14,238 (2.6%)	14,238 (2.6%)
COPD	8,696 (1.6%)	8,696 (1.6%)
CCI median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–5.0)
No. of premier hospitals	459	
Provider region		
East North Central	78,332 (14.0%)	78,332 (14.0%)
East South Central	32,122 (5.8%)	32,122 (5.8%)
Middle Atlantic	73,846 (13.2%)	73,846 (13.2%)
Mountain	23,761 (4.3%)	23,761 (4.3%)
New England	9,493 (1.7%)	9,493 (1.7%)
Pacific	73,059 (13.1%)	73,059 (13.1%)
South Atlantic	175,194 (31.4%)	175,194 (31.4%)
West North Central	37,913 (6.8%)	37,913 (6.8%)
West South Central	55,095 (9.9%)	55,095 (9.9%)
Population served		
Rural	69,749 (12.5%)	68,414 (12.2%)
Urban	489,066 (87.5%)	490,401 (87.8%)
Teaching status		
Non-teaching	337,620 (60.4%)	337,513 (60.4%)
Teaching	221,195 (39.6%)	221,302 (39.6%)
No. of hospital beds		
6–99	22,067 (4.0%)	21,777 (3.9%)
100–199	57,367 (10.3%)	56,097 (10.0%)
200–299	87,563 (15.7%)	86,639 (15.5%)
300–499	218,834 (39.2%)	220,248 (39.4%)
500+	172,984 (31.0%)	174,054 (31.2%)

(Continued)

TABLE 1. (*Continued*)

Abbreviations: APR-DRG, all patient refined diagnosis-related groups; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SIADH, syndrome of inappropriate antidiuretic hormone hypersecretion.

definitions, and then previously matched patients with the same subgroup classification constituted the final analysis set for each subgroup. The methods that were used for the overall matched analysis were then applied to each subgroup to evaluate the incremental burden of overall cost and LOS associated with hyponatremia.

RESULTS

Patient Population

Of the 606,057 HN patients eligible for matching, a total of 558,815 HN patients were matched to 558,815 non-HN patients, a 92% match ratio. Table 1 describes the overall characteristics of the patient populations. For both cohorts, median age was 70 years, 57% of patients were female, and approximately 67% were white. The majority of patients in either cohort had Medicare coverage (55%), and approximately 75% of patients entered the hospital via the emergency room with nearly 70% having a 3M APR-DRG disease severity level of major or extreme. Patients of both cohorts were most often attended by an internist or a hospitalist, with a combined percentage of approximately 60%. A small, but greater proportion of HN patients had comorbidities of cancer, pulmonary disease, and SIADH. Comorbid conditions of liver cirrhosis/hepatic disease and human immunodeficiency virus (HIV) were similarly distributed among both patient cohorts.

Hospital Characteristics

Patient cohorts had similar distributions with respect to hospital characteristics (Table 1). Approximately 30% of patients were provided care from hospitals located in the South Atlantic region, and between 10% and 15% were serviced from hospitals in the East North Central, Middle Atlantic, Pacific, and West South Central regions. Most hospitals providing care for patient cohorts served urban populations (88%) and were large, with hospital bed numbers

TABLE 2. Outcome Measurements for Matched Cohorts of Hyponatremic and Non-Hyponatremic Patients

	Hyponatremic	Non-Hyponatremic	*P* Value
Total LOS (mean ± SD)	8.8 ± 10.3	7.7 ± 8.5	<0.001
Total hospitalization cost (mean ± SD)	$15,281 ± $24,054	$13,439 ± $22,198	<0.001
ICU admission (N, %)	129,235 (23.1%)	123,502 (22.1%)	<0.001
ICU LOS (mean ± SD)	5.5 ± 7.9	4.9 ± 7.1	<0.001
ICU cost (mean ± SD)	$8,525 ± $13,342	$7,597 ± $12,695	<0.001
30-Day all cause readmission (N, %)	96,063 (17.5%)	87,058 (16.4%)	<0.001

Abbreviations: ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

≥300. Approximately 60% of hospitals were non-teaching hospitals.

Healthcare Utilization, Readmission, and Cost Differences Among Patient Cohorts

The mean LOS (8.8 ± 10.3 vs 7.7 ± 8.5, $P < 0.001$), a difference of 1.1 days and mean ICU LOS (5.5 ± 7.9 vs 4.9 ± 7.1 days, $P < 0.001$), a difference of 0.6 days were significantly greater for the HN cohort in comparison to the non-HN cohort (Table 2). The increase in healthcare resource utilization of patients with HN was reflected in their significantly higher mean total hospital costs per admission ($15,281 ± $24,054 vs $13,439 ± $22,198, $P < 0.001$), a difference of $1842; and mean costs incurred in the ICU ($8525 ± $13,342 vs $7597 ± $12,695, $P < 0.001$), a difference of $928 (Table 2). Furthermore, patients in the HN cohort were significantly more likely to be readmitted to the hospital for any cause (17.5% vs 16.4%, $P < 0.001$) (Table 2).

Multivariate Analysis

Multivariate analysis demonstrated hyponatremia was associated with an increase in mean hospital LOS of 10.9%, [95% confidence interval: 10.4%–11.5%], ($P < 0.0001$) and an increase in mean total hospital costs of 8.2%, [7.4%–9.0%], ($P < 0.0001$) (Table 3). Additionally, hyponatremia was associated with an increase in ICU LOS of 10.2%, [8.7%–11.8%], ($P < 0.0001$), and a higher ICU cost of 8.9%, [7.2%–10.7%], ($P < 0.0001$) (Table 3). Hyponatremia was not associated with a greater likelihood of ICU admission (odds ratio = 1.0; [1.0–1.0], $P = .5760$). However, the condition was associated with a significantly greater chance of hospital readmission (odds ratio = 1.2, [1.1–1.2], $P < 0.0001$) within 30 days postdischarge (Table 3).

Subgroup Sensitivity Analyses

For patients with CAP (n = 52,582), CHF (n = 46,040), a UTI (n = 28,476), or COPD (n = 17,392), the percent increases in LOS and all cause hospitalization cost of the HN cohort in comparison to the non-HN cohort were 5.4% ($P < 0.0001$) and 5.6% ($P < 0.0001$), 20.6% ($P < 0.0001$) and 19.2% ($P < 0.0001$), 2.7% ($P = 0.0003$) and 2.2% ($P = 0.0582$), and 6.7% ($P < 0.0001$) and 5.6% ($P < 0.0001$), respectively (Table 3).

DISCUSSION

This large-scale, real-world hospital database study provides healthcare utilization and cost data on the largest population of HN patients that has currently been studied. The results of this study are consistent with others in showing that HN patients use healthcare services more extensively, and represent a patient population which is more expensive to treat in the inpatient setting.[5,22] Additionally, this study yields new findings in that patients in the real-world with hyponatremia resulting from various etiologies are more likely to be readmitted to the hospital than patients with similar demographics and characteristics who do not have hyponatremia. The results of the

TABLE 3. Relative Difference (Mean [CI]) in Healthcare Utilization, Costs, and Odds for ICU and Early Readmission Based on Multivariate Analysis for Hyponatremic Patients vs Non-Hyponatremic Patients

	Overall Cohort N = 1,117,630	CAP N = 52,582	CHF N = 46,040	UTI N = 28,746	COPD N = 17,392
Total LOS difference	10.9% [10.4%, 11.5%] *P* < 0.0001	5.4% [4.4%, 6.5%] *P* < 0.0001	20.6% [19.0%, 22.2%] *P* < 0.0001	2.7% [1.2%, 4.2%] *P* = 0.0003	6.7% [4.8%, 8.5%] *P* < 0.0001
Total cost difference	8.2% [7.4%, 9.0%] *P* < 0.0001	5.6% [4.0%, 7.0%] *P* < 0.0001	19.2% [17.1%, 21.4%] *P* < 0.0001	2.2% [−1.4%, 4.4%] *P* = 0.0582	5.6% [3.0%, 8.2%] *P* < 0.0001
ICU admission* odds ratio	1.0 [1.0, 1.0] *P* = 0.5760	1.0 [1.0, 1.1] *P* = 0.8363	1.2 [1.1, 1.3] *P* < 0.0001	1.2 [1.1, 1.3] *P* = 0.0038	1.0 [0.9, 1.1] *P* = 0.5995
ICU LOS difference	10.2% [8.7%, 11.8%] *P* < 0.0001	8.4% [3.4%, 13.7%] *P* = 0.0008	24.8% [19.9%, 29.9%] *P* < 0.0001	4.9% [−4.0%, 14.7%] *P* = 0.2893	10.1% [1.5%, 19.3%] *P* = 0.0204
ICU cost difference	8.9% [7.2%, 10.7%] *P* < 0.0001	8.2% [2.7%, 14.0%] *P* = 0.0029	24.1% [18.9%, 29.7%] *P* < 0.0001	2.8% [−6.7%, 13.4%] *P* = 0.5739	8.4% [−0.6%, 18.1%] *P* = 0.6680
30-Day readmission† odds ratio	1.2 [1.1, 1.2] *P* < 0.0001	1.0 [0.9, 1.0] *P* = 0.5141	1.1 [1.1, 1.2] *P* < 0.0001	1.0 [1.0, 1.1] *P* = 0.5211	1.0 [1.0, 1.1] *P* = 0.6119

Abbreviations: CAP, community-acquired pneumonia; CHF, congestive heart failure; CI, confidence interval [lower, upper]; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; UTI, urinary tract infection. *The number and percentage of patients, hyponatremic and non-hyponatremic in each group, admitted to the ICU were the following: overall: 252,737 (22.6%); CAP: 6321 (12.0%); CHF: 8293 (18.0%); UTI: 1243 (4.4%); COPD: 1687 (9.7%). †The number and percentage of patients, hyponatremic and non-hyponatremic in each group, admitted to the hospital within 30 days of discharge were the following: overall: 183,121 (16.4%); CAP: 7310 (14.6%); CHF: 10,466 (24.0%); UTI: 4306 (15.3%); COPD: 3346 (19.7%).

subgroup analysis were generally consistent with the results for the overall matched population, as the incremental burden estimates were directionally consistent. However, among the specific subgroups of patients, although it appears that hyponatremia is predictive of hospital readmission in patients with CHF, it did not necessarily correspond with hospital readmission rates among patients with CAP, UTI, or COPD. Therefore, hyponatremia, at least for patients with these latter conditions, may not be predictive of readmission, but remains associated with increased healthcare utilization during the initial hospitalization. Further evaluation of the incremental burden of hyponatremia among patients with specific disease conditions is needed to validate the findings.

The difference in hospital LOS at first admission between HN and non-HN patients in this study was 1.1 days, and comparable to that reported by Shorr et al.[23] In the study by Shorr et al, patients hospitalized for congestive heart failure (CHF), who were HN, had a 0.5 day increased LOS, and those who were severely HN had a 1.3 day increased LOS.[23] Two other retrospective cohort analyses reported a 1.4 day[5] and 2.0 day[22] increased LOS for HN patients in comparison to non-HN patients. Zilberberg et al and Callahan et al additionally reported that HN patients had a significantly greater need for ICU (4%–10%).[5,22] In the present study, LOS in the ICU and associated costs were also compared among HN and non-HN cohorts and, after adjustment for key patient characteristics, hyponatremia was associated with an incremental increase of 10.2% for ICU LOS and an 8.9% increase in ICU cost.

In this study, patients with hyponatremia of any severity were found to have a mean increase in hospital cost per admission of $1842, with multivariate analysis demonstrating an associated incremental increase of 8.2%. These results are also comparable to that reported in other retrospective cohort analyses. Shorr et al reported that in-hospital costs attributed to hyponatremia were $509, and for severe hyponatremia were $1132.[23] Callahan et al reported a $1200 increase in costs per admission for patients with mild-to-moderate hyponatremia, and a $3540 increase for patients with moderate-to-severe hyponatremia, in comparison to non-HN patients.[22]

The Institute for Healthcare Improvement reports that hospitalizations account for nearly one-third of the $882 billion spent on healthcare in the US in 2011, and that a substantial fraction of all hospitalizations are readmissions.[13,24] A recent meta-analysis of 30-day hospital readmission rates found 23.1% were classified as avoidable.[25] Readmission rates of HN patients in comparison to non-HN patients have been reported in 3 other studies, all of which were conducted on clinical trial patients with heart failure.[7,8,26] Two of these studies, which evaluated only patients with acute class IV heart failure,[8,26] reported that hyponatremia was associated with a significant increase in readmission rates (up to 20% higher), and the other, which evaluated any patients hospitalized for heart failure, did not.[7] The differences there may be partially attributed to the differences in heart failure severity among patient populations, as hyponatremia is an independent predictor of worsening heart failure. The only published study to date on the influence of hyponatremia on readmission rates in the real-world was conducted by Scherz et al, who reported that the co-occurrence of hyponatremia in patients with acute pulmonary embolism, discharged from 185 hospitals in Pennsylvania, was independently associated with an increased readmission rate of 19.3%.[27] In the present study, hyponatremia was associated with an incremental increase ranging between 14% and 17% for hospital readmission for any cause. It was conducted on a patient population in which hyponatremia was resultant from many causes, and not all patients had a serious comorbid condition. Also, the HN and non-HN cohorts were matched for comorbidity prevalence and disease severity, and in other studies they were not. Therefore, the results of this study importantly imply that hyponatremia, whether it is resultant from a serious disease or any other cause substantially increases the healthcare burden. The implementation of strategies to prevent hospital readmissions may play an important role in reducing the healthcare burden of hyponatremia, and future studies are warranted to evaluate this hypothesis alongside evaluation of the outpatient hyponatremia burden.

The limitations of this study include, firstly, that it is only representative of inpatient hospital costs, and excludes outpatient healthcare utilization and costs. Secondly, this study utilized the Premier Hospital Database for patient selection, and laboratory testing data for serum sodium level are not available in this database; therefore, the severity of hyponatremia could not be accurately established in the HN patient population. Thirdly, the occurrence of hyponatremia in patients with some diseases is a marker of disease severity, as is the case with congestive heart failure and cirrhosis.[23,28] Our study did not adjust for the specific disease (eg, CHF) severity, which may influence the results. Future research is needed to evaluate the impact of hyponatremia on underlying disease severity of other diseases, and how its co-occurrence may influence healthcare resource utilization and cost in each case. Although the Premier Hospital Database contains information from a large number of hospitals across the US, it is possible that it may not be representative of the entire US population of HN patients. Additionally, billing and coding errors and missing data could potentially have occurred, although the large patient population size likely precludes a large impact on the results of this study. Finally, the frequency of use of fluid restriction in these hospital settings could not be chronicled, thus limiting the ability to assess therapies and treatment modalities in use.

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