Kidney Medicine

Hyponatremia Correction and Osmotic Demyelination Syndrome Risk: A Systematic Review and Meta-Analysis

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Rationale & Objective: Osmotic demyelination syndrome (ODS) is a rare but severe condition often attributed to the rate of sodium collection. We evaluated the association between the overly rapid sodium correction in adult hospitalized patients with ODS.

Study Design: Systematic review and meta-analysis.

Setting & Study Populations: Adults hospitalized hyponatremia patients.

Selection Criteria for Studies: The studies comparing the incidence of ODS with and without rapid sodium correction inception to January 2024.

Data Extraction: Two reviewers independently extracted data and assessed the risk of bias and the certainty of evidence.

Analytic Approach: The incidence of ODS following a rapid and nonrapid sodium correction was pooled using the random effects model. Subgroup and meta-regression analyses were performed for the robustness and the source of heterogeneity.

Results: Eleven cohort studies were included with 26,710 hospitalized hyponatremia patients. The definition of hyponatremia varied from <116 to <130 mmol/L, and overly rapid sodium correction was defined as >8 to 12 mmol/L within 24 hours. The overall incidence of ODS was 0.23%. The incidence of ODS in rapid and nonrapid sodium correction was 0.73% and 0.10%, respectively. Meta-analysis demonstrated that a rapid rate of sodium correction was associated with a higher incidence of ODS (odds ratio 3.16, 95% CI, 1.54-6.49, $I^2 = 27\%$), whereas some patients with hyponatremia developed ODS without rapid sodium level correction. The sensitivity analysis based on the quality of the studies was consistent with the main result.

Limitation: Various definition criteria for ODS diagnosis across studies, lack of potential electrolyte and treatment data that may affect the incidence of ODS.

Conclusions: The rapid rate of sodium correction had a statistical correlation with a higher incidence of ODS. Among ODS without rapid correction, further studies are recommended to evaluate and comprehend the relationship for better and proper management of hospitalized patients with hyponatremia.

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Hyponatremia (ie, serum sodium < 135 mEq/L) is a common electrolyte disturbance among hospitalized individuals, occurring in 5%-35% of patients.[1-4] Hyponatremia is associated with increased hospital costs along with in-hospital and long-term mortality.[4-7] Its clinical presentations vary from asymptomatic to life-threatening conditions.[8] Therefore, patients with moderate-to-severe neurologic symptoms or life-threatening complications require emergency treatment to increase serum sodium regardless of the hyponatremia chronicity.[9,10] Although treatment of hyponatremia is crucial to prevent brain osmotic stress, identifying potential risk factors (such as alcoholism, malnutrition, hypokalemia, and liver disease) and monitoring the consequences of treatment is important.[11,12]

The rapid sodium correction in patients experiencing hyponatremia for >48 hours, whose brains had already adapted to a hypotonic setting, is recognized as the leading risk factor for osmotic demyelination syndrome (ODS), a previous term known as central pontine myelinolysis (CPM).[8] ODS was initially introduced in 1986.[13] Evidence indicated the rapid correction of hyponatremia is linked to severe neurological symptoms. Notably, demyelination was observed not only in central pontine areas but also in extrapontine lesions were described. Therefore, the term ODS was adopted to provide a more inclusive definition for the previously described CPM. ODS is reported in 0.05%-0.5% patients with hyponatremia.[3,8,10,13-18] Several human studies showed that patients diagnosed with ODS typically experienced a rapid sodium correction during hyponatremia treatment.[3,8,10,13-18]

However, the association between sodium correction rate and ODS remains debated, some patients developed ODS without rapid rate correction. A study on patients with severe hyponatremia reported that 41% had a rapid correction, with an ODS incidence of 0.5%.[3] Conversely, other studies showed that ODS can develop without rapid sodium correction and less severe hyponatremia.[3,14,19] A large multicenter study[16] revealed an ODS rate of 0.05%, with 58% of patients with ODS not experiencing rapid sodium correction. Similarly, a recent study[20] showed that 71% of patients with ODS had a sodium correction rate <8 mmol/L/24 hours. Therefore, we conducted a systematic review to evaluate the association between the overly rapid correction of sodium in adult hospitalized patients with hyponatremia and ODS.

PLAIN LANGUAGE SUMMARY

Hyponatremia is a common electrolyte disorder that is essential to treat symptoms to prevent further neurologic complications, even from hyponatremia itself or following treatment. This meta-analysis evaluated the association between sodium correction rate and osmotic demyelination syndrome (ODS). The finding demonstrated that rapid correlation >8 mmol/L/24 h had a statistical correlation with a higher risk of ODS. Rapid sodium correction occurred in 21.5% of patients with hyponatremia. The overall incidence of ODS was 0.23% and 0.73% among those with rapid sodium correction. Even without rapid correction, 0.1% of patients with hyponatremia developed ODS. Further studies are needed to comprehend the relationship between hyponatremia and ODS among all individuals, including those without rapid correction, to optimize the management of hyponatremia.

METHODS

Search Strategy

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023429171). A comprehensive search was conducted from each database's inception to January 8, 2024. The databases included Ovid MEDLINE(R) (including Epub ahead of print, in process, in-data-review, and other non-indexed citations), Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. An experienced librarian (LJP) executed the search strategy with input from the study's principal investigators. The search terms used included "hyponatremia," "osmotic demyelination syndrome," and "central pontine myelinolysis." The detailed search strategies are available in Table S1. The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (online Supplementary Materials), and our protocol is available at https://www.crd.york.ac.uk/prospero/. This study did not receive any funding.

Study Selection

We included original studies comparing the incidence of ODS with and without rapid sodium correction in hospitalized hyponatremia patients using cohort, case–control, or cross-sectional study designs. The ODS definition was according to individual studies. These studies were heterogeneous and used both terms of ODS or CPM interchangeably. In addition, the defining criteria differed as some used clinical diagnosis, and/or others used imaging data. We did not restrict the publication date, race, sex, ethnicity, or language. We excluded case reports, reviews, books, unavailable full-text articles, and letters. Nonhuman studies or unspecified incidences of hyponatremia or ODS were also excluded.

Two investigators (SS and PK) independently assessed the studies using the Newcastle–Ottawa (NOS) scale[21] (Table S2) to evaluate the quality and risk of bias. Studies that scored <5 were characterized as low quality, those scoring 5-6 were defined as fair, and those scoring >6 were classified as high quality.

Outcomes

The primary outcome was the association of ODS following a rapid sodium correction compared with nonrapid correction. The secondary outcome was the incidence of rapid sodium correction and mortality outcomes in patients hospitalized with hyponatremia.

Review Process and Data Extraction

The comprehensive reviews were conducted on Covidence (https://www.covidence.org). Two reviewers (SS and PK) independently screened and extracted data from eligible full text, including publication year, study type, number of patients enrolled, and participant characteristics (age, sex, baseline serum sodium, sodium correction rate, and the number of patients with ODS). The baseline levels of osmolality and electrolytes, such as potassium and chloride, which could affect serum osmolality, were also collected. WebPlotDigitizer was used to extract the data that was not provided in the text or tables.[22] Any disagreements were resolved through the reviewer's consensus and, if necessary, the adjudication of a third reviewer (JPD).

Statistical Analysis

This meta-analysis used a random-effect model to pool the outcome of interest. The dichotomous outcomes were estimated using odds ratios (ORs) with 95% confidence intervals (CIs). The statistical heterogeneity of effect size across the studies was estimated using the Cochrane χ^2 (Q test) and I^2 statistics. A P value of < 0.1 on the Q test was considered significant. I^2 statistics below 25% represented no significant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity, and 76%-100% high heterogeneity. A meta-regression analysis was performed to evaluate the impact of the study year. The publication bias was assessed using funnel plot and Egger's test.

A sensitivity analysis was performed to ensure the robustness of the results by excluding poor and fair-quality studies. Additionally, subgroup analysis was conducted to determine the source of heterogeneity by stratified data based on cut-point criteria of the sodium correction rate. We used Review Manager (RevMan) version 5.4.1 for all analyses, along with the Cochrane Collaboration, 2020, and STATA Statistical Software version 18.

RESULTS

Characteristics of Included Studies

We identified 790 potentially relevant articles from the search strategies. After removing duplicates and excluding nonoriginal articles, we reviewed 30 full-length articles. Twenty studies were excluded because of unreported ODS incidence, unidentified treatment rate, or duplication population, as shown in Figure 1. Accordingly, 11 retrospective studies conducted between 1986 and 2023 were included in the final analyses.[3,13,15-17,20,23-26]

General Characteristics of the Patients

A total of 26,710 hospitalized patients with hyponatremia were enrolled in the 11 included studies.[3,13,15-17,20,23-26] The baseline characteristics are presented in Table 1. The hyponatremia was defined in a wide range of 116-130 mmol/L. Most patients (n=20,697; 77.5%) were enrolled when sodium levels were <125-130 mmol/L, predominantly influenced by data from 2 studies with larger sample sizes.[16,25] A total of 16.5% (n=4,403) had serum sodium levels <120 mmol/L across 6 studies[3,15,17,23-25], whereas 1.9% (n=504) of patients were included when diagnosed with severe hyponatremia with sodium levels <116 mmol/L in 2 studies.[13,26]

Among studies reporting age and sex, defined as biological and physical charactereistics,[3,15-17,20,23,24,26] the average age was 68 ± 16 (ranging from 56-72) years, and 51% were women. The mean sodium at recruitment ranged from 101 ± 1.0 to 125 ± 4.6 mmol/L in 7 studies.[3,15-17,20,23,24] The lowest sodium level of 95 mmol/L was reported in 2 studies.[17,23] The causes of hyponatremia in individual studies were syndrome of inappropriate antidiuretic hormone secretion (ranging from 25%-38%), diuretics (ranging from 22%-41%), hypovolemia (ranging from 19%-35%), and alcohol (ranging from 11%-25%).[15,17,23,26] The mean baseline serum osmolality was 271 ± 31 mOsm/kg in 5 studies.[3,15,16,20,24] Only 3 studies demonstrated serum

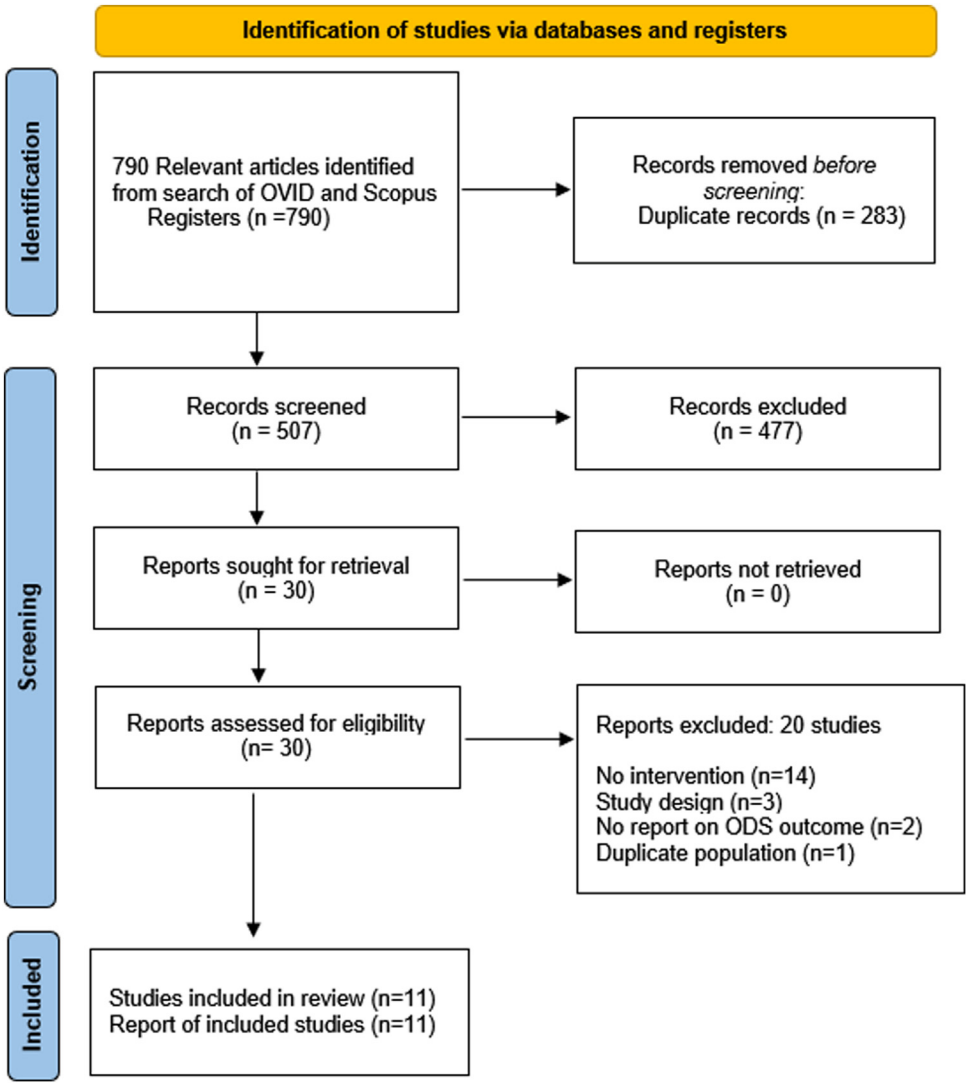

Figure 1. PRISMA flow chart for systematic review.

Table 1. Baseline Characteristics of Included Studies

Study	Year	Country	Criteria Hyponatremia (mmol/L)	Criteria of Rapid SNa Correction (mmol/L in 24 hr)	Total Patients	Number of Rapid SNa Correction	Number of Nonrapid SNa Collection	Baseline SNa Mean, SD	Patient Characteristics	Number of ODS	Diagnosis of ODS
Sterns et al[13]	1986	USA	<116	> 12	60	41 (68.3%)	19 (31.7%)	N/A	12-month follow-up period [a]Etiology: liver disease 100%, diuretic 88%, hypovolemia 12.5%, alcohol 25%	8 Incidence ODS 13.3%	Clinical and CT
Sterns et al[27]	1987	USA	<110	>13	60[b]	34	26	N/A	Hyponatremia between 1980 and 1985 Mean age: 68 years, female 73% Risk factors: diuretic 36%, SIADH 36%, polydipsia 6.3%, Addison 6.25%	3 Incidence ODS 5%	Clinical
Sterns et al[23]	1994	USA, Canada, France, Chili, Taiwan	<120	>12	56	43 (76.8%)	13 (23.2%)	101 ± 1.0	Hyponatremia between 1983 and 1988 Mean age: 59 years, female 67% Risk factors: alcoholism 21.4%, thiazide 25%	3 Incidence ODS 5.36 %	Clinical and MRI
Heng et al[24]	2007	France	<120 Osm < 250 Osm/kg	>12	22	10 (45%)	12 (55%)	113 ± 5	Hyponatremia between 1996 and 2002 Mean age: 56±16 years, sex ratio 0.57 [a]Etiology: chronic alcohol 100%	7 Incidence ODS 31.8%	Clinical and CT/ MRI
Vu et al[17]	2009	Australia	£120	>12	255	37 (14.5%)	218 (85.5%)	115 ± 6.25	Severe hypotonic hyponatremia between 2000 and 2007 Mean age: 72±14 years, female 68% Etiology: diuretic 41%, SIADH 38%, hypovolemia 24%, alcohol 11%	4 Incidence ODS 1.56%	Clinical and MRI

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Included Studies

Study	Year	Country	Criteria Hyponatremia (mmol/L)	Criteria of Rapid SNa Correction (mmol/L in 24 hr)	Total Patients	Number of Rapid SNa Correction	Number of Nonrapid SNa Collection	Baseline SNa Mean, SD	Patient Characteristics	Number of ODS	Diagnosis of ODS
Geohegan et al[15]	2015	USA	<120	>10	412	114 (27.7%)	298 (72.3%)	116 ± 1.0	Hyponatremia between 2008 and 2012 Mean age: 69 ± 6 years, female 58.3% Risk factor: hypovolemia 35%, SIADH 25%, diuretic 22%, alcohol 16%	1 Incidence ODS 0.24%	Clinical and radiological confirm
George et al[3]	2018	USA	<120	>8	1,490	606 (40.7%)	884 (59.3%)	116 ± 4.5	Severe hypotonic hyponatremia between 2001 and 2007 Mean age 66±15 years, female 55% [a]Etiology: Hypovolemia 75%, beer potomania 63%, alcohol 50%, diuretic 25%, hypokalemia 63%, malnutrition 50%	8 Incidence ODS 0.5%	ICD-9 and 10 or MRI
Park et al[25]	2019	Korea	<125	>8	125	43 (34.4%)	82 (65.6%)	N/A	Liver transplant with preoperative hyponatremia between 2005 and 2017	4 Incidence ODS 3.2%	Neurological symptoms with MRI
Mustajoki et al[26]	2023	Finland	<116	>8	384	104 (27%)	280 (73%)	N/A	Hyponatremia between 2016 and 2020 Mean age: 68±20 years, female 56% Etiology: SIADH 34%, diuretic 27%alcohol 19%, hypovolemia 19%	5 Incidence ODS 1.3%	MRI
MacMillan et al[16]	2023	Canada	<130	>8	20,572	3,632 (17.7%)	16,940 (82.3%)	125 ± 4.6	Hyponatremia between 2010 and 2020 Mean age: 68 ± 16 years, female: 50% Risk factors: - Potassium <3.4 mmol/L: 14% - Liver disease: 6.7%	12 Incidence ODS 0.05% - 5 of 10,000 patients - 3 of 1000 patients in SNa <120	1. CT/MRI 2. Chart review with ICD-10 diagnosis code and clinical report – definite ODS

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Included Studies

Study	Year	Country	Criteria Hyponatremia (mmol/L)	Criteria of Rapid SNa Correction (mmol/L in 24 hr)	Total Patients	Number of Rapid SNa Correction	Number of Nonrapid SNa Collection	Baseline SNa Mean, SD	Patient Characteristics	Number of ODS	Diagnosis of ODS
Seethapathy et al[20]	2023	Canada	<120	>10	3274	1,067 (32.6%)	2,207 (67.4%)	116 ± 4.0	Severe hyponatremia between 1993 and 2018 Mean age: 66 ± 16, female 57% [a]Etiology: Hypovolemia 57%, alcohol 57%, malnutrition 57%, hypokalemia 57%, hypophosphatemia 43%	7 Incidence ODS 0.2%	1. ICD-9 and 10 diagnosis code 2. MRI

Abbreviations: CT, computed tomography; ICD, International Classification of Disease; MRI, Magnetic Resonance Imaging; N/A, not available; ODS, osmotic demyelination syndrome; Osm, osmolarity; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SD, standard deviation; SNa, serum sodium.
[a]Etiology of patients with ODS.
[b]Total population enrollment is 62 patients, but only 60 patients had available data for analysis after treatment of hyponatremia.

potassium presentation, with a mean of 4.3 ± 1.2 mg/dL.[3,20,24] The risk factors of patients with ODS were reported liver disease (100%), alcohol use (50%-100%), malnutrition (50%-57%), hypokalemia (57%-63%), and hypovolemia (12.5%-75%).[3,13,20,24]

Rapid Sodium Correction

The definitions of rapid correction varied between the enrolled studies. Four studies[3,16,25,26] defined rapid correction as an increase of sodium ≥8 mmol/L/ 24 hours. Two studies[15,20] set the threshold at >10 mmol/L/24 hours.[15,20] The remaining studies[13,17,23,24] defined it as >12 mmol/L/ 24 hours. Among included patients, 21.5% (n = 5,731) were exposed to rapid sodium correction, which ranged from 15%-77%. The studies[13,23,26,27] that enrolled initial sodium < 116 mmol/L showed a higher incidence ODS rate at 2.9% (16 of 560). The incidence rate of ODS for the initial sodium <120 mmol/L was 0.31%.[3,15,17,20,24] The value was 0.04% in the studies that included serum sodium <130 mmol/L.[16,25] A meta-regression showed that the incidence of ODS was not influenced by the baseline sodium (Figure S1).

The ODS Diagnosis

The ODS diagnosis relied on neurological manifestation and findings on computed tomography (CT), magnetic resonance imaging (MRI), histology, or diagnosis code from the International Classification of Disease, Ninth and Tenth Revisions (ICD-9 and ICD-10, respectively). Six studies[13,15,17,23-25] included clinical symptoms combined with imaging or histology to diagnose ODS. One study[26] applied only imaging for ODS diagnosis, whereas others[3,16,20] used ICD code and imaging (Table 1).

Rates of Sodium Correction and Impact on ODS Incidence

Overall, the pooled OR for the occurrence of ODS at a rapid rate compared with nonrapid rate serum sodium correction among patients hospitalized with hyponatremia was 3.16 (95% CI, 1.54-6.49, $I^2 = 27\%$), as shown in Figure 2.

In a cohort of 26,710 patients, the overall incidence of ODS was 0.23% (N = 62), ranging from 0.05%-31.8%. Heng et al[24] reported the highest ODS rate of 31.8%, whereas MacMillan et al[16] showed the lowest rate at 0.05%. The population in the Heng et al[24] study had severe hyponatremia with a mean sodium level of 113 ± 5 mmol/L, and 45% experienced rapid correction. In contrast, patients in McMillan et al[16] had mild hyponatremia with mean sodium of 125 ± 4.6 mmol/L, and only 17% had rapid rate correction. Moreover, chronic alcohol use was found to be higher compared with the MacMillan study.[16]

ODS Characteristics

Sixty-two patients developed ODS among the 26,710 enrolled individuals with a mean age of 50 ± 11 years and 58% female. ODS occurred in 0.73% (42 of 5,731) of those with a rapid sodium correction and 0.1% (20 of 20,979) among those without. The mean baseline

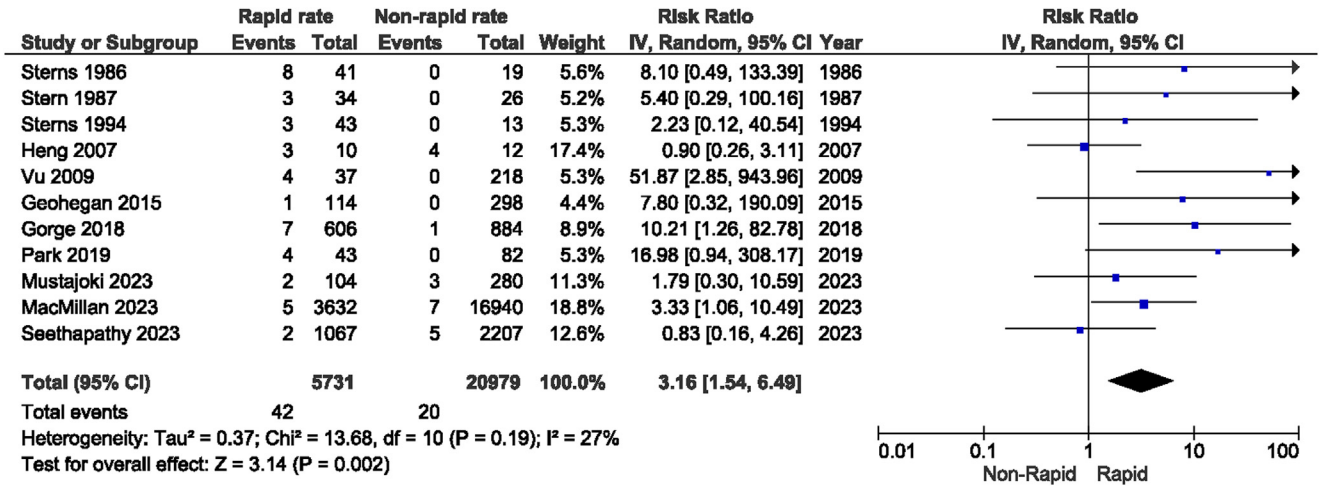

Figure 2. Forest plots of all included studies assessing the ODS outcome and rate of serum sodium correction among hospitalized hyponatremia patients.

sodium of patients with ODS was 109 ± 9.4 mmol/L. The average sodium changes in patients with ODS in 7 studies[3,13,15-17,20,25,26] among those with and without rapid serum sodium correction ranged from 9.0-21.5 to 6.2-7 mmol/L within the first 24 hours, respectively.

Moreover, in patients with ODS without rapid sodium correction, we observed common risk factors similar to those with overly rapid correction, including alcohol use, malnutrition, hypokalemia, and low baseline serum sodium. Additionally, MacMillan et al[16] demonstrated that urine sodium <30 mmol and prolonged hypernatremia after treatment were also presented in this group.

Mortality Outcomes

In total, of 10 studies[3,15-17,20,26] reported the overall mortality rate in patients with hyponatremia was 8.8% (2,336 of 26,428; 95% CI, 0.07-0.11; I^2 93%) (Figure 3). There was insufficient data available to determine whether patients died of brain edema caused by severe hyponatremia or other causes.

Two studies showed that a slow correction rate within 24 hours was associated with an increased risk of in-hospital and 30-day mortality.[16,20] These findings were consistently reported in the cancer and heart failure subgroup. Interestingly, Seethapathy et al[20] reported that treatment rates >10 mmol/L/24 h were associated with lower in-hospital, 30-day mortality, and shorter hospitalization compared with rates 6-10 mmol/L/24 hours. Higher mortality was observed with correction rate <8 mmol/L/24 hours in one study.[3] The other 2 studies report no association between rate change and mortality.[15,17]

Subgroup and Sensitivity Analysis

A prespecified subgroup analysis was performed based on the cut-point for rapid correction rate. The cut-point of 8 mmol/L/24 hours of sodium correction was associated with a significantly higher incidence of ODS compared with correction rates <8 mmol/L/24 h, with OR of 4.03 (95% CI, 1.74-9.37; $I^2 = 0\%$). Meanwhile, at other cut-points, ie, serum sodium changes at >10 and >12 mmol/L/24 hours, the incidence of ODS was not statistically significant (Figure 4).

Four studies[17,20,23,26] reported that 57.9% (11 of 19) of patients with ODS experienced sodium correction >18 mmol/L/48 hours. The mean change in serum sodium was 25.2±6.9 mmol/L over 48 hours. The sensitivity analysis showed a pool prevalence of patients with ODS with rapid correction rate >18 mmol/L/48 hours of 1.92 (95% CI, 1.14-2.69, $I^2 = 68.7\%$) (Figure S2).

In a subgroup analysis stratified by year of the study, from 2011-2020, ODS incidence was associated with the rapid rate correction with OR of 11.38 (95% CI, 2.52-51.4, $I^2 = 0\%$) (Figure 5). However, for the overall incidence, meta-regression demonstrated that the year of the study did not significantly affect the incidence of ODS ($P = 0.22$; Figure S3).

Moreover, a sensitivity analysis was performed to evaluate the quality and heterogeneity. The results consistently demonstrated an increased risk of ODS in the rapid rate sodium correction in good-quality studies (OR, 3.46, 95% CI, 1.50-7.98, $I^2 = 31$) (Figure 6).

Quality of Evidence Assessment

Based on NOS scores, all studies had scores ranging from 5-9. Two studies[13,23] were categorized as fair because of their lack of comparability, whereas the others[3,15-17,20,24-26] were considered good quality (Table S2). The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach, as presented in the summary of findings (Table S3).[28,29]

Evaluation of Publication Bias

The funnel plots in this study were symmetrical, and Egger's test demonstrated no statistically significant

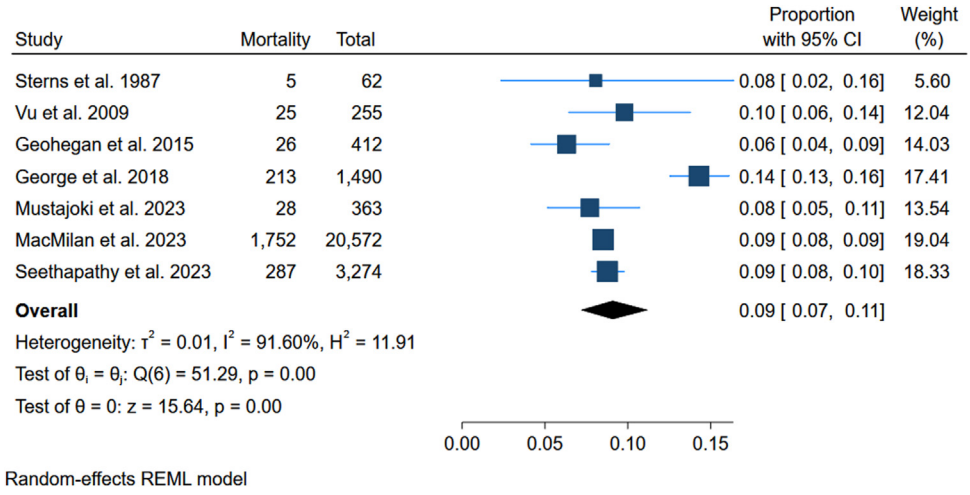

Figure 3. Forest plots of included studies in mortality outcome.

(P = 0.07) (Figure S4), which is considerably less likely to be affected by publication bias.

DISCUSSION

Our study shows that ODS is low, occurring around 1 in 1,000 patients with hyponatremia despite the frequent rapid correction in 1 out of 5 patients with hyponatremia. Also, we identified that a rapid sodium correction is associated with an increased risk of ODS compared with nonrapid correction. The body of evidence is imprecise and clinically heterogeneous, including variability of ODS diagnosis criteria used in the enrolled studies that contribute to a wide range of the reported ODS incidence.

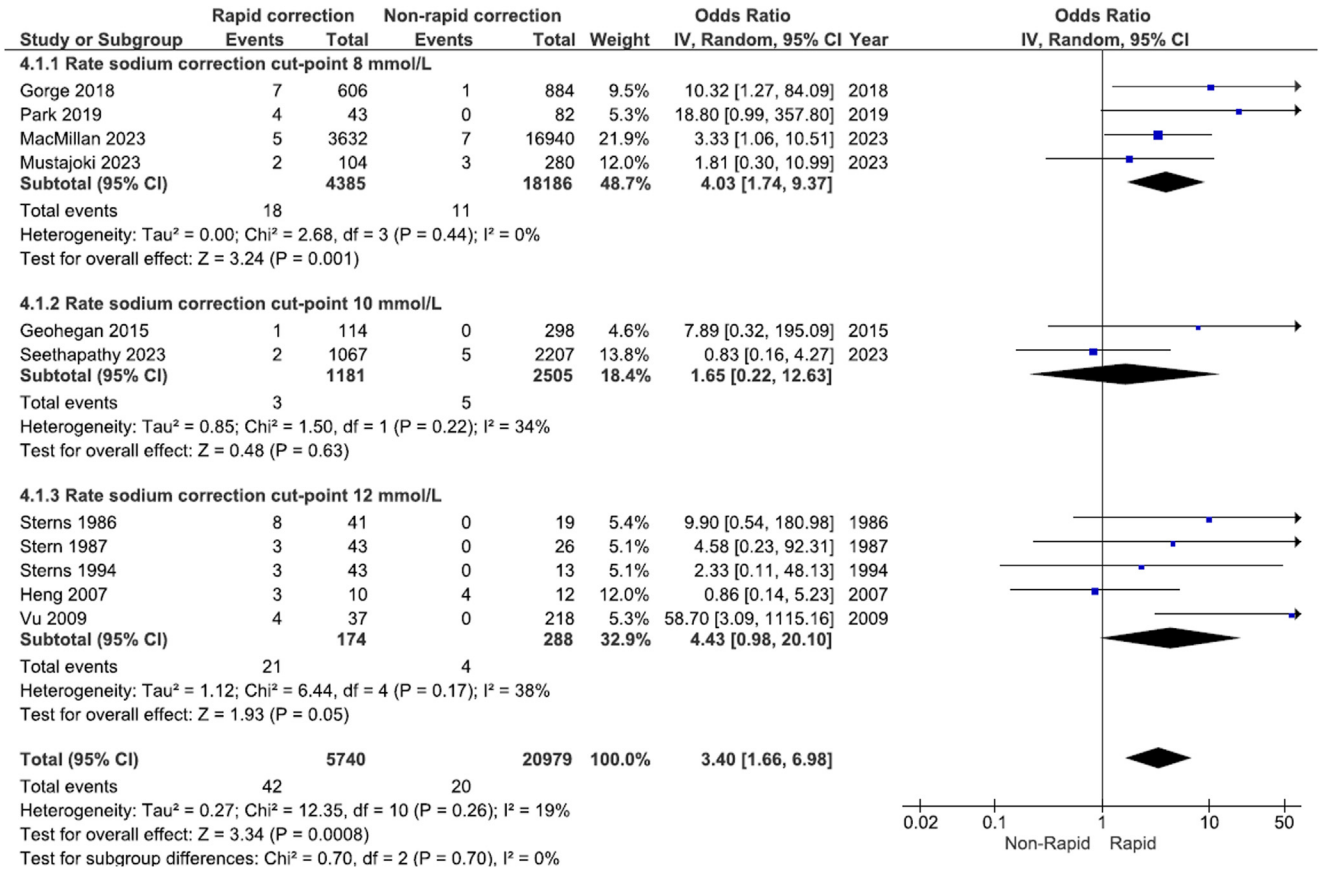

Figure 4. Forest plots of prespecified subgroups based on the cut-point in the rate of rapid sodium correction assessing the ODS outcome and rate of serum sodium correction among hospitalized hyponatremia patients.

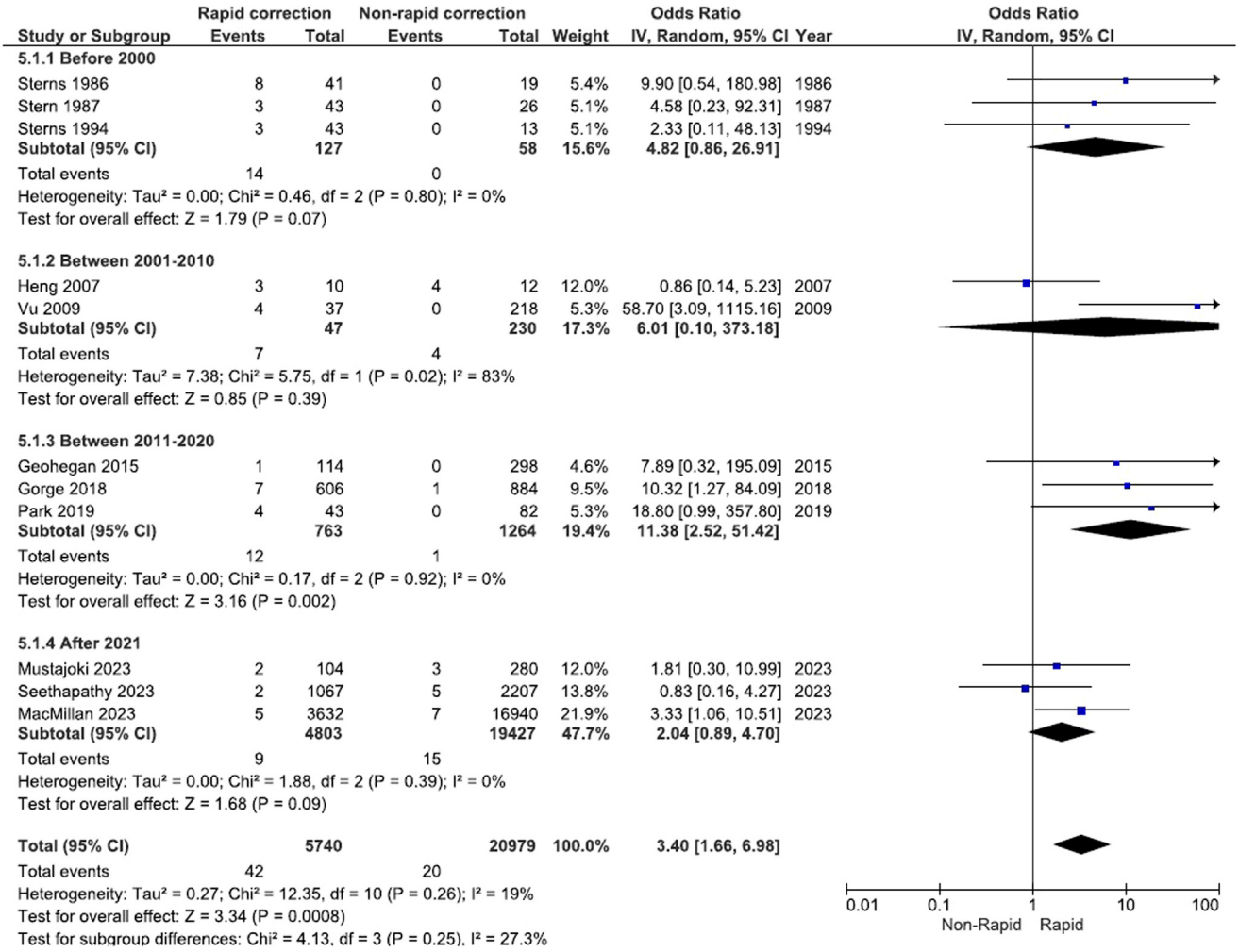

Figure 5. Forest plots of prespecified subgroups based on the year of publication evaluate the ODS outcome and the year of publication.

Therefore, overall confidence in the body of evidence is low given the low event rate and the wide CI affecting the ability of the I^2 test to detect heterogeneity.[30] Consequently, the sodium correction rate in hyponatremia is not the only aspect to be considered during the decision-making process.

A wide range of incidents highlighted that there are other risk factors for ODS than clear impact outcomes, and patient selection is of utmost importance when finding interpretation. Most studies enrolled moderate to severe hyponatremia with initial sodium <120 mmol/L (mean baseline <116 mmol/L) (Table 1). Only the study by MacMillan et al[16] included patients with mild hyponatremia (<130 mmol/L). In this study, 87% of the population had an initial sodium level >120 mmol/L, and the mean initial sodium level was 125 ± 4.6 mmol/L.[16] The risk of developing ODS is very low at these sodium levels, resulting in the lowest reported ODS incidence at 0.05%.

A previous systematic review identified 14 distinct criteria for the overcorrection of hyponatremia, with a median rate ranging from 6.48-27 mmol/L/24 hours.[31] However, we found included studies that used criteria defined as rapid correction of ≥8 mmol/L within 24 hr. We used 3 cut-off values for sodium correction rate, ie, ≥8[3,16,25,26], ≥10[15,20], and ≥12 mmol/L[13,17,23,24,27] within 24 hours. Our analysis showed that the association with ODS increases with a definition of rapid correction >8 mmol/L/24 h. Similarly, the American guidelines recommend that the sodium correction rate not exceed 10-12 mmol/L/24 h or 8 mmol/L/24 h in high-risk patients.[32,33] In contrast, the European guideline recommends a rate of 10 mmol/L/ 24 hours.[9] This highlights the need for a standardized definition of rapid correction across studies.

Notably, a higher rapid correction rate was presented in studies conducted from the 1990s to 2000s compared with recent studies. It is plausible that the clinical practice guidelines implemented from 2013-2014 for treating hyponatremia emphasized sodium correction rate as prevention against complications.[9,32] This may have affected clinical awareness and practices in later studies. Moreover,

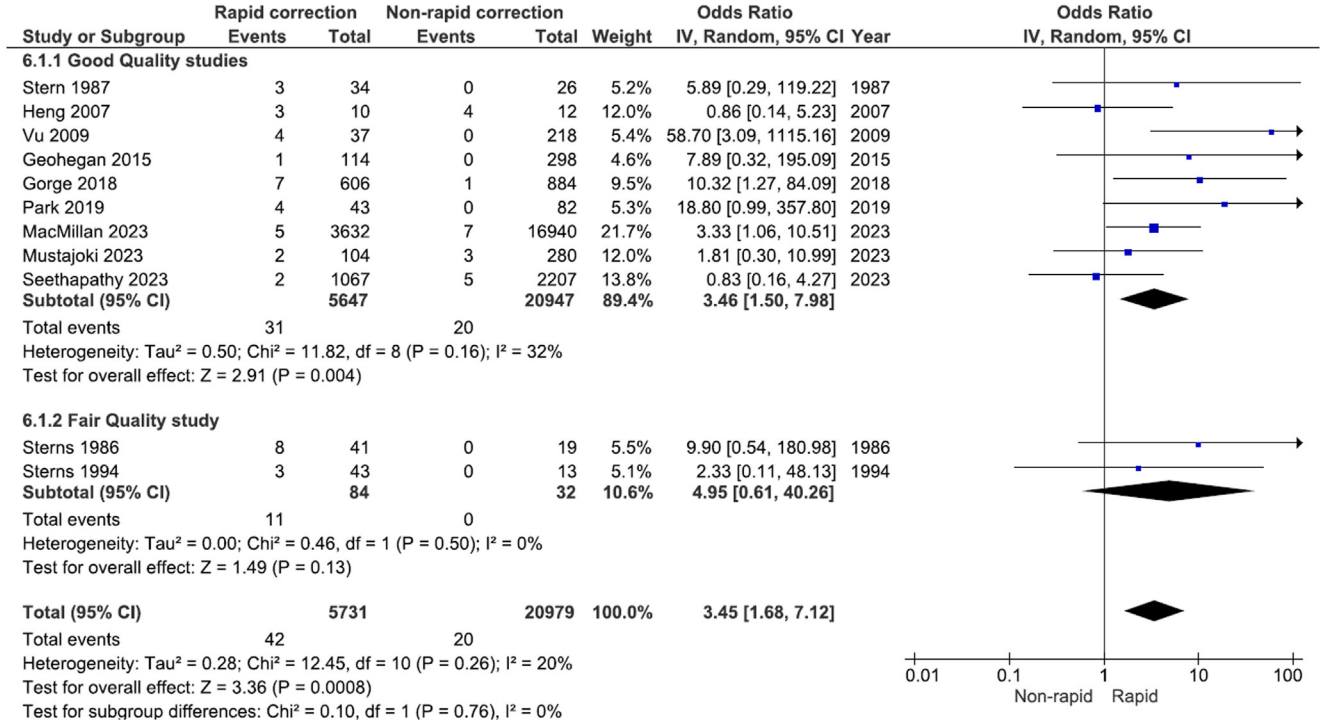

Figure 6. Forest plots of included studies subgroup based on the quality of studies.

the etiology of hyponatremia, treatment data, and treatment after rapid correction, such as desmopressin, can affect the incidence rate of ODS.[14,34–37]

In addition, our findings found that ODS occurred at a rate of 0.1%, even in the absence of rapid sodium correction. This is similar to a systematic review by Bastos et al.[37] The study reported that 67% of ODS cases experienced rapid rate correction ≥10 mmol/L on the first day of admission, whereas 10% experienced nonrapid correction. Other studies also indicated that ODS can occur even without rapid correction.[16,19,20,26,38,39] The mechanism remained unidentified. Some proposed contributing factors are the severity of hyponatremia at presentation, malnutrition, low osmolar (protein and salt) intake, alcohol use, liver disease, or electrolyte imbalances such as hypokalemia, hypophosphatemia, or hypochloremia.[3,16,19,20,24,26,38,39] In patients with hyponatremia, a rapid correction of other osmolytes can rapidly raise blood osmolality and neuronal osmotic stress, thus increasing the risk for ODS. Among chronic hyponatremia, organic (eg, glutamate, glutamine, taurine, and myo-inositol) and inorganic (eg, sodium, potassium, and chloride) osmolytes are released via passive leakage against concentration gradient or volume-sensitive potassium and chloride channels, respectively. During hyponatremia correction, a relatively hypertonic environment leads to the reuptake of osmolytes by neurons to avoid osmotic stress, which is often slower than the osmolar release process. Resulting in severe osmotic stress, potentially leading to blood–brain barrier disruption and oligodendrocyte apoptosis, therefore the risk of ODS.[40,41]

Among inorganic electrolytes, the role of chloride in neuronal osmotic stress is less defined and studied. Hypochloremia is frequently observed in patients with hyponatremia, as changes in chloride and sodium levels typically occur concordantly. In hyponatremia, chloride correction rate is often faster than sodium because of relatively higher chloride concentration in intravenous crystalloids than normal blood chloride and sodium concentration. For instance, in normal saline, sodium and chloride concentrations are 154 mmol/L, whereas the normal range of serum sodium is closer to 154 mmol/L higher than the normal range of serum chloride. The concentration differences between these 2 electrolytes could lead to rapid correction of chloride levels even though sodium corrections are within the safe range.[42] Most studies in this meta-analysis did not provide information regarding the change in chloride levels. Therefore, the relationship between chloride correction and the risk of ODS remains a hypothesis and would be the subject of research in future studies.

Strength

Our systematic review was based on the PROSPERO registered study protocol and followed PRISMA recommendations. We included sensitivity, subgroup, and meta-regression analyses on the crucial variables that could affect the outcome to ensure the robustness of the results. Notably, our results were consistent with a low degree of heterogeneity, thus indicating a robust outcome.

Limitations

This study has several limitations. First, the included studies were retrospective observational studies. Therefore, the residual confounding factors and incomplete information could have affected the result. Second, we did not limit the definition of ODS. So, there were various ODS definitions across the included studies. Some trials incorporated clinical correlation and imaging diagnosis, whereas others relied solely on imaging reports and diagnostic codes. Importantly, not all participants received imaging. Clearly, clinical criteria are crucial for ODS diagnosis. The absence of imaging data cannot exclude ODS diagnosis as myelinolysis may not be present for a few weeks after hyponatremia treatment.[43] Moreover, we used both keywords, ODS and CPM, to adjudicate the events. Patients who were not given the clinical conclusion were not counted as the event, which could potentially lead to lower rates of ODS diagnosis. Third, we used the sodium correction of >8 mmol/L within the first 24 hours as the definition of rapid sodium correction rate, which is aligned with the guidelines recommendations. We did not use other definitions for the rapid sodium correction, ie, ≥18 mmol/L within 48 hours or any other commonly reported rates. This limitation may affect the reported low incidence rate of ODS, particularly in studies conducted before the year 2000, when ODS were first identified before guideline establishment. However, after performing the sensitivity analysis, we found that ODS with a sodium correction rate of ≥18 mmol/L/48 hours had a higher prevalence of ODS with moderate heterogeneity. Fourth, the included studies span a broad timeframe from 1986-2023. The incidence of ODS may be affected by the diagnosis and treatment at different times. Therefore, we performed the meta-regression analysis to evaluate the study year's impact, which showed no statistical significance. This analysis demonstrated the robustness of our findings. However, the essential variables, such as treatment data records, were not applied to regression analysis because of inadequate information. Fifth, we could not identify the timeline of hyponatremia onset because of limited data availability, which could affect the reported incidence of ODS. It is clear that patients with chronic have a higher risk for ODS following overly rapid sodium correction rates. Finally, we did not determine all baseline serum osmolality and other potential electrolyte disturbances, which could also be an essential role of osmolality, such as potassium, phosphorus, chloride, or the delta changes from the studies because of limited data information. These might be other factors associated with the change of serum osmolality causing the development of ODS.

Conclusions

This meta-analysis of current data indicated that rapid sodium correction is associated with a higher risk of ODS. ODS is low despite the rapid correction of serum sodium being commonly identified among enrolled patients. Hyponatremia patients who experienced rapid sodium correction >8 mmol/L had a statistical correlation with ODS. It is recommended that further studies be conducted to comprehend the relationship between hyponatremia and ODS among all individuals, including those without rapid correction, for better and proper management of hyponatremia.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Meta-regression analysis of the relationship between the inclusion criteria of initial serum sodium levels and log odds ratio for ODS showed that the inclusion criteria of serum sodium levels in the included studies did not influence the incidence of ODS ($P = 0.19$). The circle represents the log event rate in individual studies. The gray zone indicates the 95% CI and prediction interval. The red line is the weighted regression.

Figure S2: Sensitivity analysis in criteria rapid rate correction of serum sodium greater than 18 mmol/L within 48 hours.

Figure S3: Meta-regression analysis of the relationship between the year of publication and the log odds ratio for ODS demonstrates that the year of the study did not affect the incidence of ODS ($P = 0.22$). The circle represents the log event rate in individual studies. The gray zone indicates the 95% CI and prediction interval. The red line is the weighted regression.

Figure S4: Funnel plot and Egger's test showed no publication bias ($P = 0.07$) with the trim and fill method (OR 2.04, 95% CI 0.93-5.86).

Table S1: Search Strategies and Keywords.

Table S2: Summary of Newcastle–Ottawa Scale Scores for Included Cohort Studies.

Table S3: Summary of Findings From the GRADE Approach: Rapid Correction of Serum Sodium Levels and Incidence of Demyelination Syndrome in Patients with Hyponatremia.

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