Observational Study

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Impact of hyponatremia in patients hospitalized in Internal Medicine units

Hyponatremia in Internal Medicine units

Jara Eloísa Ternero-Vega, MD, PhD[a], Carlos Jiménez-de-Juan, MD[a], Javier Castilla-Yelamo, MD[b,c], Vanesa Cantón-Habas, PhD[d], Elena Sánchez-Ruiz-Granados, MD[e], Miguel Ángel Barón-Ramos, MD[f], Guillermo Ropero-Luis, MD[f,g], Juan Gómez-Salgado, PhD[h,i,*], Máximo Bernabeu-Wittel, MD, PhD[j]

Abstract

The aim of this study was to analyze the impact and the clinical and evolutionary characteristics of hypotonic hyponatremia in patients hospitalized in Internal Medicine units. Prospective multicenter observational study of patients with hypotonic hyponatremia (<135 mmol/L) in 5 hospitals in southern Spain. Patients were included according to point prevalence studies carried out every 2 weeks between March 2015 and October 2017, by assessing demographic, clinical, analytical, and management data; each patient was subsequently followed up for 12 months, during which time mortality and readmissions were assessed. A total of 501 patients were included (51.9% women, mean age = 71.3 ± 14.24 years), resulting in an overall prevalence of hyponatremia of 8.3%. The mean comorbidities rate was 4.50 ± 2.41, the most frequent diagnoses being heart failure (115) (23%), respiratory infections (65) (13%), and oncological pathologies (42) (6.4%). Of the total number of hyponatremia cases, 180 (35.9%) were hypervolemic, 164 (32.7%) hypovolemic, and 157 (31.3%) were euvolemic. A total of 87.4% did not receive additional diagnostic tests to establish the origin of the condition and 30% did not receive any treatment. Hospital mortality was 15.6% and the mean length of stay was 14.7 days. Euvolemic and admission hyponatremia versus hyponatremia developed during admission were significantly associated with lower mortality rates ($P = .037$). Mortality at 1 year and readmissions were high (31% and 53% of patients, respectively). Hyponatremia was common in Internal Medicine areas, with hypervolemic hyponatremia being the most frequent type. The mortality rate was high during admission and at follow-up; yet there is a margin for improvement in the clinical management of this condition.

Abbreviations: ADH = antidiuretic hormone, CHF = chronic heart failure, EU = European Union, IM = Internal Medicine, RR = relative risk.

Keywords: hyponatremia, Internal Medicine, mortality, volume status

1. Introduction

Hyponatremia is the most prevalent electrolyte imbalance at the hospital level and its high social and health impact is well known.[1–3] Its reported prevalence, ranging from 10% to 20%, depends on the type of study, the population studied, as well as the severity of hyponatremia.[4–6]

In most cases, hyponatremia is caused by a net gain of water homeostasis.[7] The disorder is caused by a net gain of water without any real change in sodium concentration levels. In most cases, it is due to increased circulating vasopressin, that is, antidiuretic hormone (ADH), or renal sensitivity to ADH that prevents excretion of free water, resulting in the development of dilutional hyponatremia.[8]

It is widely known that this disorder is associated with poorer clinical outcomes, prolonged hospital stays, higher economic costs, as well as higher morbidity and mortality.[9–11] Hyponatremia has been mainly studied in patients with specific

All individuals signed a written informed consent to participate.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The study was approved by the Research Ethics Committee of the Virgen Macarena Hospital of Seville, on February 13, 2015 for all participating centers.

Supplemental Digital Content is available for this article.

[a] *Department of Internal Medicine, Virgen del Rocío University Hospital, Seville, Spain,* [b] *Department of Internal Medicine, San Juan de Dios Hospital, Seville, Spain,* [c] *Department of Internal Medicine, Virgen Macarena University Hospital, Seville, Spain,* [d] *Department of Nursing, Pharmacology, and Physiotherapy, University of Cordoba, Córdoba, Spain,* [e] *Department of Internal Medicine, Infanta Elena Hospital, Huelva, Spain,* [f] *Department of Internal Medicine, Serranía de Ronda Hospital, Málaga, Spain,* [g] *Department of Internal Medicine, Regional University Hospital of Malaga, Málaga, Spain,* [h] *Faculty of Labour Sciences, Department of Sociology, Social Work and Public Health, University of Huelva, Huelva, Spain,* [i] *Safety and Health Postgraduate Programme, Universidad Espíritu Santo, Guayaquil, Ecuador,* [j] *Department of Medicine, University of Seville, Seville, Spain.*

** Correspondence: Juan Gómez-Salgado, Faculty of Labour Sciences, Department of Sociology, Social Work and Public Health, University of Huelva, Avenida, Tres de Marzo, S/N, Huelva, 21007, Spain (e-mail: jgsalgad@gmail.com).*

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Key point

- This paper aims to analyze the impact and the clinical and evolutionary characteristics of hypotonic hyponatremias in patients hospitalized in Internal Medicine units.
- Euvolemic hyponatremia and hyponatremia were associated with lower mortality rates.
- Patients with severe hyponatremia and severe symptoms had more additional diagnostic tests requested and a higher treatment rate.

pathologies, such as chronic heart failure (CHF), kidney failure, chronic liver disease, respiratory pathologies, or neoplasms.[12–14] However, little data exist on the prevalence, management, and prognostic impact of hyponatremia in larger and more heterogeneous populations, such as patients admitted to Internal Medicine (IM) units. Moreover, studies that have analyzed hyponatremia based on volume status are scarce, while the management and prognosis of each subgroup are known to differ.[1,15] Also, there is limited research on long-term follow-up of volume status.

For all these reasons, we have conducted this study to explore the prevalence and main epidemiological, clinical, and prognostic characteristics of hyponatremia in IM, as well as the diagnostic and therapeutic approach applied to this condition.

2. Material and methods

2.1. Design

A prospective observational multicenter study with a 12-month follow-up was designed. Recruitment took place from March 15, 2015 to October 11, 2017. All patients with hyponatremia (plasma sodium concentration <135 mmol/L) hospitalized in the IM areas of 5 hospitals of the autonomous region of Andalusia (Spain) were included (Table S1, Supplemental Digital Content, http://links.lww.com/MD/M655).

2.2. Selection criteria: inclusion and exclusion

All patients admitted to the IM services of the participating hospitals, aged ≥18 years, who presented hypotonic hyponatremia in the analytical tests carried out during the episode that led to admission, and who agreed to participate by signing the informed consent form, were included. Patients who were in a situation of agony at the time of inclusion were excluded.

2.3. Sample size calculation

An expected frequency of hyponatremia of 40% ($P = .4$, $q = 0.6$), a 95% confidence interval (95% CI) ($z = 1.96$), an accepted error of 5% ($\beta = 0.05$), and a loss rate of 15% was assumed. The sample size was thus set at 423 patients.

2.4. Inclusion procedure, variables, and follow-up

During the study period, point prevalence studies were carried out every 2 weeks (except in the summer months). For those patients who met the inclusion criteria, blood osmolality was calculated (Formula = sodium mmol/L × 2 + Glucose mg/dL/18 + Urea mg/dL/2.8). If this was <275 mOsm/kg, demographic, clinical, and laboratory data were collected, and the different classifications of hyponatremia were considered.

Demographic data included age and sex. Clinical data included comorbidities, diagnoses on admission, hyponatremia-inducing drugs, sodium levels on admission, laboratory parameters (glucose, urea, creatinine, blood and urine osmolality, sodium in urine and cortisol), mortality during admission, and diagnostic and therapeutic management. It can be direct (aimed at correcting sodium) and indirect (treatment of the underlying disease). In addition, the classification of hyponatremia based on volume status, symptomatology, sodium levels, and chronology was performed. Follow-up of all patients was conducted for 12 months. Persistence of hyponatremia, number of admissions, and mortality were recorded during this period.

2.5. Definitions

Hyponatremia is defined as a plasma sodium concentration <135 mmol/L[1]; hypotonic hyponatremia is defined as plasma osmolality <275 mOsm/kg[1]; hypervolemic hyponatremia shows increased extracellular fluid volume; hypovolemic hyponatremia is defined by decreased extracellular fluid volume; euvolemic hyponatremia is related to normal extracellular fluid volume[1] (the determinants for this distinction were the medical history, physical examination, analytical values, and sometimes the response to treatment). In the present study, mild symptoms included nausea without vomiting, headache, and confusion. Severe symptoms included vomiting, cardiorespiratory distress, seizures, deep somnolence, and coma (Glasgow Scale <8).[1] Chronic hyponatremia was defined as >48 hours or was not classifiable. Acute hyponatremia was defined as <48 hours.[1] Mild hyponatremia was defined as sodium between 135 and 130 mmol/L; moderate hyponatremia, between 129 and 125 mmol/L; and profound hyponatremia, <125 mmol/L.[1]

2.6. Ethical aspects

All patients or their legal representatives agreed to the use of their anonymized clinical data for clinical research purposes by signing a written informed consent on receipt of the patient information sheet. The study was approved by the Research Ethics Committee of the Virgen Macarena Hospital of Seville, on February 13, 2015 for all participating centers. For this prospective project, all data were collected, processed, and analyzed anonymously and only for the intended purposes. All data were protected by the World Medical Association Declaration of Helsinki and the Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons in the processing of personal data. All authors declared no conflicts of interest concerning this work.

2.7. Statistical analysis

A descriptive analysis was carried out using absolute values and percentages for qualitative variables, as well as central values and measures of dispersion for quantitative variables. The distribution of all variables was assessed using the Kolmogorov–Smirnov test to determine the normality of the data distribution. Subsequently, after obtaining a normal distribution, bivariate inferential analysis of possible clinical and healthcare differences, as well as of factors associated with mortality at the time of the episode and 12 months, was performed using Chi-squared, Student t test, and analysis of variance. Finally, a multivariate analysis of factors associated with mortality was performed. The strength of the associations was quantified by calculating the relative risk (RR) with a 95% CI. The statistical analysis was performed using SPSS 26.0.

3. Results

A total of 8169 patients with and without hyponatremia were evaluated in 69-point prevalence studies carried out every 2 weeks during the study period. A total of 1192 (14.59%)

hyponatremias were identified among the total number of patients analyzed, of which 678 were hypotonic (8.3%) and 514 were non-hypotonic (6.3%). Of the participants with detected hypotonic hyponatremia, 501 agreed to participate in the study. The study flow diagram is detailed in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/M652.

The different classifications and the distribution according to volume status are shown in Table 1. Hypervolemic hyponatremia was the most common (35.92%), followed by hypovolemic (32.7%) and euvolemic (31.33%). The clinical characteristics of all patients are shown in Table 2. The analyzed population is characterized by being elderly and having a high number of comorbidities. Heart failure is the most frequently recorded diagnosis among patients, also one of the main etiologies of hyponatremia in this sample. The most frequent admission diagnoses are represented in Figure S2, Supplemental Digital Content, http://links.lww.com/MD/M653. The most common etiologies of hyponatremia, taking into account the volume status, are illustrated in Figure S3, Supplemental Digital Content, http://links.lww.com/MD/M654. The results on the diagnostic and therapeutic management of hyponatremia are detailed in Tables 3 and 4, where it is emphasized that the vast majority of subjects were not subjected to tests to assess this disorder, and only a limited number of patients received direct treatment to raise sodium levels. Finally, Figure 1 shows the evolution of sodium from admission to discharge or death.

Mortality rate during admission amounted to 15.6% (76 patients). The multivariate analysis (Table 5) showed that euvolemic hyponatremia (RR = 0.81 [95% CI = 0.83–0.069] P = .037) and hyponatremia present on admission (RR = 0.39 [95% CI = 0.19–0.79] P = .009) were protective factors (Table S4, Supplemental Digital Content, http://links.lww.com/MD/M658). In contrast, CHF (RR = 2.17 [95% CI = 1.17–4.02] P = .013) and active neoplasia (RR = 2.94 [95% CI = 1.49–5.80] P = .002) were identified as risk factors.

During the 12-month follow-up, 132 patients (30.9%) had died, 214 individuals had been readmitted (52.7%), and 124 (29.1%) had persistent hyponatremia, with no significant differences between the different types of hyponatremia according to volume status (P > .05).

4. Discussion

Despite various studies linking this disorder to worse clinical outcomes, as well as higher economic costs,[1–3] the results of this study demonstrate that internists are currently not convinced of the importance of this alteration. An example of this is the low number of diagnostic tests requested to clarify the origin. Only 12.6% requested at least 1 diagnostic test, and approximately 30% of subjects did not receive treatments to raise sodium levels. Furthermore, more than 40% of patients were discharged still hyponatremic.

In Spain, no prospective observational studies have been carried out in IM units that have comprehensively analyzed this condition, so this is the first study in the field.

The prevalence of hypotonic hyponatremia in IM units was 8.3% ± 7.2%. This figure is below the published prevalence (10%–20%),[5,6] and this may be mainly because plasma osmolality was obtained from formulae that included urea levels.[16] On the other hand, the prospective nature of this study has allowed us to identify non-hypotonic etiologies of hyponatremia, such as hyperglycemia or hyperproteinemia. Finally, interrupting the data collection phase during the summer months may also have contributed to this data mismatch, as several studies have reported a higher incidence of hyponatremia during this period.[17,18] The reasons for the higher prevalence of hyponatremia during these months are attributed to several predisposing factors, such as increased hypotonic fluid consumption, sweating, an increased risk of hypovolemic situations, or even increased environmental temperature as a stimulus for vasopressin.[17,18]

Table 1

Classifications of hyponatremia and comparison according to volume status.

Type of hyponatremia		Hypervolemia n = 180 (35.9%)	Hypovolemia n = 164 (37.73%)	Euvolemia n = 157 (31.33%)	Hypervolemia vs Hypovolemia	Hypervolemia vs euvolemia	Hypovolemia vs euvolemia
		Frequency n (%)			RR (CI 95%) P		
Biochemical levels							
Mild (134–130 mmol/L)	216 (43.3%)	77 (43%)	94 (57%)	46 (29%)	0.000	0.000	0.000
Moderate (125–129 mmol/L)	148 (29.4%)	58 (32%)	41 (25%)	47 (30%)	0.000	0.000	0.000
Profound (<125 mmo/L)	137 (27.3%)	45 (25%)	29 (18%)	64 (41%)	0.000	0.000	0.000
Chronology							
Chronic	417 (84.2%)	157 (87.1%)	123 (75%)	144 (92.1%)	0.000	0.000	0.000
Any symptom	265 (52.8%)	84 (47.2%)	77 (47.2%)	99 (67.7%)	0.957	2.09 (1.33–3.28) .001	2.23 (1.41–3.54) .010
Moderate symptom	230 (45.9%)	72 (40.4%)	66 (40.5%)	91 (59.5%)	0.960	2.16 (1.38–3.37) .001	2.33 (1.4–3.6) .000
Nausea	160 (31.9%)	49 (27.5%)	52 (31.9%)	58 (37.9%)	0.397	2.18 (1.34–3.57) .002	3.08 (1.79–5.31) .000
Confusion	122 (24.4%)	39 (21.9%)	27 (16.6%)	57 (37.3%)	0.054	2.24 (1.21–4.15) .009	2.58 (1.33–5.01) .004
Headache	70 (14.0%)	20 (11.2%)	17 (10.4%)	57 (37.3%)	0.823	0.610	0.071
Severe symptom	117 (23.4%)	24 (13.5%)	39 (23.9%)	54 (35.3%)	2.14 (1.21–3.89) 0.009	3.61 (2.06–6.34) .000	1.68 (1.02–2.7) .03
Vomiting	75 (15%)	12 (2.3%)	28 (5.5%)	35 (6.9%)	3.09 (1.48–6.47) 0.002	4.40 (2.14–9.06) .000	0.081
Deep somnolence	65 (12.5%)	17 (3.4%)	16 (3.2%)	32 (6.3%)	0.921	2.04 (1.24–4.62) .007	2.46 (1.24–4.88) .008
Cardiorespiratory distress	17 (3.2%)	4 (0.8%)	2 (0.4%)	11 (2.2%)	0.478	0.056	11.22 (1.41–88.7) .004
Seizures	5 (1.0%)	0 (0%)	0 (0%)	5 (1%)	1	0.45 (0.40–0.050) .015	0.47 (0.42–0.53) .021
Coma	4 (0.6%)	1 (0.2%)	2 (0.4%)	1 (0.2%)	0.508	0.922	0.5890

CI = confidence interval, RR = relative risk.

Table 2

Main global clinical characteristics and according to volume status.

	Global n = 501	Hypervolemia n = 180	Hypovolemia n = 164	Euvolemia n = 157	Hypervolemia vs hypovolemia	Hypervolemia vs euvolemia	Hypovolemia vs euvolemia
Age, yr	71.31 ± 14.24	72.37 ± 14.30	69.96 ± 14.15	71.34 ± 13.94	0.892	0.921	0.963
Sex female	260 (51.9%)	101 (56.2%)	78 (47.9%)	81 (51.9%)	0.691	0.725	0.789
Mean length of stay, d	14.72 ± 12.98	14.16 ± 11.69	15.91 ± 14.41	14.71 ± 13.07	0.297	0.728	0.214
No. of comorbidities per patient (mean ± SD)	4.50 ± 2.41	5.27 ± 2.53	4.00 ± 2.35	4.00 ± 2.35	0.078	0.078	0.989
Cardio-vascular	1.63 ± 1.36	2.50 ± 1.50	1.10 ± 0.93	1.20 ± 1.02	0.00	0.000	0.089
Endocrine	0.91 ± 0.90	1.03 ± 0.99	0.81 ± 0.85	0.93 ± 0.84	0.004	0.071	0.092
Neurological-psychiatric	0.60 ± 0.85	0.64 ± 0.84	0.64 ± 0.84	0.72 ± 0.94	0.986	0.129	0.130
Digestive	0.38 ± 0.64	0.40 ± 0.66	0.54 ± 0.74	0.20 ± 0.43	0.068	0.001	0.001
Pulmonology	0.39 ± 0.72	0.41 ± 0.77	0.26 ± 0.61	0.53 ± 0.78	0.072	0.092	0.001
Nephro-urological	0.26 ± 0.49	0.31 ± 0.51	0.33 ± 0.56	0.14 ± 0.36	NS	0.004	0.000
Oncological	0.20 ± 0.46	0.37 ± 0.2–9	0.07 ± 0.2–9	0.22 ± 0.43	0.000	0.001	0.072
Hyponatremia-inducing drugs: n (%)	378 (75.3%)	142 (79.8%)	73 (68.9%)	120 (78.4%)	0.0610	0.089	0.591
Diuretics	284 (57.8%)	108 (60.7%)	29 (27.4%)	36 (23.8%)	0.0598	0.078	0.084
ACEI	185 (36.2%)	83 (46.6%)	30 (28.3%)	46 (30.21%)	0.0684	0.093	0.182
Antidepressants	101 (20.3%)	36 (20.2%)	20 (18.9%)	28 (18.3%)	0.095	0.147	0.560
Antipsychotics	24 (3.7%)	6 (3.5%)	6 (5.7%)	9 (5.9%)	0.964	0.657	0.478
Antiepileptics	63 (12.6%)	22 (12.4%)	12 (11.3%)	24 (15.7%)	0.0698	0.098	0.0789
Antineoplastics	6 (1.2%)	1 (0.6%)	3 (2.8%)	2 (0.6%)	0.158	0.239	0.157

ACEI = angiotensin-converting enzyme inhibitors, SD = standard deviation.

Table 3

Additional diagnostic tests were requested in the overall sample and according to volume status.

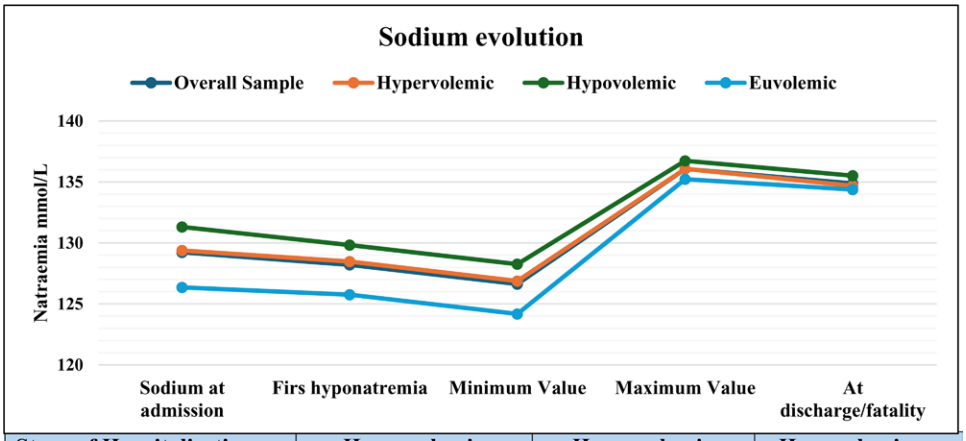
	Global n = 501	Hypervolemia n = 180	Hypovolemia n = 164	Euvolemia n = 157
ADTs		**Frequency n (%)**		
% No ADT	438 (87.47%)	160 (89.9%)	163 (92.1%)	103 (67.3%)
Total ADT	150 (29.94%)	22 (12.22%)	15 (9.14%)	113 (71.97%)
Blood osmolality	52 (34.6%)	7 (31.8%)	6 (40%)	39 (34.5%)
Venous blood gas analysis	31 (20.6%)	5 (22.7%)	4 (26.6%)	22 (19.4%)
Laboratory	21 (14.0%)	2 (9%)	2 (13.3%)	17 (15.0%)
Urine osmolality	18 (12%)	1 (4.5%)	1 (6.6%)	16 (14.1%)
Sodium in urine	57 (38%)	14 (63.6%)	6 (40%)	37 (32.7%)
Cortisol	17 (11.3%)	0 (0%)	2 (13.3%)	15 (13.2%)
Other	6 (4%)	0 (0%)	0 (0%)	6 (5.3%)

Table 4

Treatments are prescribed in the global sample and according to volume status.

	Global n = 501	Hypervolemia n = 180	Hypovolemia n = 164	Euvolemia n = 157
Treatment		**Frequency n (%)**		
No treatment	151 (30.1%)	34 (19.1%)	37 (22.7%)	78 (51%)
Total prescribed treatments	413 (82.4%)	163 (90.5%)	125 (76.2%)	125 (79.6%)
Physiological saline solution	172 (41.6%)	13 (7.9%)	117 (93.6%)	42 (33.6%)
Hypertonic saline solution	29 (7.0%)	4 (2.4%)	2 (1.6%)	23 (18%)
Water restriction	46 (11.21%)	14 (8.5%)	1 (0.8%)	31 (24.8%)
Furosemide	143 (34.6%)	126 (77.3%)	5 (4%)	12 (9.6%)
Tolvaptan	12 (2.9%)	3 (1.8%)	0 (0%)	9 (7.2%)
Urea	8 (1.9%)	1 (0.6%)	0 (0%)	7 (5.6%)
Oral sodium chloride tablets	3 (0.7%)	2 (1.2%)	0 (0%)	1 (0.8%)

The mean hospital stay in the present study was relatively extended (14 days) compared to that described in other studies carried out in IM units.[19] This finding may be justified by the population analyzed, as many studies have shown that patients with this disorder generally stay for a longer period in hospital and have a higher number of complications.[20,21] The study by Lu et al[5] is an example of this, where patients with hyponatremia had a mean length of stay of 13.4 ± 0.2 days versus 10.7 ± 0.2 days in normal sodium patients, $P < .001$. Second, the included patients were characterized by high clinical complexity. The mean number of comorbidities was high when compared to the national mean number of comorbidities in IM units



Stage of Hospitalisation	Hypervolemia vs Hypovolemia	Hypervolemia vs Euvolemia	Hypovolemia vs Euvolemia
Sodium at admission	0.001	0.001	0.000
First hyponatraemia	0.003	0.001	0.00
Minimum value	0.004	0.001	0.00
Maximum value	0.089	0.092	0.072
Clinical discharge/exitus	0.128	0.201	0.198

Figure 1. Chronological evolution of sodium levels during admission until clinical discharge.

Table 5

Factors associated with mortality in the multivariate analysis.

	Mortality		
Factors	**RR**	**95% CI**	***P***
Chronic heart failure	2.17	1.17 ± 4.02	.013
Chronic liver disease	2.07	0.97 ± 4.43	.059
Neoplasia	2.94	1.49 ± 5.80	.002
Dyslipidemia	0.35	0.17 ± 0.73	.006
Minimum sodium	0.95	0.90 ± 1.01	.054
Euvolemic hyponatremia	0.081	0.83 ± 0.069	.037
Vomiting	2.15	1.07 ± 4.45	.062
Hyponatremia admission	0.396	0.198 ± 0.79	.009

CI = confidence interval, RR = relative risk.

as reported in other studies.[22] The mean was similar to a complex chronic patient population (4.3 comorbidities/patient).[23]

The most common type detected in this study was hypervolemic hyponatremia (35.9%), followed by hypovolemic hyponatremia and euvolemic hyponatremia (32.7% and 31.1%, respectively). Even though this distribution is not consistent with other studies carried out on hospital samples, these data justify that CHF is the most prevalent pathology in IM units.[22] Therefore, hyponatremia in these units would more likely be a pathophysiological consequence of another disease, rather than the sole and main reason for admission, as may occur in the case of euvolemic hyponatremia. Notably, patients with euvolemic hyponatremia formed the group with significantly more symptoms ($P < .05$), probably because this type is associated with more severe biochemical levels ($P < .05$) and is often the sole condition for admission.

In the study at hand, the majority of hyponatremias were defined as chronic (84.2%), based on the definitions provided in the guideline.[1] However, based on the severity of the symptoms, particularly as regards individuals with severe symptoms, these subjects should have been classified as patients with acute hyponatremia. Such symptoms usually reflect the presence of brain edema, which indicates that the brain has not yet had time to rapidly adapt to hypotonicity (first 48 hours). Thus, symptomatic severity could be another supportive marker for defining chronology.

Despite several studies linking this condition to poorer clinical outcomes, as well as to higher economic costs,[20,24,25] the results of this study show that IM specialists are currently not convinced of the significance of this disorder. An example of this was the low number of additional diagnostic tests requested, only in 12.6% of cases at least 1 diagnostic test was requested, and approximately 30% of subjects did not receive any treatment whatsoever. Though it is considered that actual values exceed this figure, as for this analysis furosemide was taken as specific therapy, any patient with CHF was therefore considered as treated; the same was true for serotherapy. The percentages of additional diagnostic tests and treatment varied according to the type of volume status, being the euvolemic group the one with more additional diagnostic tests performed and receiving less specific treatment. In addition, more than 40% of patients were discharged while still in hyponatremia. These data suggest similarities with other studies that have analyzed the management of hyponatremia in different settings.[26]

Several barriers may explain this praxis inadequacy. First, it is a complex electrolyte imbalance that requires an understanding of the pathophysiology of the disease[27] and a deep knowledge of the multiple etiologies, as well as of the different classifications, as each condition requires a different approach. On top of this, the diagnostic tools used are not very robust and accurate.[27,28] To this must be added that there is no specialty responsible for the management of hyponatremia, something which also contributes to poor management of cases. The results of the study by Garrahy et al[29] demonstrated the benefits of structured input from hyponatremia specialists: higher sodium levels at discharge, shorter hospital stays, and reduced mortality. Therefore, the role of professionals with expertise in this condition should be promoted. Another likely barrier to better management is probably the lack of hard evidence of improved mortality through the treatment of hyponatremia.

At the therapeutic level, the first limitation relates to the lack of evidence concerning many therapeutic aspects, such as the most suitable treatment according to the patient's profile, most notably in the scenario of chronic hyponatremia. To date, further research is still needed to justify the benefits of reversing

mild or moderate hyponatremia. Second, due to the lack of evidence, treatment is largely based on expert opinion, which explains why different guidelines and protocols differ in some of their most basic therapeutic recommendations. Third, fear of overcorrection, as well as lack of experience with specific treatments, such as tolvaptan or urea, may be limiting their use. Finally, to successfully correct hyponatremia, laboratory tests are necessary, but as already seen, these individuals are often not sufficiently tested to deal with this condition without any guarantees.

The analyzed data suggest that patients with euvolemic hyponatremia have a significantly lower risk of death than those with hypervolemic and hypovolemic hyponatremia ($P = .037$). In this sense, Cuesta et al[30] were the first to demonstrate higher mortality rates in the hypervolemic and hypovolemic hyponatremia groups compared to euvolemic hyponatremias (syndrome of inappropriate antidiuresis). This finding may be explained by several reasons. In the first place, some of the severe hyponatremias, often euvolemic, are usually induced by reversible etiologies, for example, drugs or respiratory infections. Second, underlying medical conditions associated with hypervolemic hyponatremia (CHF, liver disease, etc) are generally associated with increased mortality. Thus, it is likely that the underlying medical pathologies that have caused the alteration of water homeostasis play an important role in mortality rates. Third, biochemically more severe sodium is often considered worthy of further study by clinicians on a more frequent basis and therefore, more optimal management is applied. This has been demonstrated in the present study, where patients with profound hyponatremia and severe symptoms had more additional diagnostic tests requested and a higher treatment rate (Table S2, Supplemental Digital Content, http://links.lww.com/MD/M656, and Table S3, Supplemental Digital Content, http://links.lww.com/MD/M657). Hence, the linear relationship between mortality and hyponatremia levels, which has been classically proposed, is being disputed here.[31,32]

Finally, this study has shown that the group of patients with in-hospital developed hyponatremia were more likely to die ($P < .005$). Therefore, hyponatremia in this group of patients may be a marker of severity. Likewise, these individuals had longer hospital stays (Table S4, Supplemental Digital Content, http://links.lww.com/MD/M658), making it likely that they suffered a greater number of complications associated with the hospitalization period (nosocomial infections, confusional syndrome, etc), which in turn contributed to mortality.

This study has some limitations that must be considered when interpreting the results. First, the observational design prevents any firm conclusions from being drawn from the suggested findings.

It is also noteworthy that the selection of diagnostic tests and the prescription of treatments was entrusted to the clinicians responsible for the patients. This limited the ability to accurately confirm the types of hyponatremia by volume status.[33]

In addition, the formula used in this study corresponds to blood osmolality and not effective osmolality or tonicity, as it took into account plasma urea.[27] Consequently, this approach has prevented the detection of a higher number of hypotonic hyponatremias.[1]

Another possible limitation has been the non-correction of sodium by total protein. Such circumstances can substantially mask hyponatremia or its biochemical severity.[34]

Lastly, the small sample size due to the prospective observational design and the fact that the participating hospitals were only located in Andalusia may raise the question of whether the results can be extrapolated to clinical practice in other areas of Spain or the world.

To conclude, hyponatremia was found to be common in patients admitted to IM units, and the population was characterized by a remarkable clinical complexity. Hypervolemic hyponatremia was the most frequently observed. Deficiencies in the diagnostic and therapeutic management of this condition have been observed. Finally, euvolemic hyponatremia and hyponatremia on admission versus during admission were associated with lower mortality rates.

Author contributions

Conceptualization: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Data curation: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Formal analysis: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Investigation: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Methodology: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Project administration: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Máximo Bernabeu-Wittel.

Resources: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Software: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo BBernabeu-Wittel.

Supervision: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Validation: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Visualization: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Writing—original draft: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

Writing—review & editing: Jara Eloísa Ternero-Vega, Carlos Jiménez-de-Juan, Javier Castilla-Yelamo, Vanesa Cantón-Habas, Elena Sánchez-Ruiz-Granados, Miguel Ángel Barón-Ramos, Guillermo Ropero-Luis, Juan Gómez-Salgado, Máximo Bernabeu-Wittel.

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