Original Article

Etiologies, Clinical Manifestations, and Factors Associated with Severe Symptomatic Hyponatremia among Hospitalized Hyponatremia Patients

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Background: Hyponatremia is associated with unfavorable outcomes in many cases. The mainstay of hyponatremia treatment depends on its symptoms and etiology. However, etiologies, clinical manifestations, and factors associated with severe symptomatic hyponatremia have been rarely reported.

Objective: To analyze and report etiologies, clinical manifestations, and factors associated with severe symptomatic hyponatremia.

Materials and Methods: In the present cross-sectional study, the authors enrolled hospitalized patients with hyponatremia who had consulted a nephrologist between October 1, 2017, and October 31, 2018. Their baseline characteristics and clinical manifestations were recorded. Etiologies were confirmed by the attending nephrology staff. Factors associated with severe symptomatic hyponatremia were evaluated using logistic regression analysis.

Results: One hundred patients were included in this study. The syndrome of inappropriate antidiuresis (SIAD), hypovolemia, and hydrochlorothiazide use were the leading hyponatremia etiologies. Hyponatremia etiologies differed between patients with community-acquired hyponatremia (n=50) and those with hospital-associated hyponatremia (n=50). Patients with community-acquired hyponatremia were older, presented with a higher frequency of severe symptomatic hyponatremia, and showed lower SNa-levels. Low SNa-levels were significantly associated with severe symptomatic hyponatremia (p=0.014).

Conclusion: Hyponatremia remains an important health problem. SIAD, hypovolemia, and hydrochlorothiazide use are among the leading etiologies of hyponatremia. Low SNa-levels are associated with severe symptomatic hyponatremia; thus, physicians should pay close attention to low SNa-levels in hospitalized patients.

Keywords: Hyponatremia, Symptomatic Hyponatremia, Community-acquired hyponatremia, Hospital-associated hyponatremia

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Hyponatremia (serum sodium [SNa] level of less than 135 mmol/L) is one of the most common electrolyte disorders[1-6]. The etiology of hyponatremia could be from numerous conditions. It can result in wide spectrum of clinical symptom from mild and non-specific to severe and life-threatening[6-9]. Factors that associated with symptomatic hyponatremia were female gender, children, hypoxia, and liver disease[10-13]. Previous studies have reported an association between hyponatremia and poor outcomes in many cases[3,4,14-21]. However, etiologies, clinical manifestations, and factors associated with severe symptomatic hyponatremia, specifically in Asian populations, have been rarely reported. Thus, in the present study, the authors aimed to analyze and report etiologies, clinical manifestations, and factors associated with severe symptomatic hyponatremia.

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Materials and Methods

Study population

The present cross-sectional study was conducted between October 1, 2017 and October 31, 2018.

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Hospitalized patients who consulted a nephrologist for hyponatremia at the authors' tertiary university hospital in Bangkok, Thailand, were enrolled. The hospital policy for nephrology consultation of hyponatremia is one of the following, with any symptom of hyponatremia, SNa equal or less than 125 with or without hyponatremic symptom, or concerning in diagnosis and treatment by primary physician. The inclusion criteria were 1) 18 to 80 years, 2) SNa-level of less than 135 mmol/L, 3) serum osmolality of less than 290 mOsm/kg, and 4) estimated glomerular filtration rate (eGFR) of more than 60 mL/minute/1.73 m^2. The main exclusion criterion was the presence of acute kidney injury, as defined by Kidney Disease: Improving Global Outcome[22]. All patients with hyponatremia were diagnosed hyponatremia, addressed etiology of hyponatremia, and treated by a nephrologist, according to the recommendations published by Spasovski et al[23]. Patient data regarding demographics, comorbidities, concurrent medication (particularly diuretic drugs), clinical manifestations, hyponatremia symptoms, hyponatremia form, and laboratory values during hyponatremia (SNa, serum creatinine [Scr], potassium, chloride, bicarbonate, eGFR, serum cortisol, thyroid function, urine osmolality, and urine sodium) were collected.

Hyponatremia symptoms

Hyponatremia was classified according to symptoms. Severe symptomatic hyponatremia was defined as the presence of at least one of the following symptoms, vomiting, seizure, coma (Glasgow coma scale of less than 8), cardiorespiratory distress, or deep somnolence. Moderately severe symptomatic hyponatremia was defined as absence of severe symptomatic hyponatremia symptoms but presence of at least one of the following symptoms, nausea, confusion, or headache. Non-symptomatic hyponatremia was defined as absence of symptoms. The other potential etiologies of symptoms were evaluated when suspected by the primary physician or the attending nephrologist, or unresolving symptom after treatment with result in appropriate increased of SNa.

Hyponatremia form

Community-acquired hyponatremia was defined as hyponatremia detected in an outpatient setting or before hospital admission. Hospital-associated hyponatremia was defined as hyponatremia detected after hospital admission in patients with normal SNa-levels at admission.

Ethical consideration

The present study was approved by the Institutional Review Board of Navamindradhiraj University (COA 110/2560) and was registered in the Thai Clinical Trial Registry (TCTR20171010004). After receiving information regarding the study from the investigators, all the patients provided written informed consents. If the patients were not capable of providing informed consent, the investigators provided information to first-degree relatives and obtained assent. The investigators did not interrupt or delay the process of treatment.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median (quartile [Q]1, Q3), depending on distribution. Categorical variables are presented as proportions. For comparisons, independent t-test was used when data were normally distributed and Mann-Whitney U test when data were not normally distributed. Additionally, chi-squared and Fisher's exact tests were used for comparing categorical variables. Demographics, symptoms, and etiologies were compared between patients with community-acquired hyponatremia and those with hospital-associated hyponatremia. Logistic regression analysis was used to assess univariate associations between severe symptomatic hyponatremia and patient characteristics. Factors associated with severe symptomatic hyponatremia in univariate analysis were included in subsequent multivariate analysis. All statistical analyses were performed using R software, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The authors identified 299 patients with hyponatremia who were hospitalized during the study period of 13 months. During that time, 14,083 adult patients were hospitalized. Thus, the incidence of hyponatremia was 2.12%. One hundred ninety-nine patients met the exclusion criteria (n=121) or whose with data missing (n=78) were excluded. Of the remaining 100 patients, 61 were females. Median patient age was 63 (49.0, 69.3) years, median weight was 52 (45.8, 60.5) kg, mean height was 161.3±8.5 cm, and mean body mass index was 20.8±3.8 kg/m^2. Median SNa-level was 125.0 (120.8, 130.0) mmol/L, and mean Scr level was 0.67±0.27 mg/dL. Active malignancies were noted in 21 patients (21%).

Table 1. Baseline characteristics, clinical features, and laboratory data of patients

	Overall n (%)	Community-acquired hyponatremia n (%)	Hospital-associated hyponatremia n (%)	p-value
Number of patients	100	50	50	
Age (year); median (Q1, Q3)	63.0 (49.0, 69.3)	66.5 (57.0, 72.0)	59.0 (46.3, 66.5)	0.011
Sex: female	61 (61)	28 (56)	33 (66)	0.412
Underlying disease				
DM	18 (18)	13 (26)	5 (10)	0.069
HT	34 (34)	20 (40)	14 (28)	0.291
Malignancy	21 (21)	7 (14)	14 (28)	0.141
Weight (kg); median (Q1, Q3)	52.0 (45.8, 60.5)	54.0 (45.5, 61.5)	52.0 (46.8, 60.0)	0.860
Height (cm); mean±SD	161.3±8.5	160.5±8.6	162.2±8.3	0.307
BMI (kg/m^2); mean±SD	20.8±3.8	20.9±3.6	20.6±4.0	0.750
HCTZ	6 (6)	6 (12)	0 (0)	
Symptoms				<0.001
Severe	23 (23)	20 (40)	3 (6)	
Moderate	9 (9)	9 (18)	0 (0)	
No	68 (68)	21 (42)	47 (94)	
SNa (mmol/L); median (Q1, Q3)	125.0 (120.8, 130.0)	121.0 (115.2, 127.0)	128.5 (124.0, 132.0)	<0.001
Scr (mg/dL); mean±SD	0.67±0.27	0.71±0.29	0.63±0.25	0.153

BMI=body mass index; DM=diabetes mellitus; HCTZ=hydrochlorothiazide; HT=hypertension; Q=quartile; Scr=serum creatinine; SD=standard deviation; SNa=serum sodium

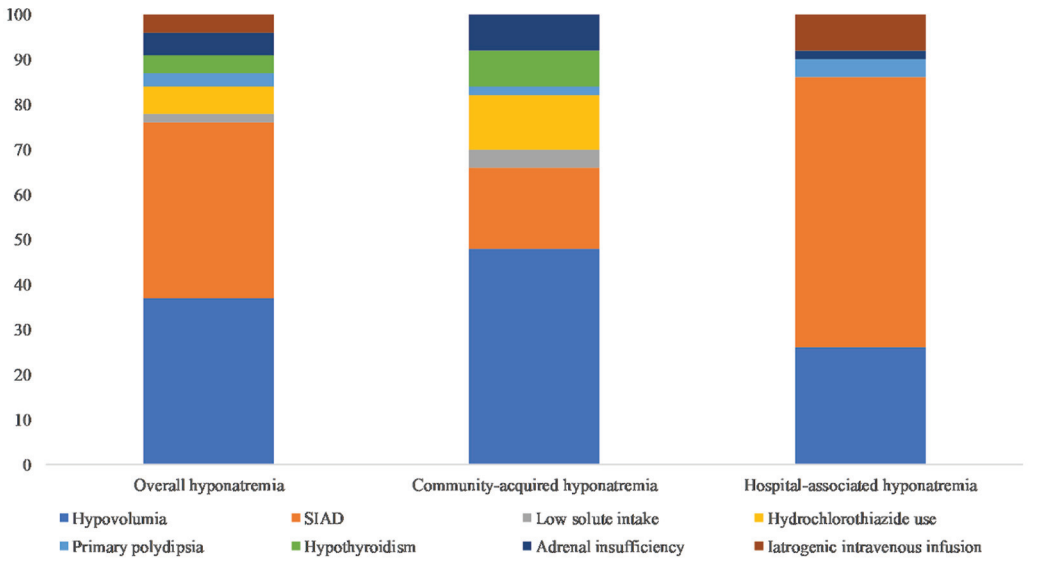

Figure 1. Hyponatremia etiology.

Overall hyponatremia: hypovolemia 37%, SIAD 39%, low solute intake 2%, hydrochlorothiazide use 6%, primary polydipsia 3%, hypothyroidism 4%, adrenal insufficiency 5%, iatrogenic intravenous infusion 4%

Community-acquired hyponatremia: hypovolemia 48%, SIAD 18%, low solute intake 4%, hydrochlorothiazide use 12%, primary polydipsia 2%, hypothyroidism 8%, adrenal insufficiency 8%

Hospital-associated hyponatremia: hypovolemia 26%, SIAD 60%, primary polydipsia 4%, adrenal insufficiency 2%, iatrogenic intravenous infusion 8%

SIAD=syndrome of inappropriate antidiuresis

Table 2. Characteristics and laboratory data according to hyponatremia etiology

	SIAD	Hypovolemia	HCTZ induce hyponatremia	Adrenal insufficiency	Hypothyroidism	Iatrogenic intravenous infusion	Primary polydipsia	Low solute intake
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients	39	37	6	5	4	4	3	2
Age (years); median (Q1, Q3)	60.0 (51.5, 58.5)	60.0 (49.0, 67.0)	73.0 (72.0, 76)	59.0 (49.0, 69.0)	72.5 (67.0, 76.0)	53.0 (44.8, 63.5)	69.0 (43.5, 79.5)	57, 66‡
Sex: female	10 (25.6)	16 (43.2)	3 (50)	2 (40)	4 (100)	3 (75)	1 (33.3)	0 (0.0)
Weight (kg); mean±SD	54.3±11.6	51.1±9.1	57.7±6.5	60.2±13.6	57.0±14.8	58.5±17.5	67.7±12.1	44, 45‡
Malignancy	10 (25.6)	8 (21.6)	0 (0.0)	0 (0.0)	1 (25.0)	1 (24.0)	0 (0.0)	1 (50.0)
Severe symptoms	5 (12.8)	7 (18.9)	2 (33.3)	2 (40.0)	3 (75.0)	0 (0.0)	2 (66.7)	2 (100)
SNa (mmol/L); median (Q1, Q3)	126.0 (124.0, 130.0)	126.0 (118.0, 129.0)	118.0 (116.0, 121.0)	121.0 (121.0, 124.0)	118.5 (113.0, 126.5)	132.5 (128.0, 133.0)	124.0 (121.5, 127.5)	94, 125‡
Potassium (mmol/L)	3.9 (0.6)	3.8 (0.6)	3.3 (0.7)	4.0 (0.8)	3.5 (0.9)	4.2 (0.7)	4.0 (0.1)	4.1, 3.5‡

HCTZ=hydrochlorothiazide; Q=quartile; SD=standard deviation; SIAD=syndrome of inappropriate antidiuresis; SNa=serum sodium

‡ Continuous variables reported by individual value

Overall, 50 patients (50%) presented with community-acquired hyponatremia. They were significantly older [66.5 (57.0, 72.0) versus 59.0 (46.3, 66.5) years, p=0.011], presented with significantly higher frequency of severe symptomatic hyponatremia (40% versus 6%, p<0.001), and showed significantly lower SNa-levels [121.0 (115.2, 127.0) versus 128.5 (124.0, 132.0) mmol/L, p<0.001] (Table 1). Twenty patients had vomiting, and three patients had alteration of consciousness during severe symptomatic hyponatremia diagnosis.

Etiology of hyponatremia

The three most common etiologies of hyponatremia included the syndrome of inappropriate antidiuresis (SIAD) (39%), hypovolemia (37%), and hydrochlorothiazide use (6%). Among patients with hospital-associated hyponatremia, SIAD was the most common etiology (60%). In contrast, among patients with community-acquired hyponatremia, hypovolemia was the most common etiology (48%) (Figure 1). Etiologies of hyponatremia were significantly different between patients with community-acquired hyponatremia and those with hospital-associated hyponatremia (p<0.001). The authors attempted to analyze patient clinical data and laboratory values according to the etiology of hyponatremia (Table 2). However, the present study was not designed to perform such an analysis, therefore, the p-value could not be estimated.

Factor associated with severe symptomatic hyponatremia

Twenty-three patients presented with severe symptomatic hyponatremia, which were older [68.0 (59.5, 72.0) versus 60.0 (48.0, 68.0) years, p=0.022] and showed lower SNa-levels [118.2±8.9 versus 125.8±5.8 mmol/L, p<0.001] than the patients in other groups (Table 3). Univariate logistic regression analysis revealed associations of severe symptomatic hyponatremia with old age (p=0.034), low SNa-levels (p<0.001), and the community-acquired form (p<0.001). Multivariate logistic regression revealed associations of severe symptomatic hyponatremia with low SNa-levels (increasing 1 mmol/L of SNa: adjusted odds ratio [OR] 0.90, 95% confidence interval [CI] 0.83 to 0.98, p=0.011] and the community-acquired form (adjusted OR 5.37, 95% CI 1.35 to 21.28, p=0.017) (Table 4).

Treatment and mortality

Twenty-three patients with severe symptomatic

Table 3. Clinical characteristics according to the hyponatremia grade (severe symptomatic vs. moderately symptomatic or asymptomatic hyponatremia)

	Severe n (%)	Non-severe n (%)	p-value
Number of patients	23	77	
Age (years); median (Q1, Q3)	68.0 (59.5, 72.0)	60.0 (48.0, 68.0)	0.022
Sex: female	15 (65.2)	46 (59.7)	0.819
Malignancy	4 (17.4)	17 (22.1)	0.775
Weight (kg); median (Q1, Q3)	54.0 (47.5, 65.0)	52 (46.0, 60.0)	0.563
BMI (kg/m^2); median (Q1, Q3)	20.0 (17.4, 22.5)	20.8 (18.0, 22.4)	0.652
SIAD	7 (30.4)	30 (39.0)	0.619
SNa (mmol/L); mean±SD	118.2±8.9	125.8±5.8	<0.001
Community-associated	20 (87.0)	30 (39.0)	<0.001

BMI=body mass index; Q=quartile; SD=standard deviation; SIAD=syndrome of inappropriate antidiuresis; SNa=serum sodium

Table 4. Univariate and multivariate logistic regression analyses of factors associated with severe symptomatic hyponatremia

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.05 (1.00 to 1.09)	0.034	1.03 (0.98 to 1.08)	0.273
Sex: female	0.79 (0.30 to 2.09)	0.637	-	-
Malignancy	0.74 (0.22 to 2.48)	0.629	-	-
Weight (kg)	1.02 (0.98 to 1.06)	0.447	-	-
BMI (kg/m^2)	0.97 (0.86 to 1.11)	0.693	-	-
SIAD	0.69 (0.25 to 1.86)	0.459	-	-
SNa (mmol/L)	0.86 (0.80 to 0.93)	<0.001	0.90 (0.83 to 0.98)	0.011
Community-associated	10.44 (2.85 to 38.21)	<0.001	5.37 (1.35 to 21.28)	0.017

BMI=body mass index; CI=confident interval; OR=odds ratio; SIAD=syndrome of inappropriate antidiuresis; SNa=serum sodium

hyponatremia were treated by hypertonic solution initially. After symptoms recovery, they were treated as etiology of hyponatremia. All SIAD patients were restricted in fluid intake. Twelve SIAD patients were prescribed diuretic to increase free water clearance (11 patients, loop diuretic and one patient, vasopressin-2 receptor antagonist). The intravenous isotonic solution was the treatment of all hypovolemic patients and low solute intake. The half strength of isotonic solution was switched to isotonic solution in four cases. The medications suspected to cause hyponatremia, especially hydrochlorothiazide, were stopped. The glucocorticoid replacement and thyroid hormone replacement were started in adrenal insufficiency and hypothyroidism patients, respectively. The in-hospital mortality was two patients of community-acquired hyponatremia and both had advanced malignancy.

Discussion

The present study was conducted to explore the characteristics of hyponatremia in an urban community in a developing Asian country. The authors noted that SIAD, hypovolemia, and hydrochlorothiazide use were the three most common etiologies of hyponatremia among hospitalized patients. As expected, patients with community-acquired hyponatremia differed from those with hospital-associated hyponatremia in terms of age, frequency of severe symptomatic hyponatremia, SNa-levels, and hyponatremia etiology. Moreover, the authors provided clues regarding clinical manifestations and laboratory values for differential diagnosis of the etiology of hyponatremia. However, the authors did not present specific tests or clinical characteristics for defining hyponatremia etiology. Furthermore, low SNa-levels and the community-acquired form were

associated with severe symptomatic hyponatremia.

A previous study from Turkey has reported that thiazide use was the leading cause of hyponatremia (48.7%, 37/76) among outpatients diagnosed with hyponatremia on admission[24]. Conversely, in the present study, hydrochlorothiazide use was the third leading cause of community-acquired hyponatremia. This result might be associated with the pattern of hypertension treatment followed by the physicians. The popularity of thiazide has reduced in Thailand. Recently, practice guidelines have recommended the use of calcium channel blockers and renin-angiotensin-aldosterone inhibitors over the use of thiazide. In the present study, hypovolemia was the leading cause of community-acquired hyponatremia, although the present study hospital is located at the center of the country. This finding reflects the need for improving health awareness and knowledge of people in the country. Regarding hospital-associated hyponatremia, SIAD was the most commonly identified etiology[25,26]. Reportedly, hospitalized patients are at risk of developing impaired water diuresis owing to the presence of factors, such as medication, pain, severe nausea, and organ failure, and the present study findings are consistent with this report. Moreover, the frequency of severe symptoms was lower but SNa-level was higher in patients with hospital-associated hyponatremia than in community-acquired hyponatremia. These findings may be attributed to frequent laboratory assessments and clinical monitoring during hospitalization. Nevertheless, iatrogenic hypotonic infusion remains an important etiology of hyponatremia[25].

The authors found that SNa-levels and community-acquired hyponatremia were associated with severe symptomatic hyponatremia. These results may be explained by the fact that patients visit the hospital when they experience symptoms. Additionally, community-acquired hyponatremia was associated with low SNa-levels. Theoretically, the rate of SNa-level decline is a crucial pathophysiological factor for symptoms related to the brain's adaptation failure. However, in the present study, the authors could not establish the last time point at which the SNa-level was normal, particularly in the community setting, and this is consistent with real-world practice. Thus, estimating the rate of SNa-level decline remains challenging. Nonetheless, SNa-level may trigger physicians to suspect severe symptomatic hyponatremia. Similar results have been noted in previous studies[24,26]. The study of Tasdemir et al[24] had reported that thiazide use was associated with severe symptoms. However, the authors did not identify such association, perhaps, because the incidence of thiazide-induced hyponatremia was low in the present cohort.

Previous studies reported that the incidence of hyponatremia was 15% to 20% among hospitalized patients[4,20]. In addition, a retrospective cohort study from China had reported that the overall prevalence of hyponatremia at some point during hospitalization was 17.5%. However, only 0.26% of the patients were diagnosed as having hyponatremia over a period of four years[1]. Therefore, the incidence in the present study appears to be lower than that reported previously, perhaps, because some patients in the present study, specifically those with mild or asymptomatic hyponatremia, did not consult a nephrologist.

The present study has several strengths. All diagnoses were confirmed by a nephrologist, and similar diagnostic guidelines were followed by all nephrologists. However, the present study might not have included all hospitalized patients with hyponatremia because the authors enrolled only the patients with hyponatremia consulted by a nephrologist. Thus, patients with other etiologies (e.g., congestive heart failure and cirrhosis) and those with asymptomatic hyponatremia who did not consult a nephrologist might not have been included in the present study, which is an important limitation.

Conclusion

SIAD, hypovolemia, and hydrochlorothiazide use are among the leading etiologies of hyponatremia. Low SNa-levels and the community-acquired form are associated with severe symptomatic hyponatremia. Thus, physicians should pay close attention to low SNa-levels in hospitalized patients and should, thereby, adopt appropriate treatment approaches.

What is already known on this topic?

Hypovolemia, SIAD, and diuretic use are already known as the most common etiology of hyponatremia in other countries.

What this study adds?

The authors confirmed that the etiology of hyponatremia of Thailand is the same. The authors also report the different rankings of the etiology of hyponatremia between community-acquired hyponatremia and hospital-associated hyponatremia. This study provides factors that associate with severe

symptomatic hyponatremia, which are SNa-level and community setting.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Hao J, Li Y, Zhang X, Pang C, Wang Y, Nigwekar SU, et al. The prevalence and mortality of hyponatremia is seriously underestimated in Chinese general medical patients: an observational retrospective study. BMC Nephrol 2017;18:328.
2. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med 2013;126:256-63.
3. Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. Am J Med 2013;126:1127-37.
4. Holland-Bill L, Christiansen CF, Heide-Jorgensen U, Ulrichsen SP, Ring T, Jorgensen JO, et al. Hyponatremia and mortality risk: a Danish cohort study of 279 508 acutely hospitalized patients. Eur J Endocrinol 2015;173:71-81.
5. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med 2006;119: S30-S35.
6. Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. Semin Nephrol 2009;29:227-38.
7. Ayus JC, Fuentes NA, Negri AL, Moritz ML, Giunta DH, Kalantar-Zadeh K, et al. Mild prolonged chronic hyponatremia and risk of hip fracture in the elderly. Nephrol Dial Transplant 2016;31:1662-9.
8. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 2006;119:71-8.
9. Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, et al. Mild hyponatremia as a risk factor for fractures: the Rotterdam Study. J Bone Miner Res 2011;26:1822-8.
10. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. N Engl J Med 1987; 317:1190-5.
11. Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. BMJ 1992;304:1218-22.
12. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med 1992;117:891-7.
13. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA 1999;281:2299-304.
14. Elmi G, Zaccaroni S, Arienti V, Faustini-Fustini M. Prevalence and in-hospital mortality of hyponatremia: a cohort study. Eur J Intern Med 2014;25:e45-e46.
15. Friedman B, Cirulli J. Hyponatremia in critical care patients: frequency, outcome, characteristics, and treatment with the vasopressin V2-receptor antagonist tolvaptan. J Crit Care 2013;28:219-12.
16. Gankam-Kengne F, Ayers C, Khera A, de Lemos J, Maalouf NM. Mild hyponatremia is associated with an increased risk of death in an ambulatory setting. Kidney Int 2013;83:700-6.
17. Gómez-Hoyos E, Cuesta M, Del Prado-González N, Matía P, Pérez-Ferre N, De Luis DA, et al. Prevalence of Hyponatremia and Its Associated Morbimortality in Hospitalized Patients Receiving Parenteral Nutrition. Ann Nutr Metab 2017;71:1-7.
18. Sajadieh A, Binici Z, Mouridsen MR, Nielsen OW, Hansen JF, Haugaard SB. Mild hyponatremia carries a poor prognosis in community subjects. Am J Med 2009;122:679-86.
19. Sturdik I, Adamcova M, Kollerova J, Koller T, Zelinkova Z, Payer J. Hyponatraemia is an independent predictor of in-hospital mortality. Eur J Intern Med 2014;25:379-82.
20. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 2009;122:857-65.
21. Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, et al. Characteristics and mortality of severe hyponatraemia--a hospital-based study. Clin Endocrinol (Oxf) 2006;65:246-9.
22. Kidney disease: Improving global outcomes (KDIGO). KDIGO clinical practice guideline for acute kidney injury. Kidney int Suppl 2012;2:1-138.
23. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant 2014;29 Suppl 2:i1-39.
24. Tasdemir V, Oguz AK, Sayin I, Ergun I. Hyponatremia in the outpatient setting: clinical characteristics, risk factors, and outcome. Int Urol Nephrol 2015;47:1977-83.
25. Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985;102:164-8.
26. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. Intern Med J 2010;40:574-80.