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Do Hyponatremia or Its Underlying Mechanisms Associate With Mortality Risk in Observational Data?

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Objectives: Whether unaccounted determinants of hyponatremia, rather than water excess per se, primarily associate with mortality in observational studies has not been explicitly examined.

Design: Retrospective cohort study of the association between hyponatremia and mortality, stratified by outpatient diuretic use in three strata.

Setting: An inception cohort of 13,661 critically ill patients from a tertiary medical center.

Measurements and Main Results: Admission serum sodium concentrations, obtained within 12 hours of admission to the ICU, were the primary exposure. Hyponatremia was associated with 1.82 (95% CI, 1.56–2.11; $p < 0.001$) higher odds of mortality, yet differed according to outpatient diuretic use (multiplicative interaction between thiazide and serum sodium < 133 mEq/L; $p = 0.002$). Although hyponatremia was associated with a three-fold higher (odds ratio, 3.11; 95% CI, 2.32–4.17; $p < 0.001$) odds of mortality among those prescribed loop diuretics, no increase of risk was observed among thiazide diuretic users (odds ratio, 0.87; 95% CI, 0.47–1.51; $p = 0.63$). When examined as a continuous variable, each one mEq/L higher serum sodium was associated with 8% (odds ratio, 0.92; 95% CI, 0.90–0.94; $p < 0.001$) lower odds of mortality in loop diuretic patients and 5% (odds ratio, 0.95; 95% CI, 0.93–0.96, $p < 0.001$) lower in diuretic naïve patients, but was not associated with mortality risk among thiazide users (odds ratio, 0.99; 95% CI, 0.95–1.02; $p = 0.45$).

Conclusions: Hyponatremia is not uniformly associated with increased mortality, but differs according to diuretic exposure. Our results suggest that the underlying pathophysiologic factors that lead to water excess, rather water excess itself, account in part for the association between hyponatremia and poor outcomes. More accurate estimations about the association between hyponatremia and outcomes might influence clinical decision-making.

Key Words: diuretic; hyponatremia; mortality; sodium; survival

Although residual confounding is a widely acknowledged limitation of observational data, it is particularly problematic in the critical illness literature. The complexity of underlying disease processes in the ICU is often difficult to delineate clinically and even more so to quantify in large datasets (1–3). Since these mechanisms might affect both the exposure and outcome of interest, they remain a source of potential confounding.

As an example, hyponatremia has been widely associated with an increased risk of mortality, thought largely due to water excess, cerebral edema, and downstream neurologic effects (4–7). However, a multitude of disparate disease mechanisms can lead to hyponatremia, including disorders of volume overload, volume depletion, thirst, and vasopressin release (8, 9). Standard binary diagnostic codes often lack the sensitivity to identify these diseases or to quantify their severity accurately. Since these diseases are likely to be associated with both hyponatremia and mortality, they are potential sources of bias due to unaccounted confounding.

To better understand how underlying pathophysiologic determinants influence the association of hyponatremia and mortality, we examined physician choice of diuretic (**Fig. 1**). Potent loop diuretics are used for the most sodium-avid states, such as heart failure, cirrhosis, and renal disease, which influence both the risk of hyponatremia and mortality. The challenge of residual confounding similarly exists for hyponatremic patients without concurrent diuretic use, since the mechanism of hyponatremia could represent untreated cardiac, liver disease, or kidney disease, or disorders of vasopressin, such as can be seen in malignancy or lung disease. Thiazide diuretics

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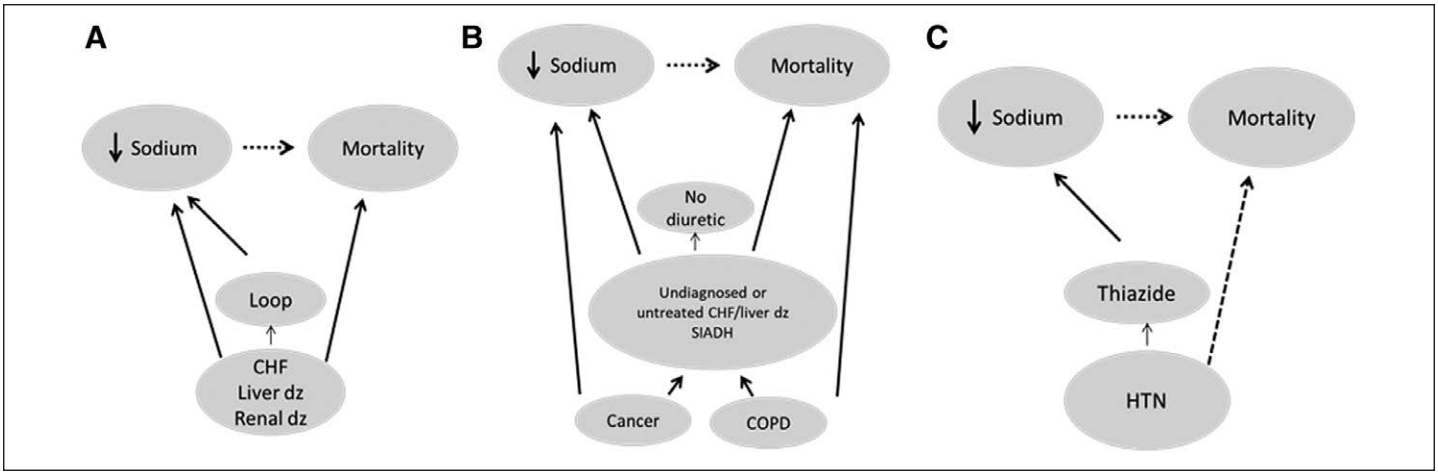

Figure 1. Proposed mechanistic pathways of hyponatremia associated mortality. **A**, Patients are prescribed potent loop diuretics due to underlying sodium avid diseases such as heart failure, kidney disease, and cirrhosis. The severity of these diseases, which can be hard to quantify clinically and in observational data, associate with both hyponatremia and mortality risk, and are therefore sources of residual confounding. **B**, The mechanism for hyponatremia in those not prescribed a diuretic is not known, and could be due to a range of diseases which similarly associate with hyponatremia and mortality, thereby introducing confounding. **C**, Thiazide diuretic associated hyponatremia is a unique scenario, since the hyponatremia is an effect of the drug, rather than underlying disease state. Since hypertension (HTN) does not directly lead to hyponatremia, the association of hyponatremia and mortality can be investigated without the confounding of underlying disease severity. CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, SIADH = syndrome of inappropriate anti-diuretic hormone.

are unique, since by inducing mild volume depletion with simultaneous preservation of renal concentration mechanisms, they can directly cause water retention, which usually improves with drug withdrawal (10). Since thiazides are primarily prescribed for hypertension, and since hypertension does not typically lead to hyponatremia otherwise, thiazide-associated hyponatremia provides an opportunity to reevaluate the question of hyponatremia and mortality in the absence of significant confounding from underlying disease. Put more formally, we hypothesize that the association of hyponatremia with mortality differs by diuretic use (i.e., effect modification) due to differences in the degree of confounding by underlying diseases and their severity across strata.

To address this hypothesis, we used a large inception cohort of critically ill medical and surgical patients admitted to a single tertiary medical center for whom pre-admission medications were available. We evaluated whether the associations between hyponatremia and 90-day mortality differed among thiazide and loop diuretic users and nondiuretic users.

STUDY POPULATION

We used the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC)–II database, a joint venture managed by the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT) and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) (11). MIMIC-II contains data from 23,455 critical care admissions between 2001 and 2008 at BIDMC, a 700-bed urban academic medical center with 77 adult ICU beds. The database contains high temporal resolution data from clinical systems, including laboratory results, electronic documentation, and bedside monitor trends and waveforms. Use of the MIMIC II database has been approved by the Institutional Review Boards of BIDMC and MIT. We developed and validated a natural language processing algorithm that searched for pre-admission home medications in the discharge summary and then processed the medications to find individual entries of diuretics (12). A total of 17,896 patients had an identifiable medication section. Of these, 15,078 had a documented serum sodium and glucose at admission. Age, gender, and race were used to impute missing admission vital signs for 746 individuals, calculated means were used for 257 with missing white count, hematocrit, or creatinine measurements, and 1,417 hypernatremic patients (serum sodium > 145 mEq/L) were excluded, leaving a final cohort of 13,661 unique first ICU admissions.

OUTCOME

The primary outcome was death within the critical illness hospitalization or within 90 days or discharge, as determined by the Social Security Death Index.

EXPOSURE

Admission serum sodium concentrations, obtained within 12 hours of admission to the ICU, were the primary exposure. Sodium concentrations were corrected for elevated serum glucose (corrected sodium = measured sodium + 0.024 × [serum glucose–100]) (13). Sodium concentrations were examined as a binary threshold according to our hospital definition of hyponatremia (≤ 133 mEq/L) and continuously.

COVARIATES

Demographic information included age and gender. Histories of heart failure, hypertension, liver disease, and kidney disease were categorized by the Elixhauser comorbidity index. Admission systolic blood pressure, heart rate, WBC count, hematocrit, and creatinine were taken from the first available laboratory data within twelve hours of ICU admission.

Diuretics were classified into the following categories; loop diuretics (furosemide, torsemide, bumetanide, and ethacrynic

acid); thiazide diuretics (hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide, and metolazone); and other diuretics (acetazolamide, spironolactone, eplerenone, amiloride, and triamterene). We categorized 101 patients prescribed both a thiazide and a loop diuretic as loop diuretic users. A sensitivity analysis excluding these 101 individuals did not significantly alter the results.

STATISTICAL ANALYSIS

We present baseline characteristics, stratified by hyponatremia, among thiazide, loop, and diuretic-native patients. We first used logistic regression to examine the adjusted association between hyponatremia and mortality using the covariates above, including separate indicator variables for each diuretic type. To explore whether the association of hyponatremia and mortality differed between thiazide and loop diuretic users, we tested individual multiplicative interaction terms between thiazide and loop diuretics users with serum sodium less than or equal to 133 mEq/L, considering diuretic-naïve patients as the reference. We then repeated our models stratified by diuretic use. We examined the associations of sodium as a continuous variable similarly.

RESULTS

Of 13,661 critically ill patients, 8% (n = 1,110) were hyponatremic upon ICU admission. The overall frequency of mortality was 17.3% (n = 2,161), and 34.1% (n = 382) among hyponatremic patients.

Admission medications included thiazide diuretics in 9% (n = 1,188) and loop diuretics in 18% of patients (n = 2,498). Hyponatremia was observed in 9% of thiazide users (n = 110) and 10% of loop diuretic users (n = 254), compared with 7% of diuretic-naïve patients (n = 722). The rates of mortality were 15% for thiazide users (n = 178), 27% for loop diuretic users (n = 663), and 17% for diuretic-naïve patients (n = 1,657).

Table 1 illustrates the characteristics of patients according to hyponatremia and their admission diuretic use. Hyponatremic and normonatremic thiazide users tended to have similar blood pressure, urine output, and IV fluid administration. In contrast, hyponatremic loop and diuretic-naïve patients tended to have lower blood pressures and urine outputs and received more IV fluid than loop and diuretic naïve patients with normal serum sodium concentrations. Among diuretic-naïve patients, hyponatremia also tended to be associated with a history of malignancy and weight loss.

The adjusted odds of mortality associated with admission hyponatremia was 2.31 (95% CI, 2.00–2.67; $p < 0.001$), but this estimate differed according to outpatient diuretic type (multiplicative interaction terms between thiazide and loop diuretics with serum sodium ≤ 133 mEq/L: ß = –0.22; 95% CI, –0.38 to –0.09; $p = 0.002$ and ß = 0.07; 95% CI, –0.01 to 1.15; $p = 0.08$, respectively). In adjusted analysis (**Fig. 2**; **Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A130), hyponatremia was associated with a three-fold higher risk of mortality among loop diuretic users and two-fold higher risk among diuretic-naïve patients, but it was not associated with an increased risk among thiazide diuretic users (odds ratio [OR], 0.87; 95% CI, 0.47–1.51; $p = 0.63$).

The association of hyponatremia severity with mortality similarly differed by according to diuretic use (multiplicative

TABLE 1. Patient Characteristics According to Hyponatremia and Diuretic Exposure

	Thiazide		Loop		Diuretic Naive	
Characteristics	Na ≤ 133, n = 110	Na > 133, n = 1,078	Na ≤ 133, n = 254	Na > 133, n = 2,244	Na ≤ 133, n = 722	Na > 133, n = 9,099
Admission characteristics						
Age	71.8 (12.2)	70.1 (13.2)	66.6 (14.5)	72.9 (13.7)	62.1 (17.3)	60.4 (18.7)
Congestive heart failure	20.0 (22)	14.0 (151)	40.2 (102)	48.1 (1,078)	19.4 (140)	13.7 (1,244)
Hypertension	55.5 (61)	63.0 (678)	21.2 (54)	31.6 (710)	31.3 (225)	31.8 (2,891)
Liver disease	6.4 (7)	3.3 (35)	24.8 (63)	6.8 (153)	8.5 (61)	4.2 (377)
Renal disease	0.9 (1)	2.9 (31)	9.1 (23)	9.4 (210)	9.0 (65)	4.9 (441)
Malignancy	10.0 (11)	19.7 (212)	19.3 (49)	17.0 (382)	22.8 (164)	17.9 (1,628)
Chronic obstructive pulmonary disease	16.4 (18)	17.6 (190)	23.3 (59)	26.4 (593)	14.9 (107)	14.5 (1,319)
Weight loss	1.8 (2)	1.2 (13)	3.9 (10)	2.4 (52)	6.0 (43)	2.3 (208)
Systolic blood pressure (mm Hg)	129.8 (25.1)	129.5 (25.8)	113 (24.7)	124 (27.1)	122 (27.5)	126 (25.4)
Creatinine (mg/dL)	1.5 (1.8)	1.2 (0.8)	2.2 (1.9)	1.7 (1.6)	1.8 (2.1)	1.3 (1.5)
ICU stay characteristics						
Total IV fluid	2.6 (3.6)	2.7 (4.1)	3.1 (8.3)	2.1 (6.3)	3.5 (4.4)	3.1 (5.7)
Urine output[a] (liters first 24 hr)	2.0 (1.3)	2.0 (1.2)	1.7 (1.3)	1.9 (1.3)	2.1 (1.8)	2.2 (1.7)

[a]Available in 12,776 patients.

Mean (SD) for continuous variables and percentile (n) for nominal variables provided. Data for other types of diuretic use not shown given low participation.

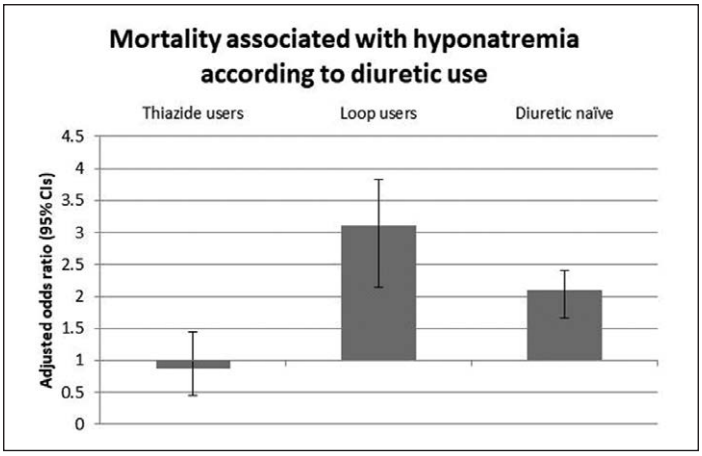

Figure 2. Hyponatremia associated mortality depends on diuretic exposure. Adjusted for age, gender, history of congestive heart failure, hypertension, liver or kidney disease, admission systolic blood pressure, heart rate, WBC count, hematocrit, and creatinine. Data for other types of diuretic use not shown given low participation. Reference group is those with serum sodium greater than 133 mEq/L within each diuretic category. The association of hyponatremia and mortality differed for thiazide users ($p = 0.002$) compared with diuretic naïve patients, but not loop users ($p = 0.08$). The odds ratio (OR) (95% CI) for hyponatremia associated mortality was OR 0.87; 95% CI, 0.47–1.51; $p = 0.63$ for thiazide diuretic users, OR, 3.11; 95% CI, 2.32–4.17; $p < 0.001$ for loop diuretic users, and OR, 2.26; 95% CI, 1.89–2.71; $p < 0.001$ for diuretic naïve patients.

interaction terms between thiazide and loop diuretics with serum sodium defined continuously: ß = 0.21; 95% CI, –0.002 to 0.04; $p = 0.02$ and ß = –0.001; 95% CI, –0.02 to 0.001; $p = 0.11$, respectively). A one mEq/L increment in serum sodium was associated with 8% (OR, 0.92; 95% CI, 0.90–0.94%; $p < 0.001$) lower odds of mortality in loop diuretic users and 5% (OR, 0.95; 95% CI, 0.93–0.96; $p < 0.001$) lower odds among diuretic-naïve patients, but it was not associated with mortality risk among thiazide users (OR, 0.99; 95% CI, 0.95–1.02; $p = 0.45$).

DISCUSSION

The context in which hyponatremia occurs modifies the association between hyponatremia and outcomes. Assuming that there is generally less underlying morbidity in thiazide users, and therefore lower risk of confounding due to unaccounted illness severity, the absence of an association between hyponatremia and mortality in thiazide users undermines a causal role for water excess (14–16). In contrast, the stronger effect of hyponatremia on mortality in loop diuretic users, where there is likely more unaccounted pathophysiology, suggests that other mechanisms, such as osmolar independent activated water retention, are pathogenically explanative.

The modifying effect of diuretic use does not eliminate the possibility of a causal effect of hyponatremia on mortality in all scenarios, but suggests that any potential link should have a plausible and identifiable biologic pathway. Hyponatremia induced alteration in neurologic function, such as might occur with cerebral edema, could potentially be explanatory, and clearly, the water excess in symptomatic hyponatremia must be carefully and judiciously ameliorated. But in the absence of such explanatory mechanisms, the observed effect might simply reflect underlying confounding. Given that osmolar intendent water retention, such as sensed volume mediated activation of vasopressin in heart failure, is often difficult to measure or quantify, yet is simultaneously closely linked with mortality, confounding seems likely.

Our analysis questions whether asymptomatic hyponatremia, barring other pathogenic signatures of water intoxication, needs to be aggressively treated. Hyponatremia remains a common cause of hospitalization and ICU admission, associated with downstream risks and costs, and whether more conservative treatment in asymptomatic patients might improve overall patient care needs to be determined.

Our analysis has important limitations. We were not able to directly measure whether confounding was less among the thiazide users than other diuretic groups, and the observation of an effect modification does not rule out the possibility that hyponatremia might contribute to mortality with more severe disease (such as loop diuretics). In addition, we did not know the cause of hyponatremia, and since we lacked longitudinal sodium data, the absence of an effect of hyponatremia on mortality in thiazide users might simply reflect the rapid correction of sodium concentrations with drug cessation.

CONCLUSIONS

In a large population of critical care patients, hyponatremia was associated with higher mortality only among loop diuretic users and nondiuretic users, but not among thiazide users. Because the association of hyponatremia and mortality is likely to be least confounded in the latter group, our results suggest that the high mortality rates observed with hyponatremia are in part due to the underlying pathophysiology that causes water retention, rather than water excess per se. Our analysis highlights how difficult it is to account for the complex determinants of many exposures in critical illness and cautions against over-interpretation of observational data.

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