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Correction Rates and Clinical Outcomes in Hospitalized Adults With Severe Hyponatremia
A Systematic Review and Meta-Analysis

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IMPORTANCE Hyponatremia treatment guidelines recommend limiting the correction of severe hyponatremia during the first 24 hours to prevent osmotic demyelination syndrome (ODS). Recent evidence suggests that slower rates of correction are associated with increased mortality.

OBJECTIVE To evaluate the association of sodium correction rates with mortality among hospitalized adults with severe hyponatremia.

DATA SOURCES We searched MEDLINE, Embase, the Cochrane Library, LILACS, Web of Science, CINAHL, and international congress proceedings for studies published between January 2013 and October 2023.

STUDY SELECTION Comparative studies assessing rapid (≥8-10 mEq/L per 24 hours) vs slow (<8 or 6-10 mEq/L per 24 hours) and very slow (<4-6 mEq/L per 24 hours) correction of severe hyponatremia (serum sodium <120 mEq/L or <125 mEq/L plus severe symptoms) in hospitalized patients.

DATA EXTRACTION AND SYNTHESIS Pairs of reviewers (N.A.F., J.R.M., J.M.A., A.C.) independently reviewed studies, extracted data, and assessed each included study's risk of bias using ROBINS-I. Cochrane methods, PRISMA reporting guidelines, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the certainty of evidence were followed. Data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES Primary outcomes were in-hospital and 30-day mortality, and secondary outcomes were hospital length of stay (LOS) and ODS.

RESULTS Sixteen cohort studies involving a total of 11 811 patients with severe hyponatremia were included (mean [SD] age, 68.22 [6.88] years; 56.7% female across 15 studies reporting sex). Moderate-certainty evidence showed that rapid correction was associated with 32 (odds ratio, 0.67; 95% CI, 0.55-0.82) and 221 (odds ratio, 0.29; 95% CI, 0.11-0.79) fewer in-hospital deaths per 1000 treated patients compared with slow and very slow correction, respectively. Low-certainty evidence suggested that rapid correction was associated with 61 (risk ratio, 0.55; 95% CI, 0.45-0.67) and 134 (risk ratio, 0.35; 95% CI, 0.28-0.44) fewer deaths per 1000 treated patients at 30 days and with a reduction in LOS of 1.20 (95% CI, 0.51-1.89) and 3.09 (95% CI, 1.21-4.94) days, compared with slow and very slow correction, respectively. Rapid correction was not associated with a statistically significant increased risk of ODS.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, slow correction and very slow correction of severe hyponatremia were associated with an increased risk of mortality and hospital LOS compared to rapid correction.

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Supplemental content

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Severe hyponatremia can result in hyponatremic encephalopathy, requiring emergency treatment with hypertonic saline to prevent death or permanent neurological impairment.[1-4] Safe limits and optimal rates of correction are uncertain, as randomized clinical trials have not been conducted.

US and European clinical practice guidelines for the diagnosis and treatment of hyponatremia were published in 2013 and 2014, respectively, putting forth limits for the treatment of severe hyponatremia to prevent osmotic demyelination syndrome (ODS).[5,6] The US guidelines set limits of 10 to 12 mEq/L or less in any 24-hour period and 18 mEq/L or less in any 48-hour period, with more stringent limits of 8 mEq/L per 24-hour period in patients at high risk for ODS (to convert serum sodium to mmol/L, multiply by 1).[5] The European guidelines set limits of 10 mEq/L or less during the first 24-hour period and 8 mEq/L or less per 24-hour period thereafter.[6] These recommendations have been based on low-quality evidence and expert consensus. Moreover, these guidelines did not address the potential impact of limiting correction on mortality. Since the publication of these guidelines, numerous large studies have evaluated the correction of severe hyponatremia,[7-11] showing consistently lower mortality among patients who received correction at rates exceeding current guidelines, and did not identify higher rates of ODS. Given that large randomized clinical trials assessing the effects of rate of correction on relevant clinical outcomes are unlikely to be performed, we conducted a meta-analysis of cohort studies to evaluate the associations of varying rates of correction of severe hyponatremia with mortality, hospital length of stay (LOS), and ODS.

Key Points

Question For hospitalized adults with severe hyponatremia, what is the association of sodium correction rate with mortality?

Findings In this systematic review and meta-analysis involving 16 studies and 11 811 patients, moderate-certainty evidence showed that rapid correction of severe hyponatremia was associated with 32 and 221 fewer in-hospital deaths per 1000 treated patients compared with slow and very slow correction, respectively. Low-certainty evidence suggested that rapid correction was associated with 61 and 134 fewer deaths per 1000 treated patients at 30 days compared with slow and very slow correction, respectively.

Meaning The available evidence suggests that slow correction of severe hyponatremia was associated with an increased risk of mortality.

Methods

Study Design and Inclusion Criteria

We followed Cochrane methods[12] to conduct the systematic review and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 reporting guidelines for reporting.[13] The protocol was registered with PROSPERO (CRD42023475592). We searched for randomized and nonrandomized clinical trials and observational comparative studies, with no restriction on publication status or language. Preclinical studies were not considered. Participants of included studies were hospitalized adults with severe hyponatremia (serum sodium <120 mEq/L) or with severe symptomatic hyponatremia (serum sodium <125 mEq/L plus severe symptoms, including cardiorespiratory distress, seizures, Glasgow Coma Scale ≤8, or decreased level of consciousness).

Exposure

We defined 4 categories of sodium correction rate based on various rates reported in articles: (1) very rapid (>12 mEq/L per 24 hours), (2) rapid (≥8-10 mEq/L per 24 hours), (3) slow (<8 or 6-10 mEq/L per 24 hours), and (4) very slow (<4-6 mEq/L per 24 hours). The main comparisons were rapid vs slow and rapid vs very slow correction rate, although we also compared each correction rate category with one another to explore dose-response gradients.

Outcomes

The primary outcome was mortality, defined as in-hospital and 30-day mortality. The secondary outcomes included hospital and intensive care unit (ICU) LOS and 90-day incidence of ODS.

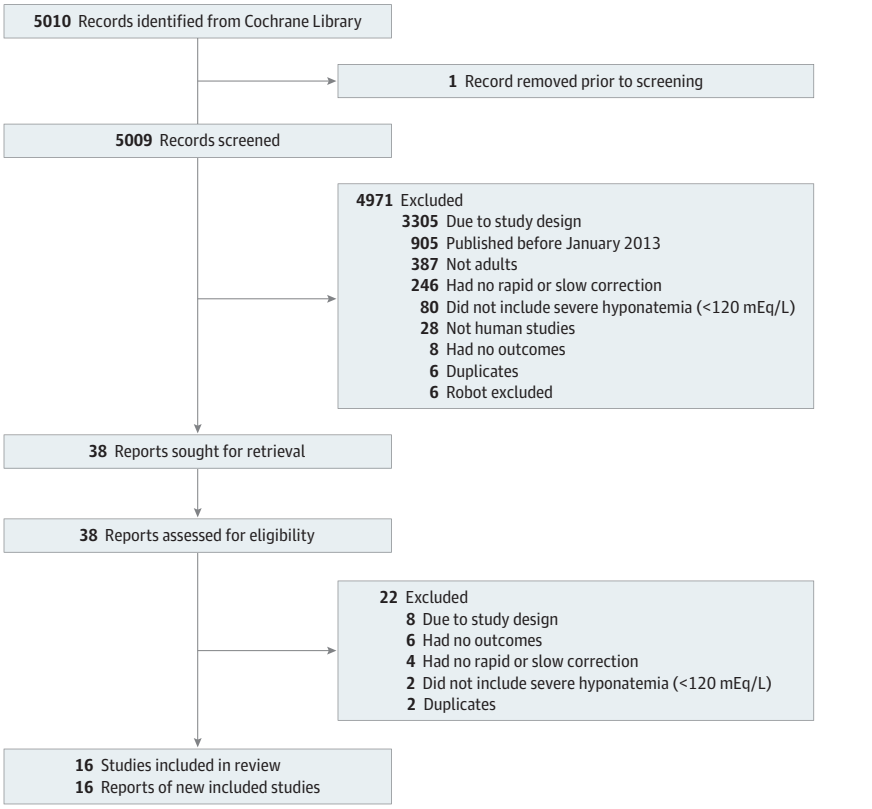
Search Methods for Identification of Studies

A literature search was conducted for articles published following the publication of the hyponatremia treatment guidelines (from January 2013 to October 2023), without restrictions on language. We searched MEDLINE, Embase, the Cochrane Library, LILACS, Web of Science, and CINAHL, as well as international congress proceedings (American Society of Nephrology annual meeting, European Congress of Nephrology annual meeting, American Society of Critical Care annual meeting, and European Society of Critical Care annual meeting). We manually searched the references of included studies and systematic reviews. We contacted authors for any additional evidence that they were able to provide. The complete search strategy for each database is presented in the eAppendix in Supplement 1.

Data Collection

Each title, abstract, and potentially eligible full texts were screened independently by a pair of review authors (N.A.F., J.R.M., J.M.A., A.C.). Disagreements were resolved through discussion with the review team and based on consensus. The selection process was performed using the web-based software Nested Knowledge.[14] This web-based software, powered by artificial intelligence, facilitated the dual independent screening by a reviewer and robot screener after training the model with 50 records. We confirmed the validity of this process because the robot did not result in any exclusions beyond those made by humans. Disagreements between humans excluding studies and the robot including them were resolved by consensus of the whole review team, reinforcing the credibility of this method. We used a predesigned general data extraction form after pilot testing the form on 5 studies. We extracted title, type of publication, year of publication, author name, methods, location, study recruitment period, and data

Figure 1. Study Flow Diagram



To convert serum sodium to millimoles per liter, multiply by 1.

related to the study population, including number of patients, patient demographics, data related to the study outcomes, adjustment variables used for the analysis, and data related to the risk of bias (RoB). Disagreements were resolved by consensus. We assessed the RoB of each included study with the ROBINS-I tool[15] and the certainty of evidence by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[16]

Statistical Analysis

We performed meta-analyses for each comparison according to the Cochrane methods,[12] using the random-effects meta-analysis[17] for the primary analysis. We used ReviewManager, version 5.4 (Cochrane), to perform the analysis. We calculated risk ratios (RRs) or odds ratios (ORs) with 95% CIs for dichotomous outcomes and mean difference (MD) for continuous outcomes. Because the analysis included studies that had among them single-arm zero-events studies and double-arm zero-events studies, the Peto OR was not the best option. Thus, we followed a framework proposed by Xu et al.[18] From the options to deal with this scenario, we chose the Mantel-Haenszel risk difference (RD), in addition to an empirical correction (adding 0.5 to each event cell) and a continuity correction in Stata, version 16 (StataCorp), and R, version 4.4.2, for Windows (R Project for Statistical Computing). If available, we used adjusted effect measures (eg, by age, sex, race, admission sodium levels, alcohol use, or Charlson Comorbidity Index) over unadjusted estimates. An I^2 greater than 60% was considered substantial statistical heterogeneity.[12] We investigated sources of heterogeneity through prespecified subgroup analyses by admission sodium levels, sex, Charlson Comorbidity Index, alcohol use, desmopressin use, setting (ICU emergencies, hospital ward), and cause of hyponatremia. If there were 8 or more studies in the meta-analysis for a given comparison, we used a funnel plot detecting and correcting for publication bias and other reporting biases. Sensitivity analyses were undertaken by excluding high-RoB studies or by using the fixed-effect model. We presented the certainty of evidence for each estimation in summary of findings tables.[19]

Results

Study Characteristics

The search strategy retrieved 5010 records, of which the full text of 38 publications was assessed, with 16 studies involving a total of 11 811 patients meeting the inclusion criteria (**Figure 1**). The included studies are described in **Table 1**. Of the 16 included studies,[7-11,20-30] 14[7-11,20,22-29] were retrospective cohort studies, 1 was a prospective cohort study,[30] and 1 was a randomized clinical trial that was analyzed as a prospective cohort study because it did not randomize sodium correction rates.[21] In 14 of the 16 included studies, the mean age of

Table 1. Characteristics of the Included Studies

Source	Country (No. of centers)	Study design (sampling)	Methods	Eligibility criteria	Outcomes	Correction rate, mEq/L per 24 h	No. of patients	Age, y	Sex, %		Mean serum sodium at admission, mEq/L	Comorbidity, %				
									Female	Male		AUD	Liver disease	HF	CKD	Cancer
Geoghegan et al,[22] 2015	US (1)	Retrospective cohort (convenience)	Long-standing electronic medical record system	Inclusion: ≥18 y old and glucose-corrected serum sodium <120 mEq/L; Exclusion: pseudohyponatremia and those who died in the ED or were discharged against medical advice in the first 24 h of treatment	IHM, ODS, hospital LOS, ICU LOS	≤5, 6-10, >10	412	Median (IQR), 69 (56-80)	58.3	41.7	116.0	16.3	7.0	33.3	12.6	NR
Krummel et al,[25] 2016	France (1)	Retrospective cohort (convenience)	Using computer retrieval of archived laboratory data	Inclusion: ≥18 y old and serum sodium ≤120 mEq/L; Exclusion: ambulatory hospital patients and patients in whom blood samples were obviously diluted	IHM, ODS	<12, ≥12	147	Mean (SD), 69.6 (13.3)	57.8	42.2	121.0	NR	12.0	29.0	23.0	57.0
Winzeler et al,[30] 2016	Switzerland (2)	Prospective cohort (convenience)	Baseline data from medical history, clinical examination, and laboratory testing; follow-up was done by a telephone interview	Inclusion: ≥18 y old, serum sodium ≤125 mEq/L, and serum osmolality <280 mOsm/kg; Exclusion: hyperglycemia	IHM, ODS	<12, ≥12	155	Mean (SD), 73 (14.07)	65.8	34.2	117.0	NR	1.9	3.9	NR	7.7
Giordano et al,[23] 2017	Italy (1)	Retrospective cohort (convenience)	Patients admitted to the ED	Inclusion: ≥18 y old, serum sodium <120 mEq/L, neurological manifestations for >48 h, and hyponatremia due to congestive HF, liver cirrhosis, or kidney failure; Exclusion: serum sodium correction rate >12 mEq/L per 24 h, patients with oliguria, patients receiving kidney replacement therapy, hyperosmolar hyponatremia combined with hyperglycemia, patients with cancer, and patients taking drugs responsible for major neurological symptoms	IHM, hospital LOS	<0.3 per h (7.2 per 24 h), ≥0.3, <0.5 (7.2-12 per 24 h)	67	Mean (SD), 75 (3)	64.0	36.0	116.5	NR	NR	NR	NR	NR
George et al,[7] 2018	US (7)	Retrospective cohort (convenience)	A fully integrated health care system serving central and northeastern Pennsylvania	Inclusion: ≥18 y old and serum sodium <120 mEq/L; Exclusion: serum glucose >300 mg/dL on admission	30-d Mortality, ODS	≤8, >8	1490	Mean (SD), 66 (15)	55.0	45.0	116.0	17.6	NR	15.9	11.1	22.4

(continued)

Table 1. Characteristics of the Included Studies (continued)

Source	Country (No. of centers)	Study design (sampling)	Methods	Eligibility criteria	Outcomes	Correction rate, mEq/L per 24 h	No. of patients	Age, y	Sex, %		Mean serum sodium at admission, mEq/L	Comorbidity, %				
									Female	Male		AUD	Liver disease	HF	CKD	Cancer
Woodfine et al,[8] 2019	Canada (1)	Retrospective cohort (consecutive)	Developed the Severe Hyponatremic Overcorrection Risk score, which had statistically significant association with overcorrection status	Inclusion: glucose-corrected serum sodium <116 mEq/L; Exclusion: patients transferred to the ED	IHM, ODS, hospital LOS	<12, ≥12	623	Mean (SD), 68 (16)	61.0	39.0	112.0	19.0	8.0	NR	0.5	18.0
Baek et al,[21] 2021[a]	Republic of Korea (3)	Randomized trial analyzed as prospective cohort (convenience)	Multicenter, open-label, randomized clinical trial to assess the risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline	Inclusion: ≥18 y old, glucose-corrected serum sodium ≤125 mEq/L, and serum osmolality ≤275 mOsm/kg; Exclusion: pseudohyponatremia (serum osmolality >275 mOsm/kg), pregnant or breastfeeding, anuria, arterial hypotension, liver disease (transaminase levels >3 times the upper limit of normal, known decompensated liver cirrhosis with ascites or diuretic use, hepatic encephalopathy, and varicose veins), uncontrolled diabetes, history of cardiac surgery, acute myocardial infarction, sustained ventricular tachycardia, ventricular fibrillation, acute coronary syndrome, cerebral trauma, and increased intracranial pressure within 3 mo before randomization	IHM, ODS, hospital LOS	<12, ≥12	178	Mean (SD), 73 (12.2)	55.0	45.0	118.2	2.8	6.2	17.4	NR	23.6
Grim et al,[24] 2021[a]	Netherlands (10)	Retrospective cohort (convenience)	Dutch National Intensive Care Evaluation registry from 10 ICUs	Inclusion: serum sodium <125 mEq/L	IHM, ICU LOS	<5, ≥5 and <7.5, ≥7.5, <10, ≥10	497	Mean (SD), 59.4 (15.4)	45.9	54.1	120.2	NR	9.7	7.2	NR	9.3
Arshad et al,[20] 2022[a]	UK (2)	Retrospective cohort (convenience)	Centralized pharmacy electronic records	Inclusion: ≥18 y old and severe symptomatic hyponatremia	IHM, 12-mo mortality, ODS, hospital LOS	<5, 5-10, >10	107	Mean (SD), 64.4 (16.0)	55.1	44.9	114.1	29.0	NR	NR	NR	NR
Turkmen et al,[29] 2022	Turkey (2)	Retrospective cohort (convenience)	Obtained from medical records	Inclusion: ≥18 y old and serum sodium ≤115 mEq/L	IHM, ODS, hospital LOS	<6, 6-10, >10	145	Median (IQR), 69 (21-93)	58.6	41.4	110.0	0.0	5.5	22.8	34.5	17.9

(continued)

Table 1. Characteristics of the Included Studies (continued)

Source	Country (No. of centers)	Study design (sampling)	Methods	Eligibility criteria	Outcomes	Correction rate, mEq/L per 24 h	No. of patients	Age, y	Sex, %		Mean serum sodium at admission, mEq/L	Comorbidity, %				
									Female	Male		AUD	Liver disease	HF	CKD	Cancer
Kinoshita et al,[10] 2023	US (208)	Retrospective cohort (convenience)	eICU Collaborative Research Database	Inclusion: ≥18 y old and serum sodium ≤120 mEq/L; Exclusion: glucose ≥360 mg/dL and dialysis	IHM, ODS, ICU LOS	≤8, >8	1024	Mean (SD), 48.2 (13.1)	51.3	48.7	116.7	NR	NR	18.0	9.2	NR
MacMillan et al,[9] 2023[a]	Canada (5)	Retrospective cohort (convenience)	General Medicine Inpatient Initiative database and data from hospitals (laboratory, imaging, pharmacy dispensing data) available electronically	Inclusion: serum sodium <130 mEq/L; Exclusion: glucose >450 mg/dL and history of diabetes insipidus	IHM, ODS, hospital LOS	<6, 8-12, >12	2956	Mean (SD), 68.87 (15.8)	NR	NR	115.2	6.3	5.4	5.9	8.1	5.7
Massop et al,[26] 2023	Netherlands (1)	Retrospective cohort (convenience)	Recording of treatments and laboratory measurements was limited to the first 24 h after the initiation of bolus treatment	Inclusion: serum sodium ≤120 mEq/L and serum osmolality ≤270 mOsm/kg; Exclusion: glucose-corrected serum sodium >120 mEq/L and hyponatremia with abnormal or high effective osmolality or unknown osmolality	IHM, ODS	<6, 6-10, >10, <8, ≥8	130	Median (IQR), 75 (67-84	63.1	36.9	116.0	10.0	NR	NR	NR	NR
Mustajoki,[27] 2023[a]	Finland (1)	Retrospective cohort (convenience)	The database of the hospital's laboratory was searched to identify patients admitted to the ED	Inclusion: serum sodium <116 mEq/L	IHM, 30-d mortality, ODS, hospital LOS, ICU LOS	<6, 6-10, >10	385	Median (IQR), 68 (17-98)	56.0	44.0	111.7	36.0	NR	NR	NR	NR
Nagase et al,[28] 2023	Japan (1)	Retrospective cohort (convenience)	The primary analysis was to investigate potential factors associated with the appropriate correction of severe hyponatremia	Inclusion: ≥18 y old and serum sodium ≤120 mEq/L; Exclusion: glucose >300 mg/dL and hypertriglyceridemia with pseudohyponatremia	IHM, ODS, hospital LOS	<4, 4-10, >10	221	Mean (SD), 77 (11.11)	47.0	53.0	117.0	NR	NR	14.0	16.0	24.0
Seethapathy et al,[11] 2023	US (2)	Retrospective cohort (convenience)	A centralized data registry	Inclusion: ≥18 y old and serum sodium <120 mEq/L; Exclusion: glucose >300 mg/dL	IHM, 30-d mortality, ODS, hospital LOS	<6, 6-10, >10	3274	Mean (SD), 66 (16)	57.0	43.0	116.0	17.0	10.0			

Abbreviations: AUD, alcohol use disorder; CKD, chronic kidney disease; ED, emergency department; HF, heart failure; ICU, intensive care unit; IHM, in-hospital mortality; LOS, length of stay; NR, not reported; ODS, osmotic demyelination syndrome.

SI conversion factor: To convert serum sodium and serum glucose to millimoles per liter, multiply by 1 and 0.0555, respectively; serum osmolality to millimoles per kilogram, multiply by 1.

[a] Complementary data obtained through contacting the authors.

participants was older than 60 years.[7-9,11,20-23,25-30] The mean percentage of women in 15 of the included studies reporting sex was 56.7%. All studies, except 1,[29] took place in high-income countries. Fifteen of the 16 included studies reported in-hospital mortality[8-11,20-30]; however, only 6 studies reported adjusted in-hospital mortality in rapid vs slow or very slow sodium correction.[9-11,22,24,29] Eleven studies reported 30-day mortality,[7,11,27] 14 reported ODS,[7-11,20-22,25-30] 10 reported hospital LOS,[8,9,11,20-24,27-29] and 6 reported ICU LOS.[10,21,22,24,27,29] (**Table 2**).

We excluded 10 studies initially considered as eligible (eTable 1 in Supplement 1).[31-40] In most cases, there were no outcomes (5 studies) or rate of correction data (3 studies).

RoB in Included Studies

We assessed 2 categories of outcomes to assess studies' limitations: adjusted in-hospital mortality and unadjusted outcomes (eFigure 1 in Supplement 1). Each ROBINS-I domain and the overall RoB are also presented in eTables 2 and 3 in Supplement 1 and in the forest plots for each study outcome. The overall RoB was serious in 11 studies[7,8,20,21,23,25-30] and moderate for the remaining 5.[9-11,22,24] Eleven studies had serious RoB in the confounding domain,[7,8,20,21,23,25-30] 4 had moderate RoB,[9,11,22,24] and 1 had low RoB.[10] Two studies presented serious RoB due to deviations from the intended interventions domain[20,28] and 1 in measurement of outcomes.[30] Bias in selection of participants, classification of interventions, missing data, and selection of the reported result were assessed as low in all of the included studies.

In-Hospital Mortality

There was a lower adjusted in-hospital mortality among 6389 patients in 6 studies with rapid vs slow/very slow sodium correction (OR, 0.59; 95% CI, 0.45-0.76; I^2, 44%), with a probable dose-response effect when comparing rapid vs slow sodium correction among 6017 patients in 5 studies (OR, 0.67; 95% CI, 0.55-0.82; I^2, 44%) and rapid vs very slow sodium correction among 372 patients in 2 studies (OR, 0.29; 95% CI, 0.11-0.79; I^2, 59%) (**Table 3**), resulting in 32 and 221 fewer in-hospital deaths per 1000 treated patients, respectively. The test for subgroup differences showing considerable heterogeneity (I^2, 61%) reinforced this hypothesis (eFigure 2 in Supplement 1 and Table 2). A meta-analysis was performed to evaluate the unadjusted in-hospital mortality, which involved more studies and participants. A similar direction and clearer estimated dose-response effect were found when comparing rapid vs slow sodium correction among 7255 patients in 1 study[2] (RR, 0.72; 95% CI, 0.62-0.85; I^2, 0%) and rapid vs very slow sodium correction among 5158 patients in 11 studies (RR, 0.50; 95% CI, 0.42-0.59; I^2, 7%), with an I^2 of 90% in the test for subgroup differences (eFigure 2 in Supplement 1 and Table 2). To further assess a potential dose-response effect, meta-analyses for adjusted (**Figure 2**) and unadjusted (eFigure 3 in Supplement 1) in-hospital mortality by rate of sodium correction were performed. In both meta-analyses, a more rapid correction was consistently associated with lower in-hospital mortality. The test for heterogeneity of subgroups showed that the subgroup estimates were statistically different (I^2, 60%; eFigure 2 in Supplement 1 and Table 2).

30-Day Mortality

There was a lower unadjusted 30-day mortality and a clear estimated dose-response effect when comparing rapid vs slow sodium correction among 3865 patients in 3 studies (RR, 0.55; 95% CI, 0.45-0.67; I^2, 75%) and rapid vs very slow sodium correction among 2514 patients in 2 studies (RR, 0.35; 95% CI, 0.28-0.44; I^2, 61%), with 61 and 134 fewer deaths per 1000 treated patients, respectively, and an I^2 of 88% in the test for subgroup differences (eFigure 2 in Supplement 1 and Tables 2 and 3).

ODS

Two cases of ODS among 594 patients (0.3%) occurred in the very rapid correction group, 18 cases among 3842 patients (0.5%) in the rapid correction group, 10 cases among 5652 patients (0.2%) in the slow correction group, and 1 case among 2466 patients (<0.1%) in the very slow correction group (Table 2). The RD in ODS was not statistically significant, and no estimated dose-response effect was found when comparing rapid vs slow sodium correction among 9484 patients in 15 studies (RD, 0.43 per 1000 patients; 95% CI, −1.69 to 2.55 per 1000 patients; I^2, 0%) and rapid vs very slow sodium correction among 5021 patients in 9 studies (RD, 1.87 per 1000 patients; 95% CI, −0.62 to 4.36 per 1000 patients; I^2, 0%), with an I^2 of 0% in the test for subgroup differences (eFigure 4 in Supplement 1). Meta-analyses for unadjusted ODS by rate of sodium correction showed similar results (eFigure 5 in Supplement 1).

Using the empirical correction for risk ratio (0 replaced by 0.5 events), there was a non-statistically significant difference and no estimated dose-response effect for rapid vs slow sodium correction among 9484 patients in 15 studies (RR, 1.66; 95% CI, 0.82-3.38; I^2, 0%) and rapid vs very slow sodium correction among 5021 patients in 9 studies (RR, 1.32; 95% CI, 0.46-3.79; I^2, 0%) (Table 3 and eFigure 6 in Supplement 1). A similar assessment showed consistent results (eFigures 7-9 in Supplement 1). A sensitivity analysis using the Peto OR indicated a higher frequency of ODS but no estimated dose-response effect for rapid vs slow sodium correction among 7164 of 9484 patients in 15 studies (Peto OR, 2.34; 95% CI, 1.01-5.46; I^2, 61%) and rapid vs very slow sodium correction among 4349 of 5021 patients in 4 of 9 studies (Peto OR, 4.03; 95% CI, 1.13-14.41; I^2, 0%) (eFigure 10 in Supplement 1).

Hospital LOS

There was a shorter LOS and a clear estimated dose-response effect when comparing rapid vs slow sodium correction among 6978 patients in 10 studies (MD, −1.20 days; 95% CI, −1.89 to −0.51 days; I^2, 48%) and rapid vs very slow sodium correction among 5110 patients in 10 studies (MD, −3.09 days; 95% CI, −4.96 to −1.21 days; I^2, 85%), with an I^2 of 71% in the test for subgroup differences (Table 3 and eFigure 11 in Supplement 1). A faster correction was consistently associated with shorter LOS, suggesting a potential dose-response

Table 2. Correction Rates and Outcomes in Patients With Severe Hyponatremia

Source	No. of patients	Correction rate, mEq/L per 24 h (% of patients)	Mortality, %	30-d Mortality, %	No. of patients with ODS	Mean LOS, d	
						ICU	Hospital
Geoghegan et al,[22] 2015	412	>10 (27.7)	5.3	NI	1	4	2
		6-10 (51.2)	5.2	NI	0	5	2
		≤5 (21.1)	10.3	NI	0	5	2
Krummel et al,[25] 2016	147	≥12 (17.7)	19.2	NI	0	NI	NI
		<12 (82.3)	25.6	NI	0	NI	NI
Winzeler et al,[30] 2016	155	≥12 (11.6)	NI	NI	0	NI	NI
		<12 (88.4)	NI	NI	0	NI	NI
Giordano et al,[23] 2017	67	<0.3 per h or 7.2 per 24 h (49.3)	39.4	NI	NI	4	NI
		≥0.3 and <0.5 or 7.2 to 12 (50.7)	76.5	NI	NI	11	NI
George et al,[7] 2018	1490	>8 (40.7)	NI	7.6	7	NI	NI
		≤8 (59.3)	NI	18.9	1	NI	NI
Woodfine et al,[8] 2019	623	≥12 (25)	NI	NI	2	NI	NI
		<12 (75)	NI	NI	0	NI	NI
Baek et al,[21] 2021	178	>10 (48.9)	2.3	NI	0	6.6	NI
		6-10 (42.7)	1.3	NI	0	10.6	NI
		<6 (8.4)	13.3	NI	0	19.3	NI
Grim et al,[24] 2021	497	≥10 (36.6)	64.8	NI	0	17.8	7.2
		5-10 (39.6)	29.4	NI	0	19.5	6.1
		<5 (23.7)	39	NI	0	23.4	7.1
Arshad et al,[20] 2022	107	≥10 (44.9)	2.1	NI	0	11.4	NI
		5-10 (41.1)	4.5	NI	0	18.4	NI
		<5 (14)	20	NI	0	21.5	NI
Turkmen et al,[29] 2022	145	>10 (40)	6.9	NI	0	9.5	NI
		6-10 (36.6)	9.4	NI	0	11	NI
		<6 (23.4)	26.5	NI	0	10	NI
Kinoshita et al,[10] 2023	1024	>8 (44)	8.4	NI	0	NI	NI
		≤8 (56)	13.4	NI	0	NI	NI
MacMillan et al,[9] 2023	2956	>12 (20.1)	4.5	NI	2	9.9	NI
		8-12 (27.8)	6.1	NI	3	10.2	NI
		<8 (52)	9.1	NI	5	10.2	NI
		<6 (27.4)	11.5	NI	0	10.2	NI
Massop et al,[26] 2023	130	>10 (20.8)	7.4	NI	0	NI	NI
		6-10 (56.9)	2.7	NI	0	NI	NI
		<6 (22.3)	17.2	NI	0	NI	NI
Mustajoki et al,[27] 2023	385	>10 (42.3)	4.3	5.5	5	7.8	2.7
		6-10 (50.1)	7.3	8.8	0	7.6	3
		<6 (7.5)	10.3	31	0	10.1	3.3
Nagase et al,[28] 2023	221	>10 (7.2)	18.8	NI	0	21	NI
		4-10 (59.7)	7.6	NI	0	25	NI
		<4 (33)	19.2	NI	0	31	NI
Seethapathy et al,[11] 2023	3274	>10 (32.6)	5.2	7.3	2	8	NI
		6-10 (29.1)	7.6	10.1	4	10	NI
		<6 (38.3)	12.7	20.3	1	10	NI

Abbreviations: ICU, intensive care unit; LOS, length of stay; NI, no information; ODS, osmotic demyelination syndrome.

SI conversion factor: To convert serum sodium to millimoles per liter, multiply by 1.

effect, though the difference in LOS was marginal for very rapid vs slow or very slow correction (eFigure 12 in Supplement 1).

ICU LOS

We found a non-statistically significant shorter ICU LOS and no estimated dose-response effect when comparing rapid vs

Table 3. Rapid vs Slow or Very Slow Correction for Severe Hyponatremia

Outcome	Anticipated absolute effects per 1000 patients[a]		Relative effect (95% CI)	No. of patients (nonrandomized studies)	Certainty of evidence, GRADE[c]	Comments
	Risk with slow/very slow correction	Risk with rapid correction (95% CI)[b]				
Adjusted in-hospital mortality	114	71 (55 to 89)	OR, 0.59 (0.45 to 0.76)	6389 (6)	⨁⨁⨁◯ Moderate[d]	Probable dose-response effect
Rapid vs slow correction	103	71 (59 to 86)	OR, 0.67 (0.55 to 0.82)	6017 (5)	⨁⨁⨁◯ Moderate[e]	Probable dose-response effect
Rapid vs very slow correction	362	141 (59 to 309)	OR, 0.29 (0.11 to 0.79)	372 (2)	⨁⨁⨁◯ Moderate[f]	Probable dose-response effect
In-hospital mortality, rapid vs slow correction	103	74 (64 to 87)	RR, 0.72 (0.62 to 0.85)	7255 (12)	⨁⨁◯◯ Low[g]	Probable dose-response effect
In-hospital mortality, rapid vs very slow correction	148	74 (62 to 87)	RR, 0.50 (0.42 to 0.59)	5158 (11)	⨁⨁◯◯ Low[g]	Probable dose-response effect
30-Day mortality, rapid vs slow correction	137	75 (61 to 91)	RR, 0.55 (0.45 to 0.67)	3865 (3)	⨁⨁◯◯ Low[g]	Probable dose-response effect
30-Day mortality, rapid vs very slow correction	206	72 (58 to 90)	RR, 0.35 (0.28 to 0.44)	2514 (2)	⨁⨁◯◯ Low[g]	Probable dose-response effect
ODS (RD), rapid vs slow correction	2	2 (0 to 5)	Not estimable	9484 (15)	⨁⨁◯◯ Low[g]	NA
ODS (0.5 correct), rapid vs slow correction		3 (1 to 5)	RR, 1.66 (0.82 to 3.38)			
ODS (RD), rapid vs very slow correction	0	2 (0 to 4)	Not estimable	5021 (9)	⨁⨁◯◯ Low[g]	NA
ODS (0.5 correct), rapid vs very slow correction		0 (0 to 2)	RR, 1.32 (0.46 to 3.79)			
Hospital length of stay, rapid vs slow correction (95% CI), d	Mean, 12.71 (11.67 to 13.75)	MD, −1.20 (−1.89 to −0.51)	NA	6978 (10)	⨁⨁◯◯ Low[g]	Probable dose-response effect
Hospital length of stay, rapid vs very slow correction (95% CI), d	Mean, 14.72 (13.61 to 15.83)	MD, −3.09 (−4.96 to −1.21)	NA	5110 (10)	⨁◯◯◯ Very low[g,h,i]	Probable dose-response effect
ICU length of stay, rapid vs slow correction (95% CI), h	Mean, 98.40 (46.24 to 150.55)	MD, −2.04 (−4.94 to 0.86)	NA	1900 (4)	⨁⨁◯◯ Low[g]	NA
ICU length of stay, rapid vs very slow correction (95% CI), h	Mean, 99.26 (25.65 to 172.87)	MD, −1.26 (−10.3 to 7.78)	NA	817 (3)	⨁⨁◯◯ Low[g]	NA

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; MD, mean difference; NA, not applicable; ODS, osmotic demyelination syndrome; OR, odds ratio; RD, risk difference; RR, risk ratio.

SI conversion factor: To convert serum sodium to millimoles per liter, multiply by 1.

[a] Inpatients with severe hyponatremia received the intervention of rapid correction (≥8 and <12 mEq/L per 24 hours) or one of the comparisons of slow (<8 or 6-10 mEq/L per 24 hours) or very slow correction (<4-6 mEq/L per 24 hours).

[b] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c] GRADE Working Group grades of evidence (profile by domains is presented in eTable 2 in Supplement 1) include high certainty (⨁⨁⨁⨁; we are very confident that the true effect lies close to that of the estimate of the effect), moderate certainty (⨁⨁⨁◯; we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), low certainty (⨁⨁◯◯; our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect), and very low certainty (⨁◯◯◯; we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[d] 5 Of 7 studies with moderate risk of bias.

[e] 3 Of 5 studies with moderate risk of bias.

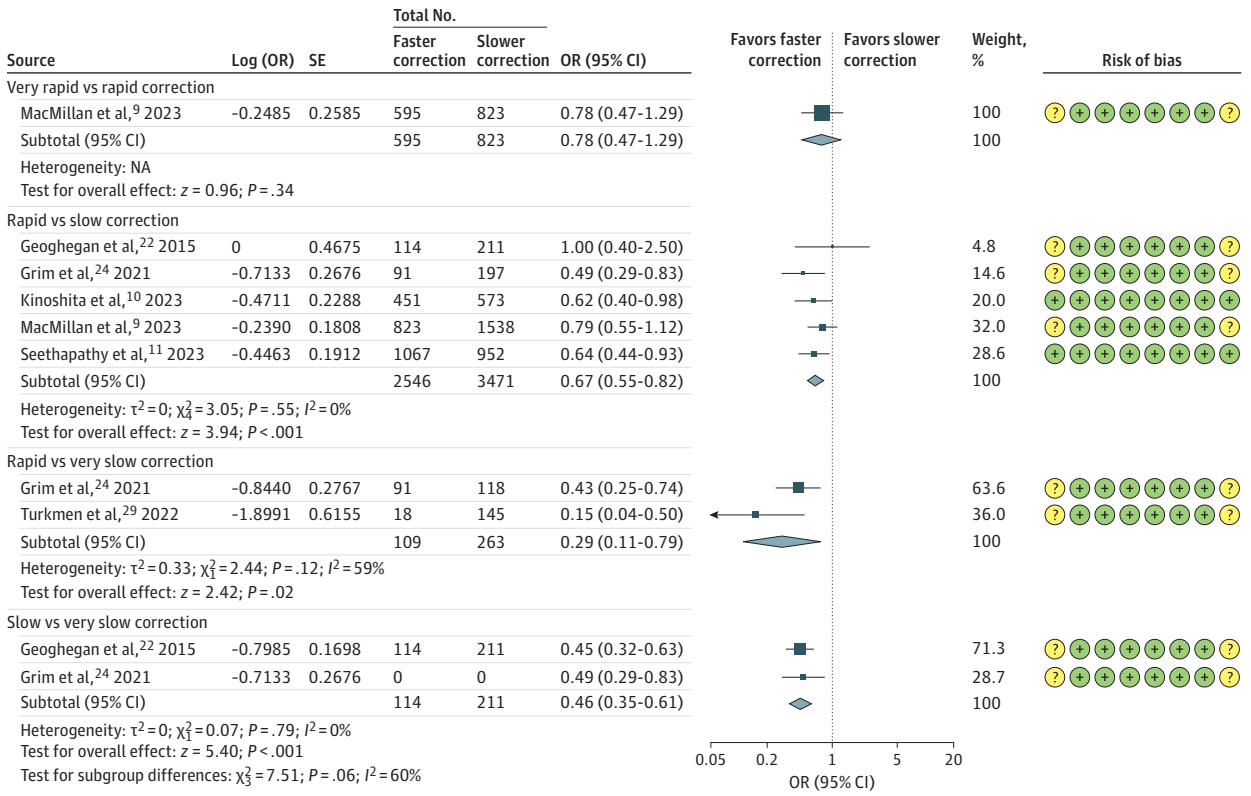
[f] 2 Of 2 studies with moderate risk of bias.

[g] All studies with serious risk of bias.

[h] I^2, 85%.

[i] Asymmetry in the funnel plot.

Figure 2. Adjusted In-Hospital Mortality by Speed of Correction



Green symbols represent low risk of bias, while yellow symbols represent moderate risk of bias. NA indicates not applicable; OR, odds ratio; SE, standard error.

slow sodium correction or very slow sodium correction (Table 2 and eFigure 13 in Supplement 1).

Subgroup Analysis

Due to the absence of data, the only subgroup analysis that could be performed was for alcohol use disorder. There was no statistically significant RD in ODS and no estimated dose-response effect when comparing rapid vs slow/very slow sodium correction in patients with and without alcohol use disorder, with an I^2 of 0% in the test for subgroup differences (eFigure 14 in Supplement 1).

Sensitivity Analyses

The results of a sensitivity analysis conducted using the fixed-effect model were not statistically significantly different from the results obtained with the random-effects model used for the primary analysis. As no included study for adjusted in-hospital mortality was classified as having serious RoB, and all studies were classified as having serious RoB for unadjusted outcomes, a sensitivity analysis excluding these studies could not be performed. LOS when comparing rapid vs very slow sodium correction presented a substantial heterogeneity (eFigure 1 in Supplement 1). By excluding the 3 more extreme MDs (cumulative weight, 8.8%), the heterogeneity persisted, and MD was lower but still statistically significant among 4827 participants in 7 studies (MD, −2.37; 95% CI, −4.25 to −0.49; I^2, 88%) (eFigure 15 in Supplement 1).

Assessment of Reporting Biases

There was no evidence of publication/reporting biases in the funnel plots for the outcomes with at least 8 studies in a meta-analysis, including unadjusted mortality (RD), unadjusted ODS (RD), and unadjusted ODS (Peto OR) (eFigures 16-18 in Supplement 1). For the unadjusted hospital LOS meta-analysis of rapid vs slow correction, there was an asymmetry; however, after excluding the 3 more extreme MDs, this asymmetry disappeared, and the estimated effect remained statistically significant (eFigures 19-20 in Supplement 1).

Discussion

This systematic review and meta-analysis of 16 cohort studies published in the 10 years following the 2013 hyponatremia treatment guidelines evaluated the estimated effects of varying sodium correction rates on mortality, LOS, and ODS and among 11 811 patients with severe hyponatremia, following the PRISMA statement (eTable 4 in Supplement 1). Moderate-certainty evidence showed that rapid correction (≥8-10 mEq/L per 24 hours) was associated with 32 fewer in-hospital deaths per 1000 treated patients compared with slow correction (<8 or 6-10 mEq/L per 24 hours) and 221 fewer in-hospital deaths per 1000 compared with very slow correction (<4-6 mEq/L per 24 hours). Low-certainty evidence suggested that rapid correction compared to slow and very slow

correction was associated with 61 and 134 fewer deaths per 1000 patients at 30 days and may reduce hospital stay by 1.20 and 3.09 days,[41] respectively. The analyses of the association between rapid correction and ODS did not identify a statistically significant higher risk. Nevertheless, larger studies are needed because analyses of rare events are often underpowered. The association between a slower correction rate and mortality and the absence of a clear association with ODS suggest a beneficial effect, considering both the absolute numbers and the importance of mortality compared to ODS, which is nonfatal and usually has a favorable long-term outcome.[42,43] However, the evidence only implies associations and not causality. There are numerous mechanisms to explain why hyponatremia could contribute to mortality and why treatment is beneficial. Hyponatremia leads to altered cellular function via osmotic stress and ionic strength,[44] affecting apoptotic pathways[45] and cytokine production and leading to oxidative stress.[46] Hyponatremia could, therefore, contribute to increased mortality risk when in combination with serious medical conditions. It is well recognized that hyponatremia is an independent predictor for mortality,[47] particularly in patients with comorbidities,[48-55] and affects multiple organs.[56-60] Treatment of hyponatremia is also independently associated with improved patient outcomes.[61]

Analogous to the present findings that rapid correction of hyponatremia is associated with improved outcomes, recent studies have similarly found that rapid correction of hypernatremia has been associated with improved patient survival.[62] To adjust for the main influential cofounders, including confounding by indication, in the primary analysis of mortality, we only included studies accounting for relevant confounders, and we assessed their RoB by using ROBINS-I, the best available tool to evaluate nonrandomized studies of interventions.[15] The GRADE assessment for adjusted in-hospital mortality was considered as moderate-certainty evidence because of moderate bias due to confounding in 5 of 7 studies. The differences in effects of faster corrections and the test for subgroup differences showing a considerable heterogeneity suggest a probable dose-response effect, supporting the present findings. The consistency of estimated dose-response effects also observed for unadjusted in-hospital mortality and 30-day mortality highlights the robustness of the findings.

Limitations

Limitations of this study were the heterogeneity of inclusion/exclusion criteria, correction rate comparisons, cointerventions, and ODS definitions among the included studies. To compare correction rate categories, we used reasonable ranges rather than single discrete cutoff to aggregate studies for each comparison of faster vs slower correction rates. Nonetheless, the estimated effects of sodium correction were not severely influenced by these factors because the management of patients with severe hyponatremia followed treatment standards.[5,6] To address the frequent zero-events in both arms for ODS, we used meta-analysis of RD and empirical and continuity corrections. Although we obtained additional data beyond publications by contacting the authors of 5 studies, there was insufficient information to conduct subgroup analyses by acuity (it is mostly impossible to determine it), severity, osmolarity, cause of the hyponatremia, or the rate of corrections over 24 hours; however, the findings still apply to severe hyponatremia regardless of these factors. We were unable to classify patients as experiencing acute or chronic conditions, as in most patients presenting to the emergency department, the duration of hyponatremia was unknown, and treatment guidelines recommend that the condition be considered chronic.[6] While slow correction was associated with increased adjusted mortality, it is possible that more patients in the slow correction group had increased severity of illness, such as advanced liver disease, heart failure, or cancer. A 2023 study by Seethapathy et al,[11] however, found that slow correction of hyponatremia was associated with increased adjusted mortality in patients with liver disease, heart failure, and cancer. While we are unable to conclude that slow correction is the cause of increased mortality, rapid correction did not lead to worse outcomes with increased mortality or ODS. An additional limitation in this study is that ODS may have been underreported in the included studies, as it required confirmatory imaging findings. It is possible that less severe cases went unrecognized. In most circumstances, patients with mild cases improve over time and have favorable outcomes. We were also unable to determine if rate of correction played a role in ODS in the presence of other electrolyte abnormalities or by alcohol misuse. Mean serum sodium was greater than 115 mEq/L among patients in 13 of the 16 included studies; therefore, the findings are more applicable to this severity of hyponatremia. Due to the absence of data, the subgroup analyses were uninformative.

Conclusions

In this systematic review and meta-analysis, available evidence suggests that slow correction of sodium was associated with an increased risk of mortality and longer hospital LOS. These findings are further supported by dose-response effects with no statistically significant higher risk of ODS, suggesting a very favorable net benefit with rapid correction.

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