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ORIGINAL ARTICLE

# Sodium evolution in hyponatremia: A retrospective analysis in a tertiary care center

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**KEYWORDS**
Hyponatremia;
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**Abstract**
*Introduction:* Hyponatremia is the most common electrolyte disorder in hospitals. This study analyses the evolution of serum sodium levels during hospitalization.
*Materials and methods:* This is an observational, retrospective, and analytical study. Patients hospitalized for hyponatremia in a tertiary care hospital were included. Demographic and laboratory variables were collected, and hyponatremia was classified according to severity and etiology. Criteria and risk factors for serum sodium overcorrection were defined, and the effectiveness of treatments used for hyponatremia was described. The Chi-square test was used for qualitative variables, while Student's *t*-test and Mann–Whitney *U* test were applied for quantitative variables. Predictive models were also used to determine the risk of an event.
*Results:* A total of 216 patients hospitalized for hyponatremia were included, with a higher prevalence in patients over 75 years of age and females. Longer hospital stays were associated with older age and male gender. Severe hyponatremia and hypokalemia were linked to a higher risk of overcorrection. The therapies for hyponatremia correction across the three groups were effective either alone or in combination. Additionally, severe hyponatremia was associated with increased 5-year mortality.
*Conclusions:* Hyponatremia in hospitalized patients is more prevalent in those over 75 years old and in females. Severe hyponatremia increases 5-year mortality. There are factors that increase the risk of overcorrection, so treatment should be carefully managed to avoid osmotic demyelination syndrome (ODS).


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**PALABRAS CLAVE**
Hiponatremia;
Hospitalización;
SIADH;
Tiazidas

**Evolución del sodio en la hiponatremia: análisis retrospectivo en un centro de tercer nivel**

**Resumen**
*Introducción:* La hiponatremia es el trastorno hidroelectrolítico más frecuente a nivel hospitalario. El estudio muestra la evolución de la natremia durante el ingreso hospitalario.
*Materiales y métodos:* El estudio es observacional, retrospectivo y analítico. Se incluyeron pacientes ingresados por hiponatremia en un hospital de tercer nivel.

Se recogieron variables demográficas, analíticas y se clasificó la hiponatremia según la gravedad y la etiología. Se definieron criterios y factores de riesgo para la sobrecorrección de la natremia. Se describió la efectividad de los tratamientos utilizados para la hiponatremia. Para variables cualitativas se utilizó la prueba de Chi cuadrado. Para variables cuantitativas: t de student, U Mann–Whitney. Se utilizaron también modelos predictivos para determinar el riesgo de un evento.
*Resultados:* Se incluyeron 216 pacientes ingresados por hiponatremia, siendo más frecuente en mayores de 75 años y mujeres. El aumento de estancia hospitalaria se asoció con mayor edad y el género masculino. La hiponatremia grave y la hipopotasemia se asociaron a mayor riesgo de sobrecorrección. Las terapias para la corrección de la hiponatremia en los 3 grupos fueron efectivas solas o en combinación. Además, la hiponatremia grave se asoció con una mayor mortalidad a los 5 años.
*Conclusiones:* La hiponatremia en pacientes hospitalizados tiene más prevalencia en mayores de 75 años y mujeres. La hiponatremia grave aumenta la mortalidad a los 5 años. Hay factores que aumentan el riesgo de sobrecorrección por lo que se debe tratar de manera cuidadosa para evitar el síndrome de desmielinización osmótica (SDO).


## Introduction

Hyponatremia is the most frequent electrolyte disorder, affecting 15–28% of hospitalized subjects. Hyponatremia increases hospital stay and appears to be an independent risk factor for increased mortality, probably due to organic dysfunction produced even in mild hyponatremia.[1–3]

Approximately one-third of cases are due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The other major cause of hyponatremia is that associated with thiazide use, which vies for the top spot depending on the series studied and can affect up to 5–10% of hospitalized patients. The remaining causes of hyponatremia (hypocortisolism, hypothyroidism, diarrhea, vomiting, and hypervolemia, among others) are much less common.[1]

The clinical signs of hyponatremia are predominantly neurological and resolve upon correction of the hyponatremia. Cerebral edema, induced by the movement of water into the intracellular space, is the primary reason for these clinical signs. Symptoms can range in severity from headache, instability with increased falls, memory loss, confusion, cognitive impairment, lethargy, coma, and seizures to death. More severe clinical presentations are more frequent with a more acute and pronounced decrease in serum sodium levels.[4–10] A rapid decrease (in less than 24—48 h) and of moderate degree (approximately 10 mEq/L of sodium) could already cause such cerebral edema with an increase in neuronal cell volume and risk of herniation and death.[7,10,11]

It is important to differentiate between chronic and acute hyponatremia. The former usually presents with more nonspecific symptoms, although patients are rarely asymptomatic. In cases of mild/moderate hyponatremia, greater cognitive impairment and an increase in bone catabolism leading to a decrease in bone mineral density have been demonstrated when compared with individuals with eunatremia. Consequently, there is a greater risk of gait disturbance, falls, and an increased prevalence of fractures.[2,7,12,13]

It is essential to correct hyponatremia with appropriate treatment even before knowing its etiology. However, the rate of increase in natremia is fundamental to avoid overcorrection within the first 24—48 h and thus prevent the risk of osmotic demyelination syndrome (ODS). There are factors that can increase the risk of overcorrection such as severe hyponatremia, hypokalemia, malnutrition, and liver disease. The target increase will be between 4–6 mEq/L within the first 6 h and should not exceed 8 or 10 mEq/L within the first 24 h and 16 and 18 mEq/L at 48 h depending on whether or not there is a risk of ODS.[10]

In this study, we analyzed the evolution of natremia during hospitalization in a tertiary referral center in patients who were admitted with hyponatremia or developed it during the episode.

## Materials and methods

The study was approved by an ethics committee for its implementation. Patients with SIADH-induced hyponatremia, thiazides, and other causes (miscellaneous) who were admitted to a tertiary referral hospital from 2016 through 2022 were selected. The study is observational: no standardized diagnostic or treatment protocols were imposed. The determination of volemia and its diagnosis was made by the responsible physician.

### Inclusion and exclusion criteria

#### Inclusion criteria

Patients admitted to a tertiary referral center from January 1st, 2016 through August 12th, 2022, who were admitted for hyponatremia or developed it during admission, and who were under the care of endocrinology and nutrition (as the responsible or consulting service). Hyponatremia diagnoses recorded in the hospital discharge report were considered.

#### Exclusion criteria

- Patients younger than 18 years or pregnant women
- Patients in palliative care
- Patients on dialysis
- Patients on parenteral nutrition

### Definitions and statistical methods

Hyponatremia was defined as sodium levels <136 mEq/L, being mild between 126–135 mEq/L, moderate between 120–125 mEq/L, and severe <120 mEq/L. Overcorrection of natremia was defined as >8 mEq/L in 24 h and > 16 mEq/L in 48 h. The effectiveness of natremia correction therapy was defined as the need to meet one of these 2 criteria: correction of >5 mEq/L, but <8 mEq/L in 24 h, or reaching a natremia of >130 mEq/L during the course of treatment. Active therapies for hyponatremia included: fluid restriction, urea, tolvaptan, hypertonic saline, diuretics, and thiazide withdrawal. Severe hyponatremia and hypokalemia ($K^+ < 3.5$ mEq/L) were considered risk factors for natremia overcorrection.

Patient demographics including age and gender were described. The identification of patients with hyponatremia in the 3 mentioned groups (SIADH-induced hyponatremia, associated with thiazide use, and miscellaneous) was done through the hospital discharge diagnosis. Since the study was exclusively observational the diagnostic criteria for classifying the etiology of hyponatremia, as well as for determining volemia, were established by the treating physicians. SIADH-induced hyponatremia was considered in patients with euvolemia who met the biochemical criteria for osmolarity and ions in urine and blood, in addition to additional criteria such as uric acid and urea levels, ruling out adrenal, thyroid, or renal insufficiency. Thiazide-induced hyponatremia was categorized in patients who were on this drug as part of their treatment. Finally, the Miscellaneous group included: hypervolemia due to heart failure, hypovolemia due to increased GI losses, excess treatment with desmopressin, or hypothyroidism.

The comparison of the variables will be drawn according to their nature. To study the association between qualitative variables, the chi-square test or Fisher's exact test will be used when conditions require it. In the case of quantitative variables, the Kolmogorov-Smirnov test will be used to determine the normality of the distributions.

To study the differences between independent means, the parametric or non-parametric statistical tests required by the application conditions will be used (Student's *t*-test or Mann–Whitney *U* test in the case of 2 categories; ANOVA with Bonferroni post hoc test or Kruskal-Wallis H test for comparisons of more than 2 categories). Predictive models are also used to determine risk based on certain factors to be determined by the researcher.

Finally, the relationship between quantitative variables will be analyzed using Pearson's correlation tests (under parametric conditions) or Spearman's correlation tests (under non-parametric conditions). The significance level for all tests in the study will be 5% ($\alpha = 0.05$), and two-tailed tests will be used in all cases.

## Result

A total of 79 of the patients admitted for hyponatremia were categorized as SIADH-induced hyponatremia (36.5%), 89 as thiazide-induced hyponatremia (41.2%), and 48 as hyponatremia due to other causes (miscellaneous: 22.2%), which means that the most frequent cause of hyponatremia in this work was thiazides-related hyponatremia. The distribution in the miscellaneous group was as follows: 58%, clinical hypervolemia; 35%, clinical hypovolemia due to extrarenal losses, while the remaining 7%, hypocortisolism, hypothyroidism, or excessive use of desmopressin.

The demographic data and clinical characteristics of the 3 hyponatremia groups are described in Table 1. Hyponatremia was more frequent in the female gender and in those older than 75 years. When analyzed by groups, there were no statistically significant differences between age and gender.

The group of patients with SIADH had significantly longer lengths of stay vs the other 2 groups. There were no significant differences in the length of stay between patients with thiazide-induced hyponatremia and due to other causes (Table 2).

Patient age correlated positively with the length of stay ($p < 0.001$). Similarly, when applying a predictive model, it was identified that both age and male gender are significant predictors of hospitalization time with longer lengths of stay in older patients and men (Fig. 1).

Both severe hyponatremia and hypokalemia were significantly associated with overcorrection of natremia (Tables 3 and 4).

The correction of hyponatremia was effective in the 3 groups, being 86% (68/79) in SIADH, 92% (83/89) in the thiazide group, and 94% (45/48) in the miscellaneous group.

In the SIADH group, the most effective combination of therapies was hypertonic saline and tolvaptan with an effectiveness of 100%.

In the thiazide-induced hyponatremia group, the most effective combination was that which included fluid restriction, with or without physiological saline, and early thiazide withdrawal.

**Table 1** Demographic data of the 3 studied groups (SIADH, thiazides, and miscellaneous).

| Parameter | SIADH n = 79 | Thiazides n = 89 | Miscellaneous n = 48 |
|---|---|---|---|
| *Age years, median (IQR)* | 81.0 (71.5–86.0) | 81.0 (68.0–87.0) | 74.5 (61.75–81.25) |
| *Age, n years* | | | |
| ≤50 | 4 | 3 | 7 |
| 51–64 | 11 | 14 | 7 |
| 65–74 | 10 | 21 | 10 |
| ≥75 | 54 | 51 | 24 |
| *Gender* | | | |
| Male | 31 | 32 | 16 |
| Female | 48 | 57 | 32 |
| *Previous hyponatremia, n (%)* | | | |
| Yes | 48 (60.7%) | 46 (51.6%) | 21 (43.7%) |
| Unknown | 0 | 1 | 0 |

IQR: interquartile range; n: number; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

**Table 2** Comparison across hyponatremia groups (SIADH, thiazides, and miscellaneous).

| Comparison | Median length of stay (days) | *U* statistic | p Value |
|---|---|---|---|
| SIADH vs thiazides | 6 | 4831 | 0.001 |
| SIADH vs miscellaneous | 4 | 2564 | 0.001 |
| Thiazides vs miscellaneous | 4 | 2155 | 0.93 |

SIADH: syndrome of inappropriate antidiuretic hormone secretion; p: statistical significance; U: Mann–Whitney *U* test statistic; vs: versus. There was no statistical correlation between emergency sodium levels and days of admission (R, −0.05; p ns).

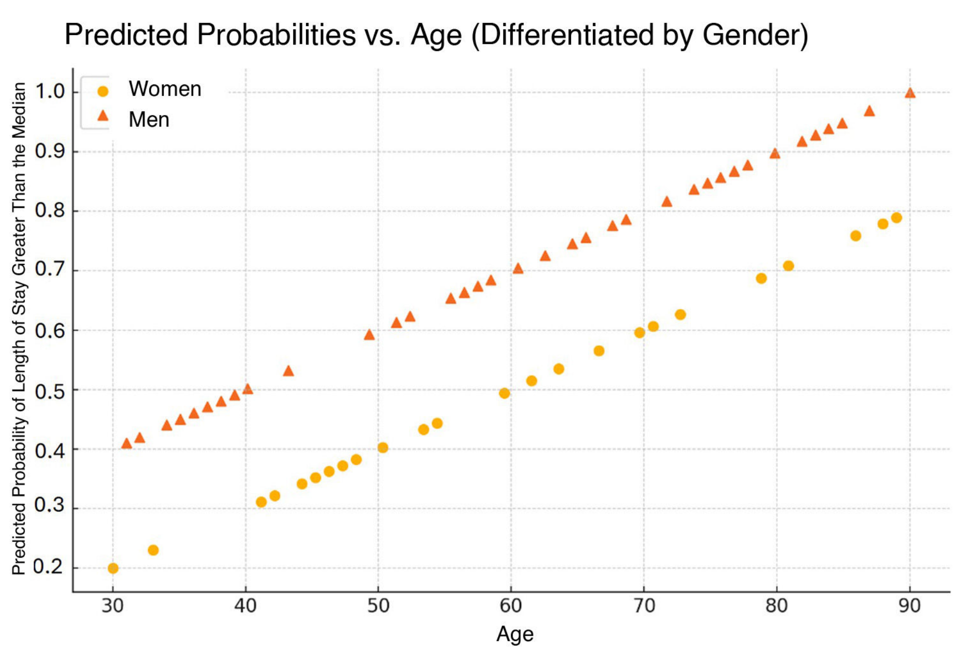


**Figure 1** Predictive model on length of stay in relation to age (years) and gender.

In the miscellaneous causes of hyponatremia group, the most effective combination of therapies was the treatment of the underlying cause.

When comparing the hyponatremia groups by severity, there were no differences (80.5 ± 12.7 years vs 79.0 ± 14.07 years; p n.s) in age between patients with severe and non-severe hyponatremia (Fig. 2).

Although there is a trend towards significance, severe hyponatremia could not be shown to be associated with higher mortality at 2 years (9.5% in patients without severe hyponatremia vs 18.6% in those with severe hyponatremia; p n.s). This association is demonstrated at 5 years (11.1% in patients without severe hyponatremia vs 30.3% in those with severe hyponatremia; p < 0.001). The statistical trend,

**Table 3** Association between sodium level and overcorrection of natremia.

| Observed values | $Na^+ < 120$ mEq/L | $Na^+ > 120$ mEq/L | Total |
|---|---|---|---|
| Yes OC | 34 | 9 | 43 |
| No OC | 88 | 85 | 173 |
| Total | 122 | 94 | 216 |
| % OC | 27.8% | 9.5% | $p < 0.05$ |
| Critical value (chi-square test) | 3.84 | Calculated value | 11.14 |

Na: sodium level in milliequivalents per liter; p: statistical significance; OC: overcorrection.

**Table 4** Association between potassium level and overcorrection of natremia.

| Observed values | $K^+ < 3.5$ mEq/L | $K^+ > 3.5$ mEq/L | Total |
|---|---|---|---|
| Yes OC | 14 | 29 | 43 |
| No OC | 27 | 146 | 173 |
| Total | 41 | 175 | 216 |
| % OC | 34.1% | 19.8% | $p < 0.05$ |
| Critical value (chi-square test) | 3.84 | Calculated value | 6.43 |

K: potassium level in milliequivalents per liter; p: statistical significance; OC: overcorrection.

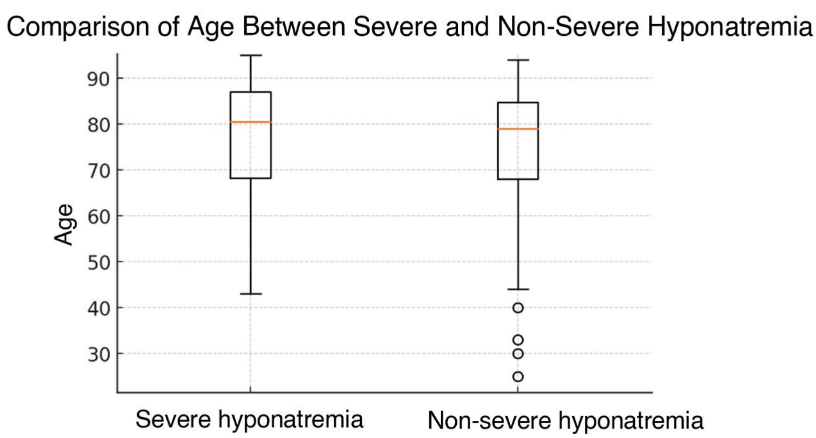


**Figure 2** Comparison of age between patients with severe (Na < 120 mEq/L) and non-severe hyponatremia (Na > 120 mEq/L).

without reaching significance, is also observed in the number of readmissions during the first year in patients with severe hyponatremia, with a mean of 0.60 readmissions vs 0.46 in those without severe hyponatremia (p n.s).

## Discussion

Although this is an exclusively observational and retrospective work, the study includes a large number of patients admitted to a center with extensive experience on the part of the endocrinology and nutrition service in the management of hyponatremia of various etiologies.

Depending on the reviewed literature, the most common etiology of hyponatremia in the hospital setting is debated between that caused by thiazides and SIADH.[1,6,14] As described by Burst et al., the relative frequencies of the various types and causes of hyponatremia vary considerably depending on the patient group studied, given that reliable data in unselected populations with community-acquired hyponatremia are scarce, mainly because the essential criteria for accurate diagnostic differentiation are often not available in large retrospective analyses and even in most prospective studies. In our study, the most frequent cause of hyponatremia in hospitalized patients was that associated with thiazides, followed by hyponatremia due to SIADH, and thirdly hyponatremia due to other causes.[1,7,15,16]

According to the reviewed studies, the prevalence of hyponatremia increases with age in both sexes and is somewhat more frequent in women than in men. An overall prevalence of 16.7% has been found, being lower in the group of patients between 65 and 69 years (12.2%) and higher in those older than 90 years (22.4%). Data from studies in more than 110,000 patients show that sodium levels were significantly lower in hospitalized patients older than 65 years. It is hypothesized that women would be more exposed to the development of hyponatremia partly due to hormonal factors and an alteration in cellular sodium transport and body water distribution.[1,3,17,18]

In the reviewed literature, the risk of developing thiazide-induced hyponatremia is especially increased in elderly patients and in the female gender.[1,7,15,16]

In our analysis, the prevalence of hyponatremia is higher in people older than 75 and is more common in women vs men, as shown in the literature, although when divided by subgroups, no differences are found.

In general, the different studies analyzed show a mean increase of more than 3 days of hospital stay in patients with hyponatremia. A logistic regression analysis proved that the length of stay related to hyponatremia was longer in men. In addition, there was an association between the length of stay in days and age, that is, the older the age, the longer the length of stay.[3,19]

In our study, a positive correlation ($p < 0.05$) between age and the length of stay is demonstrated, as in the literature. When performing predictive models with the patient sample, it is suggested that older age and male sex are associated with longer lengths of stay.

Although some studies report the association between sodium level at admission and the length of stay, in others there was no association. In our study, sodium levels at the time of admission do not directly predict the length of time patients will remain hospitalized.[20,21]

When establishing the factors associated with ODS in the context of overcorrection of hyponatremia, hypokalemia (<3.5 mEq/L), severe hyponatremia (defined as Na < 120 mEq/L), malnutrition, liver disease, and alcohol consumption are included. For the last 3 circumstances, there are no objective cut-off points. In our study, we decided to analyze only the first 2 factors, demonstrating a higher risk of overcorrection in cases of severe hyponatremia and hypokalemia, as indicated by the literature.[10]

In the meta-analysis by Corona et al. published in 2013 (which included 81 studies with more than 850,000 patients, >140,000 of whom had hyponatremia), it is concluded that the risk of hyponatremia-induced mortality was independent of age, gender, or the existence of diabetes as an associated comorbidity. In addition, an increased risk of mortality was found in hospitalized hyponatremic patients with myocardial infarction, cirrhosis, and lung infections. The relative risk of mortality increases between 2.47 and 3.34 in patients with hyponatremia versus eunatremic subjects, indicating that the electrolyte disorder strongly predicts the prognosis of all hospitalized patients.[22]

In our study, there is a statistically significant association between severe hyponatremia and mortality at 5 years. Although the mean number of readmissions in the first year is higher in patients with severe hyponatremia, statistical significance was not reached. Since there were no differences in the mean ages by groups according to the severity of hyponatremia, we believe that age can be ruled out as a confounding factor.

The therapies used for the correction of hyponatremia in our center are the usual ones and are repeated in the reviewed literature, including thiazide withdrawal, fluid restriction, physiological and hypertonic saline, urea, tolvaptan, use of loop diuretics.[7,23–30]

In our study, the effectiveness of correction was >80% in all 3 groups. In the SIADH group, the most effective therapy was hypertonic saline and tolvaptan. In the thiazide group, early withdrawal of the diuretic, and fluid restriction with or without physiological saline, was most effective. And in the miscellaneous group, treatments were directed at the underlying cause.

Urea therapy was not as useful as expected and as we perceive in clinical practice, being one of the most used treatments, which could be explained by the fact that urea was started after using other treatments such as hypertonic saline or fluid restriction and that, in general, it increases natremia more slowly than tolvaptan. This could mask its effectiveness, which underscores the need for additional studies to evaluate the impact of urea on natremia correction and the prevention of overcorrection.

## Conclusions

Hyponatremia especially affects individuals older than 75 years and women. Older age and male gender increase the length of stay. Severe hyponatremia is associated with higher mortality at 5 years, regardless of age, suggesting the need for special vigilance in this group of patients.

It is essential to identify the pathophysiological cause of hyponatremia to guide the specific treatment for each of them. The therapies available for the correction of global hyponatremia are effective alone or in combination. In thiazide-induced hyponatremia, the most effective measures were early withdrawal of the diuretic and fluid restriction with or without physiological saline. Close monitoring is recommended to avoid overcorrection, especially in cases of severe hyponatremia or when hypokalemia coexists.

Finally, severe hyponatremia was associated with higher mortality at 5 years, regardless of the patients' age, which reinforces the importance of adequate management of this disorder.

## Funding

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## Declaration of competing interest

None declared.

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