

# Etiology and Clinical Features of Patients With Hyponatremia in the Emergency Department: A Cross-sectional Study

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## Abstract

**Objective:** Hyponatremia, a common electrolyte disorder, affects a significant portion of the population, particularly in emergency and hospitalized settings. This study aimed to investigate the causes and clinical characteristics of hyponatremia in emergency department patients.

**Methods:** This cross-sectional study included 997 patients diagnosed with hyponatremia in the emergency department between June 2019 and May 2024. We investigated the causes of hyponatremia through medical interviews, blood tests, and urinalysis.

**Results:** We found that for every 1-year increase in age, serum sodium levels in patients with hyponatremia decreased by 0.14 mmol/L, whereas for every 1 mg/dL increase in serum uric acid, the serum sodium levels increased by 0.125 mmol/L. The leading cause of hyponatremia was the syndrome of inappropriate antidiuresis (SIAD), accounting for 357 cases (35.8%). However, a significant number of patients showed a similar diagnostic pattern to that of SIAD but were diagnosed with other conditions, such as cerebral salt wasting (31 cases, 5.8%), renal salt wasting (23 cases, 3.8%), and mineralocorticoid-responsive hyponatremia of the elderly (17 cases, 1.8%). Many patients initially diagnosed with SIAD were later found to have 1 of these alternative conditions upon further evaluation. Fractional excretion values of phosphate and uric acid effectively distinguished SIAD from other conditions.

**Conclusion:** Hyponatremia in the emergency department has diverse causes, with overlapping diagnostic criteria for SIAD and related conditions, though treatment strategies vary significantly. Accurate differential diagnosis is crucial to optimizing patient outcomes. Recognizing the range of underlying causes can help clinicians improve treatment strategies for hyponatremia in emergency settings.

**Key Words:** hyponatremia, syndrome of inappropriate antidiuresis, cerebral salt wasting, renal salt wasting, mineralocorticoid responsive hyponatremia of the elderly

**Abbreviations:** AVP, arginine vasopressin; CSW, cerebral salt wasting; FE<sub>P</sub>, excretion fraction of phosphorous; FE<sub>UA</sub>, excretion fraction of uric acid; MRHE, mineralocorticoid responsive hyponatremia of the elderly; RAA, renin-angiotensin-aldosterone; RSW, renal salt wasting; SIAD, syndrome of inappropriate antidiuresis.

Hyponatremia is 1 of the most common electrolyte disorders and is frequently encountered in daily clinical practice. The prevalence of hyponatremia among adults varies based on individual health and setting, with studies reporting rates of 1% to 7% in the general population (1, 2), 20% to 35% in hospitalized patients (3, 4), 14% to 30% in the intensive care unit patients (5, 6), and 26% to 40% in adults aged 65 and older (7, 8). Hyponatremia is classified on the basis of serum levels as mild (130–134 mmol/L), moderate (125–129 mmol/L), and severe (<125 mmol/L). Not only severe but also prolonged moderate hyponatremia can lead to confusion, deteriorating consciousness, and a higher risk of mortality (9, 10). A certain proportion of patients who visit the emergency department have hyponatremia in addition to their primary illness. However, when hyponatremia is mild to moderate and not

the primary concern, patients are often admitted to departments that do not specialize in electrolyte imbalances. In such cases, physicians usually focus on addressing the primary illness, which can result in hyponatremia being left untreated. Therefore, hyponatremia may persist or worsen, leading to re-hospitalization due to symptoms exacerbated by hyponatremia after the primary condition has been cured and the patient is discharged (10).

In hospitalized patients, the mortality among those with hyponatremia is 1.47-fold higher [95% confidence interval (CI) 1.33–1.62] than in those without it. Even when considering only patients with mild hyponatremia (130–134 mmol/L), the mortality rate remains elevated, increasing by 1.37-fold (95% CI 1.23–1.52) (11). In intensive care unit patients, the mortality rate for those with hyponatremia is 25%, compared

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to 16% in patients with normal serum sodium levels, representing a 1.75-fold increase (12). On the other hand, the resolution of hyponatremia after hospitalization has been associated with a reduced mortality risk (odds ratio 0.57; 95% CI 0.40-0.81) (13). In summary, inadequate initial treatment can exacerbate hyponatremia and increase the risk of complications, ultimately leading to higher mortality. Consequently, identifying the cause of hyponatremia and providing appropriate treatment at the time of admission or during hospitalization are crucial.

This study aimed to investigate the underlying causes of patients who presented to our emergency department with hyponatremia (serum sodium levels < 135 mmol/L). Our findings suggest that while patients were diagnosed with the syndrome of inappropriate antidiuresis (SIAD) upon admission, subsequent evaluations indicated that some patients showed the pattern of SIAD but were more likely to have other disorders, such as cerebral salt wasting (CSW), renal salt wasting (RSW), and mineralocorticoid responsive hyponatremia of the elderly (MRHE). We also report the characteristics of SIAD, CSW, RSW, and MRHE and discuss how to differentiate these disorders.

## Materials and Methods

### Study Design and Participants

We performed a 5-year, single-center, cross-sectional study on patients who presented to the emergency department between June 1, 2019, and May 31, 2024. The inclusion criteria were male and female patients aged  $\geq 18$  years with hyponatremia (serum sodium levels < 135 mmol/L). The exclusion criteria included pregnant patients; those who had participated in other clinical trials; and individuals with severe liver dysfunction, renal dysfunction, or mental disorders for whom their physician determined that participation in this study would be inappropriate. This study was approved by the institutional review board at Shinkomonji Hospital. Written informed consent was obtained from all participants before enrollment in the study. To determine the causative disease of hyponatremia, we performed interviews, blood tests (ie, serum electrolytes, serum lipids, uric acid, plasma osmolality, fractional excretion, liver function, renal function, thyroid function, adrenal function, and IgG, IgM, and IgA as required), and urine tests. In addition, patients who did not initially participate in the study and those whose causal diagnosis of hyponatremia was made by another department were referred to our department for further evaluation if their serum sodium levels did not improve after initiating treatment in another department.

After determining the cause of the hyponatremia, we classified SIAD, CSW, RSW, and MRHE, which have overlapping diagnostic criteria, into distinct groups and conducted a detailed analysis to compare their clinical characteristics.

### Statistical Analyses

A multiple regression analysis was performed to investigate whether the variables of age, sex, serum uric acid levels, and blood pressure affected serum sodium levels. The analysis of categorical variables was conducted using the  $m \times n$  chi-square test. An ANOVA and Dunnett's test were performed to compare the SIAD-induced hyponatremia group as a control group with other hyponatremia groups. Statistical analyses were conducted using R software, version 4.11 (R Foundation for

Statistical Computing, Vienna, Austria). Two-sided  $P$ -values < .05 were considered statistically significant. However, since comparisons between the control (SIAD) and the 3 groups (CSW, RSW, and MRHE) were conducted separately using Dunnett's test,  $P$ -value correction was applied based on the concept of multiple comparisons, and  $P$ -values < .05/3 = 0.016 were considered statistically significant.

## Results

Of the 11 027 patients who presented to our emergency department during the 5-year study period, 7208 had blood samples taken and serum electrolytes measured. Of these 7208 patients, 1098 (15.2%) had hyponatremia. Of these patients with hyponatremia, 965 patients were contacted by our department and underwent a close examination according to our study protocol. However, 121 patients were not contacted by our department on admission and were diagnosed in another department. Among these patients, 32 were later referred to our department because of a lack of improvement in serum sodium levels. Therefore, 997 (13.8%) patients with hyponatremia were included in the study (Fig. 1).

We investigated the relationships between serum sodium levels and age, sex, serum uric acid levels, and blood pressure, as described here. With every 1-year increase in age and 1 mg/dL increase in serum uric acid, the serum sodium levels in patients with hyponatremia decreased by 0.14 mmol/L and increased by 0.125 mmol/L, respectively. However, sex and blood pressure did not affect serum sodium levels. The following equation was obtained:

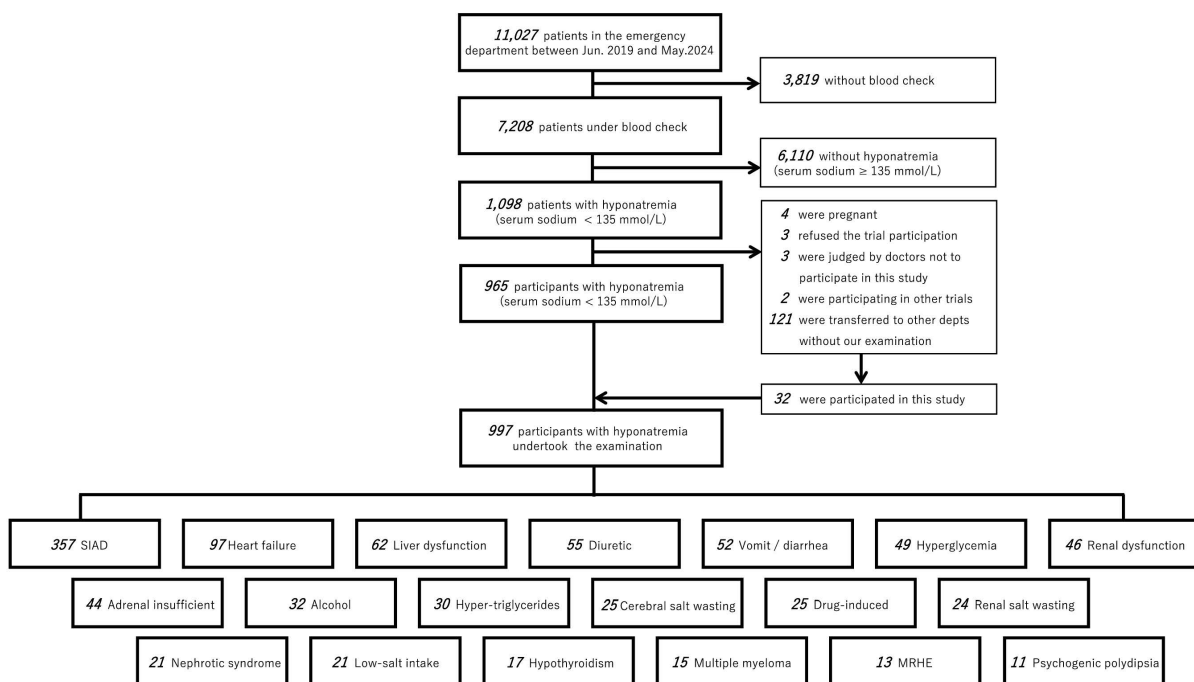
$$\hat{y} = 137.97 - 0.14x_1 + 0.03x_2 + 0.125x_3 + 0.005x_4,$$

where  $\hat{y}$  = serum sodium levels (mmol/L),  $x_1$  = age (years),  $x_2$  = sex (male, 1; female, 0),  $x_3$  = serum uric acid levels (mg/dL), and  $x_4$  = systolic blood pressure (mmHg).

Therefore, patients with hyponatremia were divided according to age, and serum sodium levels were plotted. Serum sodium levels significantly decreased with age ( $P < .001$ , Fig. 2).

The patients with hyponatremia were divided according to age and related to the number of patients with their primary condition at the time of the emergency department visit (Fig. 3). We found that the proportion of orthopedic diseases such as fractures was high in the younger age groups, but this proportion gradually decreased with age and started to increase again after 60 years of age. The proportions of respiratory illnesses, such as pneumonia and lung cancer, cerebral disorders, and malignant tumors (other than lung cancer), gradually increased with age. The proportion of heart failure increased gradually with age until the 60s. In contrast, the proportion of renal diseases, such as renal failure and nephrotic syndrome, increased gradually with age until the 70s, after which they reached a plateau. The proportion of gastrointestinal diseases such as liver disease increased with age until the 50s, when it peaked and then decreased. The proportion of patients with hyponatremia of an unknown cause on arrival at the emergency department decreased with age. The proportion of endocrine diseases, such as those of thyroid and adrenal gland, remained the same with age until the 60s and then slightly decreased and remained the same in the 70s.

The proportion of each causal disease is shown in Fig. 4. Thirty-two patients were diagnosed with SIAD in other departments and were treated with water restriction, sodium



**Figure 1.** Flow diagram of the study. During the 5-year study period, 997 patients with hyponatremia who visited the emergency department of our hospital participated in this study. The underlying causes of hyponatremia were identified through various examinations, as shown in the figure.

supplementation, and tolvaptan, but their serum sodium levels showed little improvement. Therefore, they were referred to our department. A subsequent close examination showed that there were 2 patients with SIAD, 12 with adrenal insufficiency, 7 with CSW, 6 with RSW, 3 with MRHE, and 2 with hypothyroidism.

The causal diseases of SIAD in 357 patients were as follows: 132 (37.0%) patients with pulmonary diseases, including lung cancer; 49 (13.7%) with neurological disorders; 38 (10.6%) with idiopathic cases; 35 (9.8%) with drug-induced cases; 30 (8.7%) with malignant tumors (excluding lung cancer); 27 (7.6%) with gastrointestinal diseases, 24 (6.7%) with kidney diseases; 12 (3.4%) with exercise-related cases; 7 (2.0%) pain and stress-related cases; and 3 (0.8%) gain-of-function mutation of the V2 vasopressin receptor.

The baseline characteristics of patients with SIAD and those with CSW, RSW, and MRHE, which share the same diagnostic criteria pattern as SIAD, except for extracellular fluid volume, are shown in Table 1. Patients in the MRHE group had significantly older age, lower serum sodium levels, higher serum uric acid levels, and lower excretion fraction of uric acid ( $FE_{UA}$ ) than those in the other groups of disorders. After saline supplementation, serum sodium levels showed better improvement in the CSW, RSW, and MRHE groups than in the SIAD group. In contrast, water restriction worsened serum sodium levels in the CSW, RSW, and MRHE groups compared with the SIAD group. The  $FE_{UA}$  was elevated in the SIAD group and was increased in the other 3 groups. After correcting for serum sodium levels,  $FE_{UA}$  was normalized in the SIAD group but remained high in the other 3 groups. The fractional excretion of phosphorus ( $FE_P$ ) was also significantly higher in the CSW, RSW, and MRHE groups than in the SIAD group. Plasma renin activity and plasma

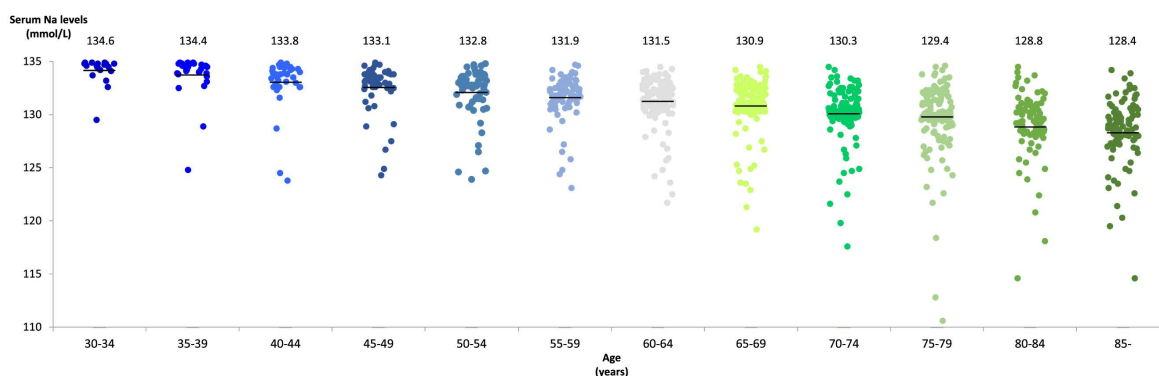
aldosterone levels were elevated only in the RSW group compared with the other 3 groups.

# Discussion

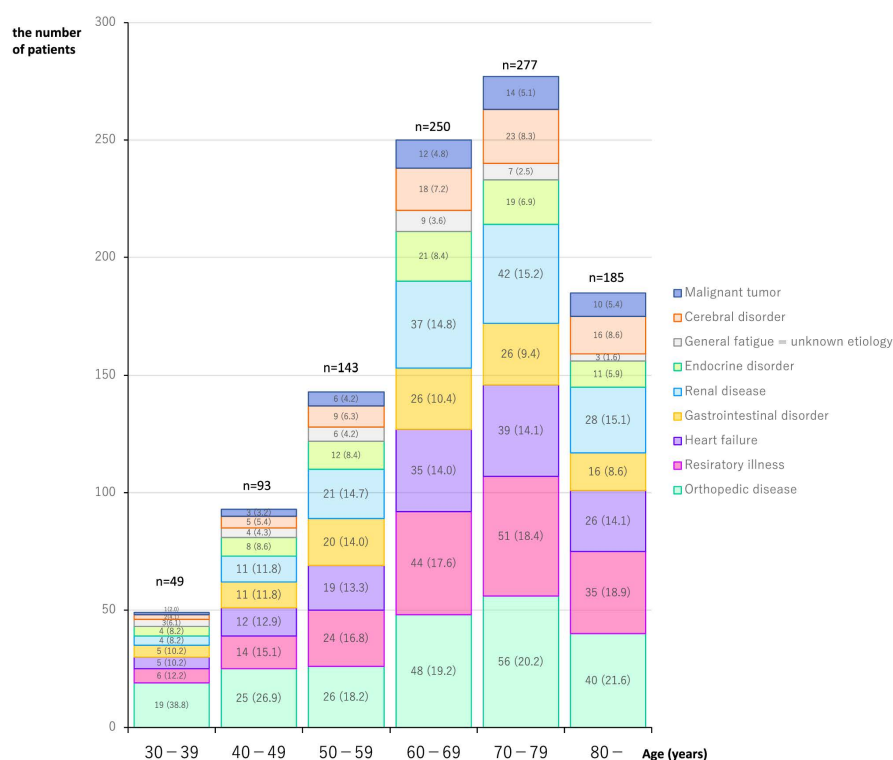
This study showed that the rate of hyponatremia in the emergency department was 15.2%, and this frequency increased with age. Previous studies have reported that 1% to 7% of the general population (1, 2) and 20% to 35% of hospitalized patients (3, 4) have hyponatremia. Patients in the emergency department, who present with more severe illnesses and have a higher proportion of hospital admissions than general outpatient visits, are considered to have a proportion of hyponatremia in between these 2 (1-7% and 20-35%).

The gradual decline in serum sodium levels observed during emergency department visits with increasing age is associated with an age-related deterioration in organ function, such as reduced renal function and a decline in the renin-angiotensin-aldosterone (RAA) system. Additionally, the increased prevalence of illnesses that can cause hyponatremia such as malignancies contributes to this trend. In contrast, the incidence of hyponatremia at younger ages is low and its symptoms are mild, and the prevalence of various diseases is also low. Therefore, hyponatremia is often discovered incidentally during emergency visits for orthopedic diseases such as fractures caused by accidents. Mild chronic hyponatremia has been reported to subtly reduce gait stability and significantly increase the risk of falls and fractures (4).

Among gastrointestinal (digestive) diseases, liver dysfunction is the most common cause of hyponatremia. Autoimmune hepatitis tends to develop at a younger age, whereas non-alcoholic fatty liver disease/nonalcoholic steatohepatitis



**Figure 2.** Age distribution of patients with hyponatremia. The numbers represent each age group's mean serum sodium levels (mmol/L). Patients with hyponatremia were categorized into 5-year age groups, starting at age 30. The results showed a gradual decline in serum sodium levels with increasing age ( $P < .001$ ).



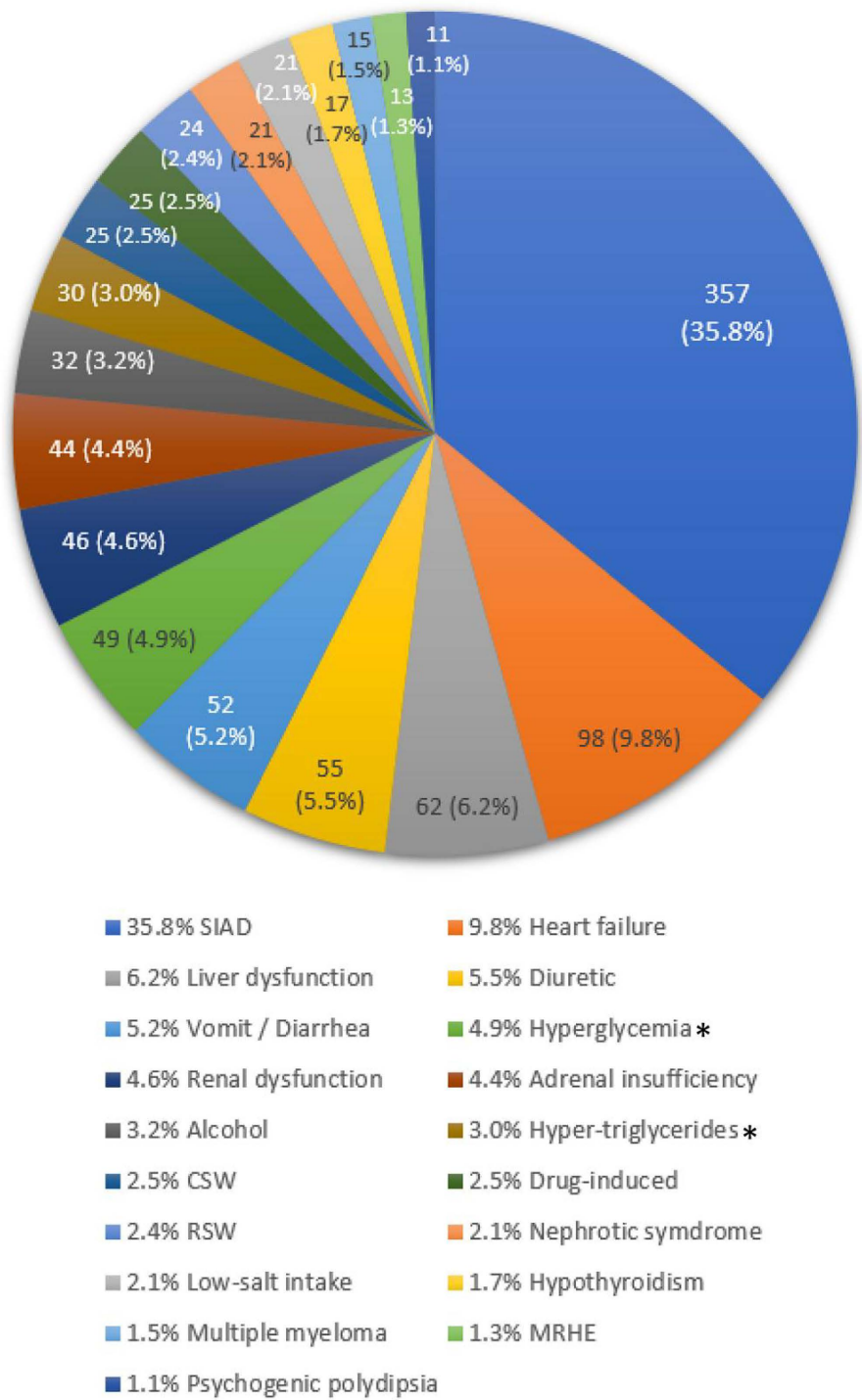
**Figure 3.** Primary conditions at emergency visits by age group in patients with hyponatremia. The primary conditions for which patients with hyponatremia visited the emergency department were categorized by age in 10-year increments, starting at age 30. The ranking of conditions in the 30 to 39 age group was used as a reference, with other age groups being presented in the same order.

typically manifests in middle-aged adults. Although the predominant age of onset for liver cirrhosis varies depending on the underlying disease, it is between 40 and 60 years in the overall population (14, 15), which is similar to our findings.

Among endocrine disorders resulting in hyponatremia, the predominant age of Hashimoto's disease is from 30 to 60 years (16, 17). The predominant age of onset for adrenal insufficiency is between 30 and 60 years. Reports have shown that the mean age for immune checkpoint inhibitor-induced ACTH deficiency is  $64.3 \pm 12.6$  years, while that for isolated ACTH deficiency without this treatment is  $49.2 \pm 19.6$  years

(18, 19). Additionally, the peak age for secondary Addison's disease is 30 years (20, 21). These predominant onset ages of each disease are believed to influence the age-specific incidence rates shown in Fig. 3.

In this study, SIAD was the most common causative disease of hyponatremia (35.8%). This finding is in line with reports that SIAD accounts for 25% to 40% of hyponatremia (10, 22). Notably, however, there was an unexpectedly high proportion of CSW, RSW, and MRHE, which share the same diagnostic criteria pattern as SIAD. The only difference between the diagnostic criteria for these 3 disorders and SIAD



**Figure 4.** Proportion of underlying causes of hyponatremia. This figure shows the proportion of underlying diseases responsible for hyponatremia among patients who visited the emergency department of our hospital. Among the 997 patients, 357 (35.8%) had SIAD, 98 (9.8%) had heart failure, 62 (6.2%) had liver failure, and 55 (5.5%) had been using diuretics. CSW, which has diagnostic criteria similar to SIAD, was identified in 25 (2.5%) patients, RSW in 24 (2.4%) patients, and MRHE in 13 (1.3%) patients. \*Hyperglycemia and hypertriglycerides were classified as causes of pseudo-hyponatremia.

Abbreviations: CSW, cerebral salt wasting; MRHE, mineralocorticoid responsive hyponatremia of the elderly; RSW, renal salt wasting; SIAD, syndrome of inappropriate antidiuresis.

is that extracellular fluid volume is normal in SIAD, whereas it is reduced in the other 3 disorders. However, fluid volume assessment was not quantified, and clinical evaluation of the

extracellular fluid volume status demonstrated a low diagnostic performance, with sensitivity ranging from 50% to 80% and specificity from 30% to 50% (23). Therefore, we listed

Table 1. Baseline characteristics

	SIAD (n = 357)	CSW (n = 25)	RSW (n = 24)	MRHE (n = 13)	P-value <sup>a</sup>
Age, years	62.5 ± 8.5	65.1 ± 8.7 <sup>b</sup>	64.6 ± 8.4	76.8 ± 4.1 <sup>b</sup>	<.001
Female	176 (49.3)	12 (48.0)	13 (54.2)	6 (46.2)	.541
Serum sodium level (mmol/L)	131.6 ± 2.8	129.4 ± 2.5	130.6 ± 2.7	127.3 ± 2.9 <sup>b</sup>	.016
No secretion of AVP	22 (6.2)	0 (0.0) <sup>b</sup>	0 (0.0) <sup>b</sup>	0 (0.0) <sup>b</sup>	<.001
Frequency, % (hyponatremia n = 997)	35.8	2.5 <sup>b</sup>	2.4 <sup>b</sup>	1.3 <sup>b</sup>	<.001
Decreased extracellular fluid volume <sup>c</sup>	31 (8.7)	17 (68.0) <sup>b</sup>	15 (62.5) <sup>b</sup>	11 (84.6) <sup>b</sup>	<.001
Serum sodium after saline administration (mmol/L)	131.4 ± 3.0 (n = 31)	135.5 ± 2.8 (n = 18) <sup>b</sup>	135.9 ± 2.9 (n = 18) <sup>b</sup>	136.2 ± 3.0 (n = 10) <sup>b</sup>	.007
Serum sodium after water restriction (mmol/L)	138.6 ± 3.2 (n = 216)	128.9 ± 2.9 (n = 7) <sup>b</sup>	129.7 ± 3.1 (n = 6) <sup>b</sup>	128.2 ± 2.7 (n = 3) <sup>b</sup>	<.001
Serum uric acid level [male, 3.6-7.0 mg/dL; female, 2.7-7.0 mg/dL]	3.4 ± 0.5	3.1 ± 0.5 <sup>b</sup>	3.2 ± 0.4	4.6 ± 0.5 <sup>b</sup>	<.001
FE <sub>UA</sub> [5.5-11.1%]	14.2 ± 3.5	20.6 ± 5.1 <sup>b</sup>	19.7 ± 4.8 <sup>b</sup>	12.6 ± 3.3 <sup>b</sup>	<.001
FE <sub>UA</sub> after correction for serum sodium level	10.8 ± 2.9	18.7 ± 3.7 <sup>b</sup>	17.5 ± 4.0 <sup>b</sup>	12.2 ± 2.5 <sup>b</sup>	<.001
FE <sub>P</sub> [10-19%]	11.4 ± 3.3	20.1 ± 5.3 <sup>b</sup>	21.3 ± 5.4 <sup>b</sup>	19.8 ± 4.6 <sup>b</sup>	<.001
PRA [0.2-3.9 ng/mL/h]/PAC [4.0-82.1 pg/mL]	0.4 ± 0.01/5.7 ± 0.3	0.3 ± 0.01/8.1 ± 0.5	2.6 ± 0.11 <sup>b</sup> /73.5 ± 6.4 <sup>b</sup>	0.8 ± 0.03 <sup>b</sup> /28.4 ± 3.2 <sup>b</sup>	<.001

Data are n (%) or mean ± standard deviation. Reference ranges are shown in square brackets.  
Abbreviations: AVP, arginine vasopressin; CSW, cerebral salt wasting; FE<sub>P</sub>, fractional excretion of phosphorus; FE<sub>UA</sub>, fractional excretion of uric acid; MRHE, mineralocorticoid responsive hyponatremia of the elderly; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RSW, renal salt wasting; SIAD, syndrome of inappropriate antidiuresis.  
<sup>a</sup>P-values were analyzed using ANOVA.  
<sup>b</sup>P-values were analyzed using Dunnett's test, where  $P < 0.05/3 = 0.016$  is considered statistically significant.  
<sup>c</sup>The attending physician evaluated the presence or absence of the following items to assess a decrease in the extracellular fluid volume. Physical examination findings: decreased skin turgor, dryness in the oral cavity, dry tongue, dryness in the armpits, sunken eyeballs, and prolonged capillary refill time in the fingernails (adults: > 2-3 seconds, older people: > 4 seconds). Vital signs: weight loss (more than 3% of body weight in a short period), increased pulse rate, decreased blood pressure, and orthostatic hypotension. Laboratory test findings: decreased urine output (<500 mL/day), FE<sub>UN</sub> < 35%, increased serum albumin levels, elevated hematocrit, and an increase in the blood urea nitrogen/creatinine ratio.

**Table 2. Supplementary diagnostic criteria for SIAD, CSW, RSW, and MRHE**

	SIAD	CSW	RSW	MRHE
Frequency of occurrence	High	Low	Low	High in the elderly?
Extracellular fluid volume	Euvolemia	Hypovolemia		
Serum sodium after saline administration	Unchanged to worse	Unchanged to improve		
Serum sodium after water restriction	Improve	Worsening		
Serum uric acid level [male, 3.6–7.0 mg/dL; female, 2.7–7.0 mg/dL]	Low	Low		Unknown
FE <sub>UA</sub> [5.5–11.1%]	Increase	Remarkable increase		Unknown
FE <sub>UA</sub> after correction for serum sodium level	Normalized	Remained increased		Unknown
FE <sub>P</sub> [10–19%]	Normal	Increased		Unknown
PRA [0.2–3.9 ng/mL/h] / PAC [4.0–82.1 pg/mL]	Decreased	Decreased	Increased	Normal to decreased
Treatment	water restriction, salt load, tolvaptan (fludrocortisone)			

Reference ranges are shown in square brackets. Abbreviations: CSW, cerebral salt wasting; FE<sub>P</sub>, fractional excretion of phosphorus; FE<sub>UA</sub>, fractional excretion of uric acid; MRHE, mineralocorticoid responsive hyponatremia of the elderly; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RSW, renal salt wasting; SIAD, syndrome of inappropriate antidiuresis.

the features of these 4 disorders in Table 2 (24–27) and compared them with our results shown in Table 1.

### SIAD

The diagnostic criteria of SIAD are that the patient's extracellular fluid volume is in the normal range (euvolemic) and the following conditions are met (28): (1) plasma osmolality <275 mOsm/kg; (2) urinary osmolality >100 mOsm/kg; (3) urinary sodium levels >30 mmol/L; (4) normal thyroid, adrenal, and pituitary functions; and (5) no recent history of diuretic use.

However, supplementary diagnostic criteria (24–27) (Table 2) should also be considered. Serum uric acid levels <4 mg/dL support the diagnosis of SIAD. Additionally, an FE<sub>UA</sub> (reference range: 5.5–11.1%) of between 10% and 12% supports the diagnosis of SIAD (29), whereas an FE<sub>UA</sub> <8% suggests a differential diagnosis from SIAD (30). We found that all 4 disorder groups with the same SIAD diagnostic pattern, except for the MRHE group, had serum uric acid levels <4 mg/dL, and the FE<sub>UA</sub> in the SIAD group was between 10% and 12%.

The secretion of arginine vasopressin (AVP), which is an antidiuretic hormone, is typically triggered by an increase in plasma osmolality and a decline in hemodynamic stability, and it ceases when plasma osmolality falls below 280 mOsm/kg (31, 32). However, in SIAD, AVP is inappropriately secreted even under this condition, resulting in free water retention. Excessive AVP secretion is not required for the diagnostic criteria; an abnormal AVP secretion is simply observed as a result. Therefore, in recent years, blood AVP levels have not been included in the diagnostic criteria of SIAD, and the notation is often changed from the syndrome of inappropriate antidiuretic hormone secretion to SIAD. There have been cases of SIAD without AVP secretion, and another study reported that 5% to 10% of those diagnosed with SIAD had no AVP secretion (33). These findings correspond to type C of SIAD, a reset osmostat, and type D, which involves an abnormality in AVP receptors (33–35). Of the 419 individuals who showed the SIAD pattern (357 with SIAD, 25 with CSW, 24 with RSW, 13 with MRHE) in our study, the number of patients whose AVP levels were below the level of detection was 22 (6.2%), 0 (0.0%), 0 (0.0%), and 0 (0.0%), respectively. Our findings also support these previous studies.

The main treatments for SIAD consist of water restriction, salt supplementation, and oral vaptans (antidiuretic hormone receptor blockers) therapy. The use of vaptans has been associated with side effects such as thirst, frequent urination, and fatigue (33). Additionally, rapid correction of serum sodium levels by vaptans poses a risk of osmotic demyelination syndrome (36). This condition can be life-threatening, particularly in elderly patients with chronic hyponatremia, requiring vigilant monitoring and caution. On the other hand, recent evidence has increasingly supported the efficacy and safety of oral urea therapy for SIAD-related hyponatremia (2, 37, 38). Based on these findings, we did not use urea for SIAD treatment in this trial; however, we would like to consider it as a potential treatment option in the future.

### CSW

SIAD and CSW are the main differential disorders of hyponatremia associated with intracranial disorders, such as head trauma, brain tumor, subarachnoid hemorrhage, and neurosurgery. CSW occurs owing to reduced sympathetic input to the juxtaglomerular apparatus of the kidney, leading to a suppression of the RAA system (39). This suppression decreases renal reabsorption of sodium and uric acid while increasing water diuresis, ultimately causing hyponatremia and a reduction in the extracellular fluid volume (40). In addition, increased secretion of atrial natriuretic peptide and brain natriuretic peptide promotes excessive excretion of sodium and water, worsening hyponatremia and hypovolemia (41).

The differentiation between SIAD and CSW is based on supplementary diagnostic criteria other than the evaluation of extracellular fluid. Specifically, symptoms of CSW are characterized by improvement after saline administration and worsening with water restriction, but distinguishing between these 2 disorders at presentation is often difficult. In fact, in our study, after the treatment of water restriction, we did not observe a significant improvement in serum sodium levels in the CSW, RSW, or MRHE groups. The treatment for SIAD is water restriction and tolvaptan, while that for CSW is saline supplementation and fludrocortisone, which are fundamentally different. Therefore, careful observation and investigation after hospitalization are necessary.

In patients with CSW, the  $FE_{UA}$  remains elevated after correction of serum sodium levels, which is useful in differentiating CSW from SIAD. Persistent proximal tubular damage in CSW is the reason for the sustained elevation of the  $FE_{UA}$  (24). In our study, the  $FE_{UA}$  in the CSW group was significantly higher than that in the SIAD group, and the elevated  $FE_{UA}$  persisted even after correcting for serum sodium levels. CSW as well as RSW can lead to significantly high urinary sodium levels (42, 43). Measuring urinary sodium levels at the initial diagnosis is also important for differentiating from SIAD.

Hyponatremia following intracranial disorders or head surgery can aid in the diagnosis of probable CSW. In our study, all (100%) of the 24 patients with CSW also had intracranial disorders or had received head surgery. In contrast, of the 357 patients with SIAD, only 49 (13.7%) had these conditions.

## RSW

In patients with RSW, tubular damage impairs sodium reabsorption and increases the excretion of sodium and water into the urine, causing hyponatremia and extracellular fluid depletion. As a result of this process, the RAA system is enhanced (40). Human and animal studies have demonstrated that the inwardly rectifying potassium channel Kir5.1 (KCNJ16) controls electrolyte homeostasis and blood pressure. Previous studies have identified several biallelic mutations of KCNJ16 in humans, and these can cause RSW (44).

The difference between RSW and hyponatremia due to renal failure is that the former shows hypovolemia and the latter shows hypervolemia (ie, in RSW, urine output is normal or excessive, whereas in renal failure, it is reduced).

One of the key distinguishing factors between SIAD and CSW/RSW is the  $FE_{UA}$ . While an  $FE_{UA}$  of 10% to 12% suggests SIAD, an  $FE_{UA}$  greater than 11% is indicative of CSW/RSW (45, 46). Therefore, the  $FE_{UA}$  in CSW/RSW is higher than that in SIAD. Furthermore, the  $FE_P$  is useful in distinguishing between SIAD and CSW/RSW. While the  $FE_P$  in SIAD is normal, it is elevated in CSW/RSW, often exceeding 20% (24). In our study, the  $FE_P$  was significantly higher in the CSW and RSW groups than in the SIAD group.

RSW is considered the only disorder that shows an SIAD pattern with a hyperactive RAA system. Despite the hyperactivity of the RAA system, urinary sodium reabsorption does not function well because of proximal tubular damage and continued urinary sodium excretion. In our study, patients in the RSW group also had a significantly hyperactive RAA system compared with those in the other 3 disorder groups.

Of the 25 patients diagnosed with RSW, none of them had an intracranial disorder or head surgery, which is also a strong indicator for differentiating RSW from CSW.

Notably, RSW and CSW are treated with saline administration and a mineralocorticoid such as fludrocortisone.

## MRHE

MRHE is characterized by increased sodium excretion in the urine due to reduced sodium reabsorption in the proximal tubules, diminished activity of the RAA system, or decreased responsiveness of aldosterone receptors, all of which are associated with aging. This situation leads secondarily to a decrease in the extracellular fluid volume. As a response, AVP secretion is increased, which exacerbates hyponatremia (47).

Few studies have reported MRHE and its poorly known features (Table 2). One study reported that MRHE was present in 8 (24%) of 33 cases of hyponatremia in older people (47). In our study, the mean age of patients diagnosed with MRHE was 76.8 years, which was significantly older than the overall mean age of 64.1 years. However, a meta-analysis showed that all 27 patients diagnosed with MRHE did not undergo a rapid ACTH test and were likely to have adrenal insufficiency (25). We performed a rapid ACTH test on all 34 patients who were formerly diagnosed with MRHE and found that 21 had adrenal insufficiency and 13 had MRHE. The frequency of MRHE is unknown, but it may be less common than CSW and RSW.

Previous reports have shown that the only difference between MRHE and SIAD is that urinary sodium excretion is increased and there is a reduction in extracellular fluid volume in MRHE (25, 47). However, in our study, in the MRHE group, the  $FE_{UA}$  was the lowest among the 4 disorders, and the blood uric acid level was the highest. This finding may be due to hypovolemia (decreased extracellular fluid) (48).

This study was based on data from a single hospital. Therefore, the characteristics of the hospital may have affected the proportion of diseases causing hyponatremia. The hospital in this study has a large number of patients with endocrine disorders or cranial nerve diseases, and it does not have a psychiatric department. However, a high proportion of SIAD was observed in patients with hyponatremia, as well as higher than expected proportions of CSW, RSW, and MRHE.

## Conclusion

In sum, 35.8% of patients presenting to our emergency department with hyponatremia were diagnosed with SIAD. However, other conditions such as CSW, RSW, and MRHE were also observed among patients initially identified with SIAD. Accurate differential diagnosis is crucial, as these disorders require distinct treatment approaches. Incorporating  $FE_P$  and  $FE_{UA}$  measurements in the evaluation of hyponatremic patients in the emergency department can enhance diagnostic precision and potentially improve patient outcomes.

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## Disclosures

All the authors declare no competing interests.

## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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