Etiology and Clinical Features of Patients with Hyponatremia in the Emergency Department: A Cross-Sectional Study

Tetsuya Kawahara [1,2]*, Mikio Toda [1], Maiko Kanagawa [3], Nagahiro Toyama [3], Chie Kawahara [2], and Tetsuya Inazu [4]

[1] Division of Endocrinology and Metabolism, Shinkomonji Hospital, 800-0057 Kitakyushu, Japan
[2] First Department of Internal Medicine, University of Occupational and Environmental Health, 525-0058 Kitakyushu, Japan
[3] Department of Emergency Medicine, Shinkomonji Hospital, 800-0057 Kitakyushu, Japan
[4] Department of Pharmacy, College of Pharmaceutical Science, Ritsumeikan University, 807-8555 Kusatsu, Japan

*Correspondence to: Tetsuya Kawahara, MD, PhD (ORCID ID: 0000-0002-1268-4871)
Division of Endocrinology and Metabolism, Shinkomonji Hospital, 2-5 Dairishinmachi, Moji, 800-0057 Kitakyushu, Japan. E-mail: k-tetsuy@med.uoeh-u.ac.jp

Disclosures

All the authors declare no competing interests.

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 one 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.

Keywords: Hyponatremia, syndrome of inappropriate antidiuresis, cerebral salt wasting, renal salt wasting, mineralocorticoid responsive hyponatremia of the elderly.

Abbreviations: CSW, cerebral salt wasting; FE_P, excretion fraction of phosphorous; FE_{UA}, excretion fraction of uric acid; MRHE, mineralocorticoid responsive hyponatremia of the elderly; RSW, renal salt wasting; SIAD, syndrome of inappropriate antidiuresis.

INTRODUCTION

Hyponatremia is one 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%–7% in the general population (1,2), 20%–35% in hospitalized patients (3,4), 14%–30% in the intensive care unit patients (5,6), and 26–40% 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 rehospitalization 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-hold higher (95% 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-hold (95% CI 1.23–1.52) (11). In intensive care unit patients, the mortality rate for those with hyponatremia is 25%, compared 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 (OR 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 1 June 2019 and 31 May 2024. The inclusion criteria were male and female patients aged ≥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 (i.e., serum electrolytes, serum lipids, uric acid, plasma osmolality, fractional excretion, liver function, renal function, thyroid function, adrenal function, and immunoglobulin [Ig] G, 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×n chi-square test. An analysis of variance (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 < 0.05 were considered statistically significant. However, since comparisons between the control (SIAD) and the three 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 $<0.05/3 = 0.016$ were considered statistically significant.

RESULTS

Of the 11027 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 below. 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 <0.001, 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 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 three groups. After correcting for serum sodium levels, FE_{UA} was normalized in the SIAD group but remained high in the other three 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 three 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 1–7% of the general population (1,2) and 20–35% 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 two (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 nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis 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 adrenocorticotropic hormone (ACTH) deficiency is 64.3 ± 12.6 years, while that for isolated ACTH deficiency without this treatment is 49.2 ± 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 Figure 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 three disorders and SIAD is that extracellular fluid volume is normal in SIAD, whereas it is reduced in the other three 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 the features of these four 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): (i) plasma osmolality <275 mOsm/kg; (ii) urinary osmolality >100 mOsm/kg; (iii) urinary sodium levels >30 mmol/L; (iv) normal thyroid, adrenal, and pituitary functions; and (v) 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_{UA} (reference range: 5.5%-11.1%) of between 10% and 12% supports the diagnosis of SIAD (29), whereas an FE_{UA} <8% suggests a differential diagnosis from SIAD (30). We found that all four disorder groups with the same SIAD diagnostic pattern, except for the MRHE group, had serum uric acid levels <4 mg/dL, and the FE_{UA} 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 (SIADH) 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 (ADH 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 two 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 bi-allelic 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 (i.e., 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%–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 three 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 four 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

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.

Acknowledgment

The authors thank all participants and investigators. We thank Ellen Knapp, PhD, from Edanz (http://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding

This study was supported by a grant from the Fukuoka Medical Association. The sponsor did not contribute to the design, collection, management, analysis, interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

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.

REFERENCES

1. Kutz A, Ebrahimi F, Aghlmandi S, Wagner U, Bromley M, Illigens B, Siepmann T, Schuetz P, Mueller B, Christ-Crain M. Risk of Adverse Clinical Outcomes in Hyponatremic Adult Patients Hospitalized for Acute Medical Conditions: A Population-Based Cohort Study. *J Clin Endocrinol Metab*. 2020;105(11):3428-3436.
2. Adrogue HJ, Madias NE. The Syndrome of Inappropriate Antidiuresis. *N Engl J Med*. 2023;389(16):1499-1509.
3. Burst V. Etiology and Epidemiology of Hyponatremia. *Front Horm Res*. 2019;52:24-35.

4. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *The American journal of medicine*. 2006;119(7 Suppl 1):S30-35.
5. Itoh J, Aoki Y, Omoto M, Katsuragawa T, Mimuro S, Nakajima Y. Association Between Early Hyponatremia and Clinical Outcomes in Critically Ill Patients: A Retrospective Cohort Study. *Cureus*. 2024;16(3):e56138.
6. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med*. 2014;40(3):320-331.
7. Adrogue HJ, Tucker BM, Madias NE. Diagnosis and Management of Hyponatremia: A Review. *JAMA*. 2022;328(3):280-291.
8. Cumming K, Hoyle GE, Hutchison JD, Soiza RL. Prevalence, incidence and etiology of hyponatremia in elderly patients with fragility fractures. *PloS one*. 2014;9(2):e88272.
9. Seay NW, Lehrich RW, Greenberg A. Diagnosis and Management of Disorders of Body Tonicity-Hyponatremia and Hypernatremia: Core Curriculum 2020. *Am J Kidney Dis*. 2020;75(2):272-286.
10. Warren AM, Grossmann M, Christ-Crain M, Russell N. Syndrome of Inappropriate Antidiuresis: From Pathophysiology to Management. *Endocr Rev*. 2023;44(5):819-861.
11. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *The American journal of medicine*. 2009;122(9):857-865.
12. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care*. 2008;12(6):R162.
13. Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. *PloS one*. 2015;10(4):e0124105.
14. Sajja KC, Mohan DP, Rockey DC. Age and ethnicity in cirrhosis. *J Investig Med*. 2014;62(7):920-926.
15. Orman ES, Roberts A, Ghabril M, Nephew L, Desai AP, Patidar K, Chalasani N. Trends in Characteristics, Mortality, and Other Outcomes of Patients With Newly Diagnosed Cirrhosis. *JAMA Netw Open*. 2019;2(6):e196412.
16. Mincer DL, Jialal I. Hashimoto Thyroiditis. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Ishwarlal Jialal declares no relevant financial relationships with ineligible companies.2024.
17. Taylor PN, Medici MM, Hubalewska-Dydejczyk A, Boelaert K. Hypothyroidism. *Lancet*. 2024;404(10460):1347-1364.
18. Hannon AM, Hunter S, Smith D, Sherlock M, O'Halloran D, Thompson CJ, Irish Pituitary Database G. Clinical features and autoimmune associations in patients presenting with Idiopathic Isolated ACTH deficiency. *Clin Endocrinol (Oxf)*. 2018;88(3):491-497.
19. Wang F, Shi X, Yu X, Yang Y. Immune checkpoint inhibitor-induced isolated adrenocorticotropic hormone deficiency: a systematic review. *Front Endocrinol (Lausanne)*. 2024;15:1326684.
20. Ten S, New M, Maclaren N. Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab*. 2001;86(7):2909-2922.
21. Betterle C, Morlin L. Autoimmune Addison's disease. *Endocr Dev*. 2011;20:161-172.
22. Cuesta M, Garrahy A, Slattery D, Gupta S, Hannon AM, McGurren K, Sherlock M, Tormey W, Thompson CJ. Mortality rates are lower in SIAD, than in hypervolaemic or hypovolaemic hyponatraemia: Results of a prospective observational study. *Clin Endocrinol (Oxf)*. 2017;87(4):400-406.
23. Hoorn EJ, Zietse R. Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines. *J Am Soc Nephrol*. 2017;28(5):1340-1349.
24. Maesaka JK, Imbriano LJ, Ali NM, Ilamathi E. Is it cerebral or renal salt wasting? *Kidney Int*. 2009;76(9):934-938.
25. Katayama K, Tokuda Y. Mineralocorticoid responsive hyponatremia of the elderly: A systematic review. *Medicine (Baltimore)*. 2017;96(27):e7154.

26. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *The American journal of medicine*. 2013;126(10 Suppl 1):S1-42.
27. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E, Hyponatraemia Guideline Development G. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *European journal of endocrinology / European Federation of Endocrine Societies*. 2014;170(3):G1-47.
28. Martin-Grace J, Tomkins M, O'Reilly MW, Thompson CJ, Sherlock M. Approach to the Patient: Hyponatremia and the Syndrome of Inappropriate Antidiuresis (SIAD). *J Clin Endocrinol Metab*. 2022;107(8):2362-2376.
29. Decaux G, Musch W. Clinical laboratory evaluation of the syndrome of inappropriate secretion of antidiuretic hormone. *Clin J Am Soc Nephrol*. 2008;3(4):1175-1184.
30. Bassi V, Fattoruso O. The Role of Fractional Excretion of Uric Acid in the Differential Diagnosis of Hypotonic Hyponatraemia in Patients with Diuretic Therapy. *Cureus*. 2020;12(4):e7762.
31. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342(21):1581-1589.
32. Rondon-Berrios H, Berl T. Physiology and Pathophysiology of Water Homeostasis. *Front Horm Res*. 2019;52:8-23.
33. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med*. 2007;356(20):2064-2072.
34. Robertson GL. Antidiuretic hormone. Normal and disordered function. *Endocrinology and metabolism clinics of North America*. 2001;30(3):671-694, vii.
35. Feldman BJ, Rosenthal SM, Vargas GA, Fenwick RG, Huang EA, Matsuda-Abedini M, Lustig RH, Mathias RS, Portale AA, Miller WL, Gitelman SE. Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med*. 2005;352(18):1884-1890.
36. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. *The American journal of medicine*. 2007;120(11 Suppl 1):S1-21.
37. Wendt R, Fenves AZ, Geisler BP. Use of Urea for the Syndrome of Inappropriate Secretion of Antidiuretic Hormone: A Systematic Review. *JAMA Netw Open*. 2023;6(10):e2340313.
38. Pelouto A, Monnerat S, Refardt J, Zandbergen AAM, Christ-Crain M, Hoorn EJ. Clinical factors associated with hyponatremia correction during treatment with oral Urea. *Nephrol Dial Transplant*. 2024.
39. Momi J, Tang CM, Abcar AC, Kujubu DA, Sim JJ. Hyponatremia-what is cerebral salt wasting? *Perm J*. 2010;14(2):62-65.
40. Bernal A, Zafra MA, Simon MJ, Mahia J. Sodium Homeostasis, a Balance Necessary for Life. *Nutrients*. 2023;15(2).
41. Cui H, He G, Yang S, Lv Y, Jiang Z, Gang X, Wang G. Inappropriate Antidiuretic Hormone Secretion and Cerebral Salt-Wasting Syndromes in Neurological Patients. *Front Neurosci*. 2019;13:1170.
42. Harrigan MR. Cerebral salt wasting syndrome: a review. *Neurosurgery*. 1996;38(1):152-160.
43. Maesaka JK, Imbriano LJ. Cerebral Salt Wasting Is a Real Cause of Hyponatremia: PRO. *Kidney360*. 2023;4(4):e437-e440.
44. Xu B, Levchenko V, Bohovyk R, Ahrari A, Geurts AM, Sency V, Xin B, Wang H, Staruschenko A. Characterization of a novel variant in KCNJ16, encoding K(ir)5.1 channel. *Physiol Rep*. 2024;12(20):e70083.
45. Maesaka JK, Imbriano LJ, Grant C, Miyawaki N. Haptoglobin-Related Protein without Signal Peptide as Biomarker of Renal Salt Wasting in Hyponatremia, Hyponatremia-Related Diseases and as New Syndrome in Alzheimer's Disease. *Biomolecules*. 2023;13(4).
46. Maesaka JK, Imbriano LJ, Grant C, Miyawaki N. New Approach to Hyponatremia: High Prevalence of Cerebral/Renal Salt Wasting, Identification of Natriuretic Protein That Causes Salt Wasting. *J Clin Med*. 2022;11(24).

47. Ishikawa S, Saito T, Fukagawa A, Higashiyama M, Nakamura T, Kusaka I, Nagasaka S, Honda K, Saito T. Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. *J Clin Endocrinol Metab*. 2001;86(4):1665-1671.
48. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. *Clin Interv Aging*. 2017;12:1957-1965.

Figure Legends

Figure 1. Flow diagram of the study

During the five-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.

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 ($p<0.001$).

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 30–39 age group was used as a reference, with other age groups being presented in the same order.

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 hyper-triglycerides were classified as causes of pseudo-hyponatremia.

Table 1. Baseline characteristics

	SIAD (n=357)	CSW (n=25)	RSW (n=24)	MRHE (n=13)	*p* value *
Age, years	62.5±8.5	65.1±8.7 †	64.6±8.4	76.8±4.1 †	< 0.001
Female	176 (49.3)	12 (48.0)	13 (54.2)	6 (46.2)	0.541
Serum sodium level (mmol/L)	131.6±2.8	129.4±2.5	130.6±2.7	127.3±2.9 †	0.016
No secretion of AVP	22 (6.2)	0 (0.0) †	0 (0.0) †	0 (0.0) †	< 0.001
Frequency, % (Hyponatremia n=997)	35.8	2.5 †	2.4 †	1.3 †	< 0.001
Decreased extracellular fluid volume ‡	31 (8.7)	17 (68.0) †	15 (62.5) †	11 (84.6) †	< 0.001
Serum sodium after saline administration (mmol/L)	131.4±3.0 (n=31)	135.5±2.8 (n=18) †	135.9±2.9 (n=18) †	136.2±3.0 (n=10) †	0.007
Serum sodium after water restriction (mmol/L)	138.6±3.2 (n=216)	128.9±2.9 (n=7) †	129.7±3.1 (n=6) †	128.2±2.7 (n=3) †	<0.001
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 †	3.2±0.4	4.6±0.5 †	< 0.001
FE_{UA} [5.5–11.1%]	14.2±3.5	20.6±5.1 †	19.7±4.8 †	12.6±3.3 †	<0.001
FE_{UA} after correction for serum sodium level	10.8±2.9	18.7±3.7 †	17.5±4.0 †	12.2±2.5 †	< 0.001
FE_P [10–19%]	11.4±3.3	20.1±5.3 †	21.3±5.4 †	19.8±4.6 †	< 0.001
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† / 73.5±6.4†	0.8±0.03† / 28.4±3.2†	< 0.001

Data are n (%) or mean ± standard deviation. Reference ranges are shown in square brackets.
SIAD, syndrome of inappropriate antidiuresis; CSW, cerebral salt wasting; RSW, renal salt wasting; MRHE, mineralocorticoid responsive hyponatremia of the elderly; AVP, arginine vasopressin; FE_{UA}, fractional excretion of uric acid; FE_P, fractional excretion of phosphorus; PRA, plasma renin activity; PAC, plasma aldosterone concentration.
* *p* values were analyzed using analysis of variance.
† *p* values were analyzed using Dunnett's test, which $p < 0.05/3 = 0.016$ considered statistically significant.
‡ 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), fractional excretion of urea nitrogen (FE_{UN}) < 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

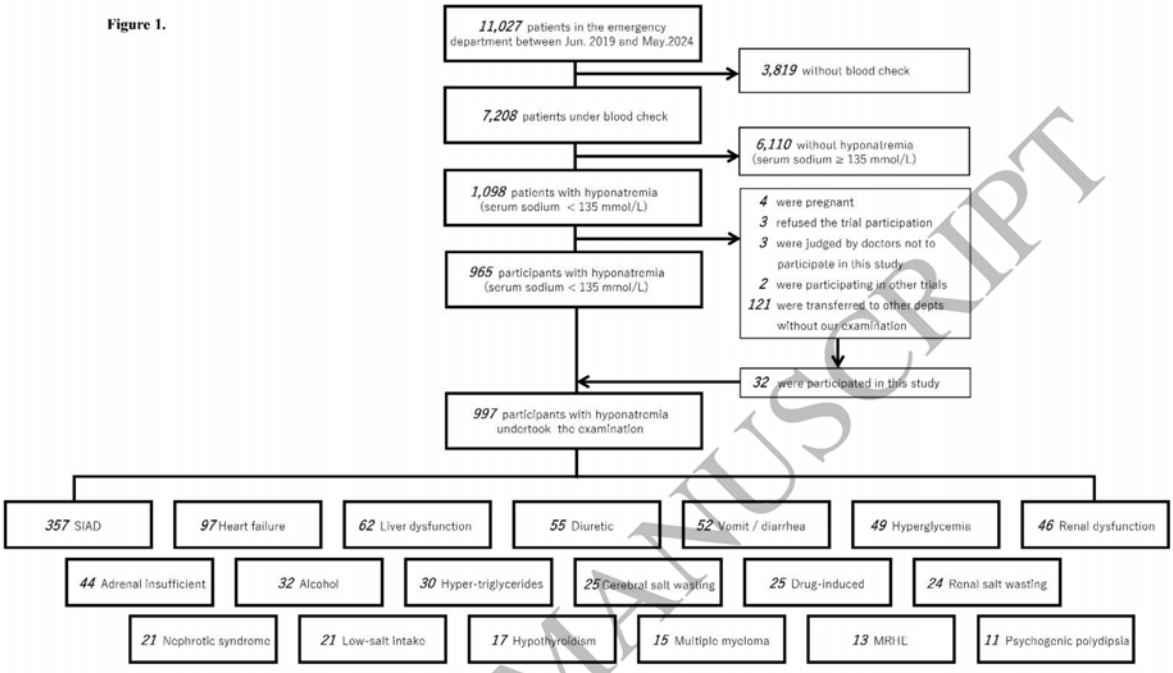
	SIAD	CSW	RSW	MRHE
Frequency of occurrence	High	Low	Low	High in the elderly ?
Extracellular fluid volume	Euvolemia	Hypovolemia		
Serum sodium after saline administration	Unchanged to worse	Unchanged to improve		
Serum sodium after water restriction	Improve	Worsening		
Serum uric acid level [male, 3.6–7.0 mg/dL; female, 2.7–7.0 mg/dL]	Low	Low		**Unknown**
FE_{UA} [5.5–11.1%]	Increase	Remarkable increase		**Unknown**
FE_{UA} after correction for serum sodium level	Normalized	Remained increased		**Unknown**
FE_{P} [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	saline administration, mineralocorticoid (fludrocortisone)		

SIAD, syndrome of inappropriate antidiuresis; CSW, cerebral salt wasting; RSW, renal salt wasting; MRHE, mineralocorticoid responsive hyponatremia of the elderly; FE_{UA}, fractional excretion of uric acid; FE_{P}, fractional excretion of phosphorus; PRA, plasma renin activity; PAC, plasma aldosterone concentration.

Reference ranges are shown in square brackets.

1

Figure 1.



2

3 *Figure 1*

4 *319x180 mm (DPI)*

5

Figure 2.

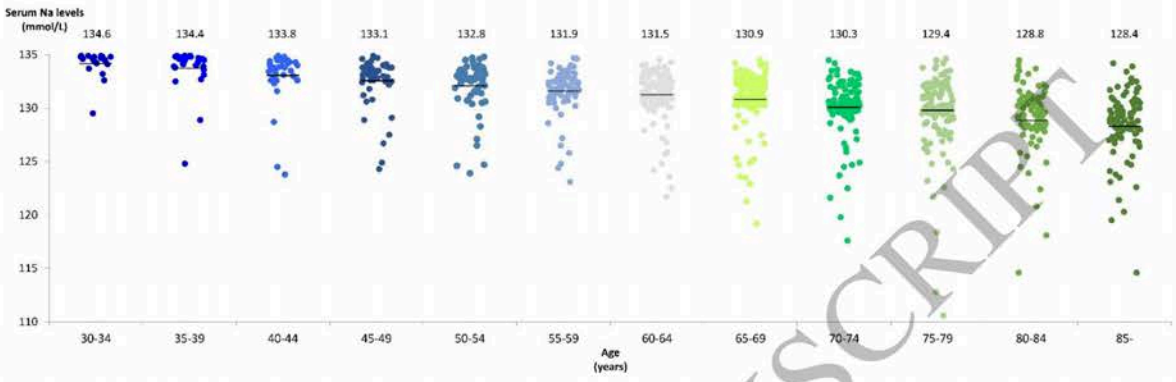


Figure 2
332x132 mm (DPI)

Figure 3.

Figure 3
255x186 mm (DPI)

Figure 4.

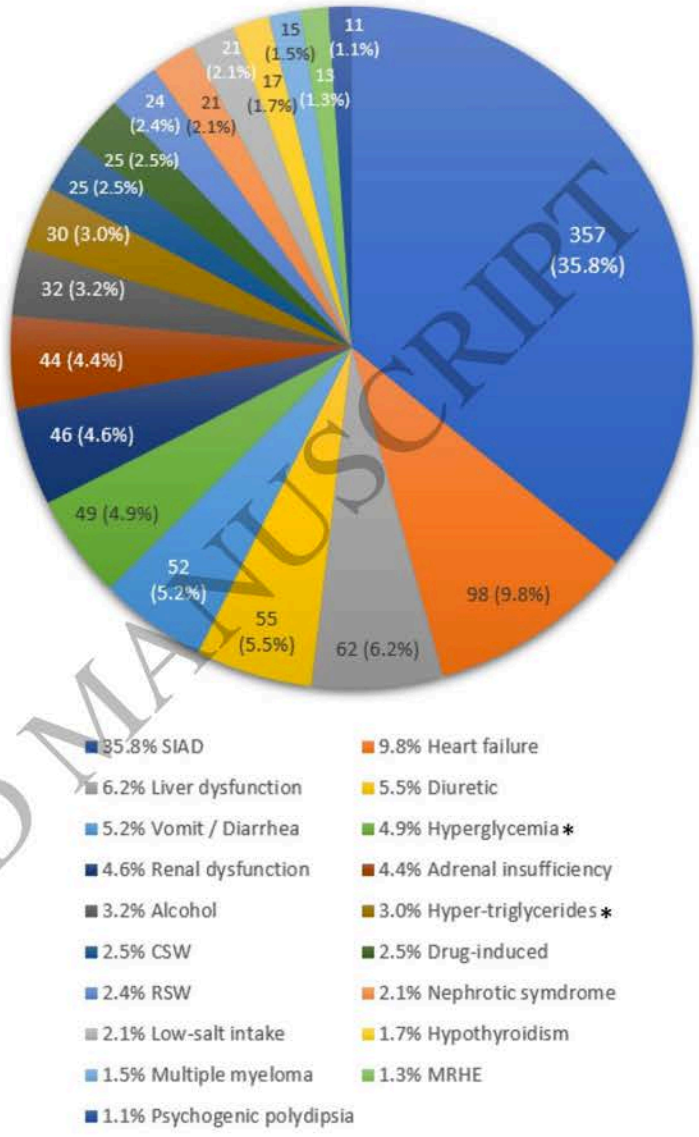


Figure 4
191x185 mm (DPI)