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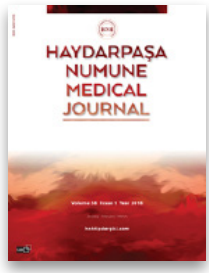

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ORIGINAL ARTICLE

Hospital-acquired Hyponatremia: Risk Factors and Outcomes

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Abstract

Introduction: Hyponatremia is the most common electrolyte disorder. This study aims to specify the clinical and demographical features of the patients who have a hospital- acquired hyponatremia, to identify the risk factors and to analyze the effects of these factors on clinical outcomes.

Methods: This study was conducted retrospectively over a one-year period between 2012-2013 at Haydarpasa Numune Research and Education Hospital on 133 patients who developed hyponatremia during the hospitalization for any kind of reasons. The clinical features of the patients, comorbid diseases, symptoms related to hyponatremia, pathophysiological causes of hyponatremia and treatments that could be related to hyponatremia were also identified and the relationship between all above and plasma sodium concentrations, hospital length of stay, also mortality was investigated.

Results: Among the 133 patients (median age 69.0 years) included to this study whose length of stay was between 2 -150 days, according to minimum plasma sodium concentrations (median 125.0 mEq/L), the overall incidence of mild hyponatremia was 8.3%; moderate hyponatremia 46.6% and severe hyponatremia was 45.1%. It was observed that 33.8% of the patients developed symptoms related to hyponatremia and also 100% of the patients who developed coma were classified as severe hyponatremia. The ratio of normalized hyponatremia was 27.1% and the overall mortality was 28.6%. Mortality was 83.3% among the patients who developed coma (p=0.007) and 71.4% who had dementia (p=0.020).

Discussion and Conclusion: The findings showed that mortality rates were higher among the patients who developed coma, and who had dementia as a comorbid disease. We believe that this study will be a guide for further case-controlled, prospective studies that can explain the relationship between hospital-related hyponatremia and comorbid diseases.

Keywords: Hospital-acquired hyponatremia; mortality; risk factors.

Hyponatremia is defined as serum sodium levels below 135 mEq/L [1]. Hyponatremia is the most common electrolyte disorder in general medical practice [2]. This electrolyte disorder [3], which is observed in 30% of the hospitalized patients, remains a problem for clinicians with a range of mild to severe and even life-threatening clinical findings.

Several studies have reported that mortality rates associated with hospital-acquired hyponatremia range from 9% to 51% in several studies [4]. This undesirable outcome may be due to brain edema which is the direct complication of hyponatremia, or it may arise from osmotic demyelination syndrome, which may develop during its rapid correction, or it may occur as a result of its adverse effect with a potential to affect the course of a serious underlying disease.

Acute hyponatremia has different etiologies concerning volume status. However, a limited number of studies has

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been performed on the search for factors contributing to hospital-acquired hyponatremia in the general patient population. This study aims to investigate the demographic and clinical characteristics of the patients with hospital-acquired hyponatremia and to determine the relationship between hyponatremia and related mortality after the treatment they received before the development of hyponatremia.

Materials and Methods

This study was conducted retrospectively on 133 patients who developed hyponatremia during patient treatment in inpatient wards of our hospital between 2012 and 2013 for any reason. The data of adult patients who met the inclusion criteria were obtained from the hospital registry system. Exclusion criteria were as follows: the presence of hyponatremia at the time of hospitalization, failure to control sodium levels after the development of hyponatremia, pseudohyponatremia and being younger than 18 years.

Information of the patients, including age (year), sex, duration of hospital stay in days, Na value (mEq/L) measured at admission, the final Na (mEq/L) measurement during hospitalization, the presence of comorbid diseases (hypertension, diabetes mellitus, malignancy, chronic renal failure, congestive heart failure, coronary artery disease, previous SVO, dementia, hypothyroidism, nephrotic syndrome, COPD, cirrhosis), which might contribute directly or indirectly to hyponatremia, the presence or absence of symptoms developed due to hyponatremia (nausea, vomiting. confusion, coma) and whether hospitalizations ended with mortality were recorded.

As evaluation parameters, the hyponatremia threshold was considered to be less than 135 mEq/L, and the patients were divided into three groups in light of the recommendations of the most current guideline described by "Hyponatraemia Guideline Development Group (HGDG)" at the beginning of 2014 as mild (130-135 mEq/L), moderate (125-129 mEq/L) in light of and severe (<125 mEq/L) hyponatremia. The improvement was determined as the final measured sodium value exceeding 135 mEq/L.

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. In addition to descriptive statistical methods (median, range), Mann-Whitney U test was used for the comparison of two independent groups, and Kruskal Wallis Test was employed for comparisons between more than two independent groups. The Pearson Chi-Square Test, Yates Continuity Correction Test, or Fisher's Full Probability Tests were used to compare qualitative data between groups. Shapiro-Wilk test was used to evaluate the fitness of continuous variables to a normal distribution, and Pearson Correlation Analysis was employed to assess correlations between parametric variables and Spearman Correlation Analysis for nonparametric variables.

The results were expressed within a 95% confidence interval and $p<0.05$ level of significance.

Results

Sixty-nine (51.9%) female and 64 (48.1%) male patients who developed hyponatremia during hospitalization (total n=133) were included in this study. Median age of the patients was 69.0 years (min. 18 and max. 94 years) and median hospitalization period was 21.0 days (min. 2, and max. 150 days) (Table 1).

The lowest, and highest Na values of the patients measured during their hospitalization period were 101 mEq/L and 131 mEq/L (median: 125.0), respectively. The patients had mild (n=11: 8.3%), moderate (n=6246.6%) and severe (n=60 : 45.1%) hyponatremia (Fig. 1).

Table 1. Patient characteristics

	Min - Max	Median (Range)
Age (years)	18 - 94	69.0 (76)
Duration of the hospital stay (days)	2 - 150	21.0 (148)
The lowest Na (mEq/l)	101 - 133	125.0 (30)
	n	**%**
Female	69	51.9
Male	64	48.1
Mild Hyponatremia	11	8.3
Moderate Hyponatremia	62	46.6
Severe Hyponatremia	60	45.1

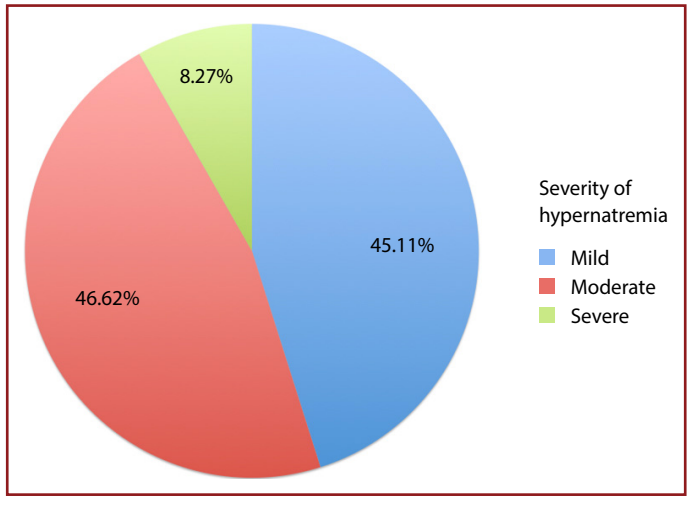

Figure 1. Distribution of the patients according to sodium levels.

In 45 (33.8%) of the patients, at least one of the symptoms (nausea, vomiting, confusion, coma) that was thought to be related to hyponatremia developed after hyponatremia. Fifty-one (82.3%) of 62 patients with moderate hyponatremia were asymptomatic (p=0.001); six (100.0%) of six patients with coma included in severe hyponatremia group (p=0.022) (Table 2).

The distribution of comorbid diseases according to the severity of hyponatremia is shown in Table 2. Seven (63.6%) out of 11 patients in the mild hyponatremia group had Chronic Renal Failure (p=0.009).

The proportional relationship of comorbid diseases to each other and to the severity of hyponatremia is also shown in Figure 2.

Thirty-six (27.1%) of the 133 patients had normal control sodium at follow-up and 97 were still hyponatremic before death or discharge. In addition, 38 patients (28.6%) died during the follow-up period (Table 3).

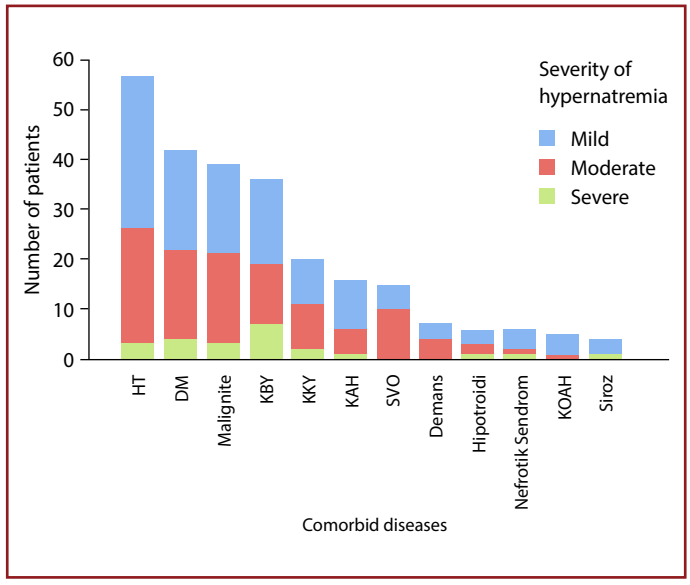

Figure 2. Distribution of comorbid diseases according to the severity of hypernatremia.

Table 2. The relationship between clinical characteristics and risk factors with hyponatremia

	Total (n=133) n (%)	Mild (n=11) n (%)	Moderate (n=62) n (%)	Severe (n=60) n (%)	p
			General Characteristics		
Age, med (range) (years)	69.0 (76)	64.0 (41)	69.5 (71)	71.0 (76)	[a]0.290
Hospital stay, med (range) (days)	21.0 (148)	16.0 (58)	23.0 (148)	23.5 (75)	[a]0.151
M/F	64/69	2/9	28/34	34/26	[a]0.520
			Symptoms		
Nausea	27 (20.3)	3 (11.1)	7 (25.9)	17 (63.0)	[b]0.054
Vomiting	20 (15.0)	3(15.0)	5(25.0)	12 (60.0)	[b]0.090
Confusion	20 (15.0)	1 (5.0)	5 (25.0)	14 (70.0)	[b]0.052
Coma	6 (4.5)	0(0.0)	0 (0.0)	6 (100.0)	[b]0.022*
Asymptomatic	88 (66.2)	7 (63.6)	51 (82.3)	30 (50.0)	[b]0.001**
			Comorbid Diseases		
Hypertension	57 (42.9)	3 (27.3)	23 (37.1)	31 (51.7)	[b]0.147
Diabetes Mellitus	42 (31.6)	4 (36.4)	18 (29.0)	20 (33.3)	[b]0.824
Malignancy	39 (29.3)	3 (27.3)	18 (29.0)	18 (30.0)	[b]0.981
Chronic Renal Failure	36 (27.1)	7 (63.6)	12 (19.4)	17 (28.3)	[b]0.009*
Heart Failure	20 (15.0)	2 (18.2)	9 (14.5)	9 (15.0)	[b]0.952
Coronary Artery Disease	16(12.0)	1 (9.1)	5 (8.1)	10 (16.7)	[b]0.328
Previous CVE	15 (11.3)	0 (0.0)	10 (16.1)	5 (8.3)	[b]0.185
Dementia	7 (5.3)	0 (0.0)	4 (6.5)	3 (5.0)	[b]0.672
Hypothyroidism	6 (4.5)	1 (9.1)	2 (3.2)	3 (5.0)	[b]0.668
Nephrotic Syndrome	6 (4.5)	1 (9.1)	1 (1.6)	4 (6.7)	[b]0.302
COPD	5 (3.8)	0 (0.0)	1 (1.6)	4 (6.7)	[b]0.270
Cirrhosis	4 (3.0)	1 (9.1)	0 (0.0)	3 (5.0)	[b]0.127

[a]Mann-Whitney U Test; [b]Pearson Chi-square test; [c]Fisher's Exact Test; *p<0.05; **p<0.001.

Table 3. Improvement in sodium levels and mortality rates

	Absence		Presence	
	n	%	n	%
Improvement	97	72.9	36	27.1
Mortality	95	71.4	38	28.6

The changes in the control sodium values measured before discharge or death of the patients compared to the lowest sodium values are shown in Figure 3. It is seen that control sodium levels did not increase in some patients. In some patients, they reached normal range and in others, hypernatremia developed.

The relationship between demographic and clinical characteristics and mortality is summarized in Table 4. There was no statistically significant relationship between demographic characteristics, length of hospital stay, lowest Na value measured, etiologic factors, and mortality. However, when the relationship between symptoms and mortality was examined, five (83.3%) of the six patients with coma (p=0.007) exited. When the relationship between comorbid diseases and mortality was examined, five (71.4%) of the seven patients with dementia exited (p=0.020).

Mortality rates related to comorbid diseases and intergroup comparisons of mortality rates are summarized in Figure 4. Proportionally high mortality rates among dementia patients are immediately noticeable.

Discussion

In this retrospective study, we aimed to determine the relationship between hospital-acquired hyponatremia and risk factors and mortality. When the results were evaluated, it was observed that each of the treatments that were applied by clinicians for various reasons which might cause hyponatremia prolonged the duration of hospitalization and that the development of hyponatremia on the basis of dementia led a more mortal course more mortal compared to other comorbid conditions as previously undefined findings.

Most of the studies performed so far with inpatient hyponatremic patients have focused on groups of patients with hyponatremia present at admission [5–7] or with severe hyponatremia [2, 8, 9, 10]. In this study, the characteristics of an unselected group with only hospital-acquired hyponatremia have been demonstrated.

The most comprehensive study on this subject was retrospectively conducted by Ron Wald et al. [11] in 2010 involving a population of 29904 (38.2% of total admissions) patients and 53236 hospitalizations due to hospital-acquired hyponatremia observed among 8341 patients, and 10662 hospitalizations. Priorly, Ewout J. Hoorn et al. [10] in 2006 and Carolien M. Beukhof et al. in 2007 investigated the relationship between hospital-acquired hyponatremia and comorbid diseases and mortality. The characteristics and comparative findings of these studies are summarized in Table 5.

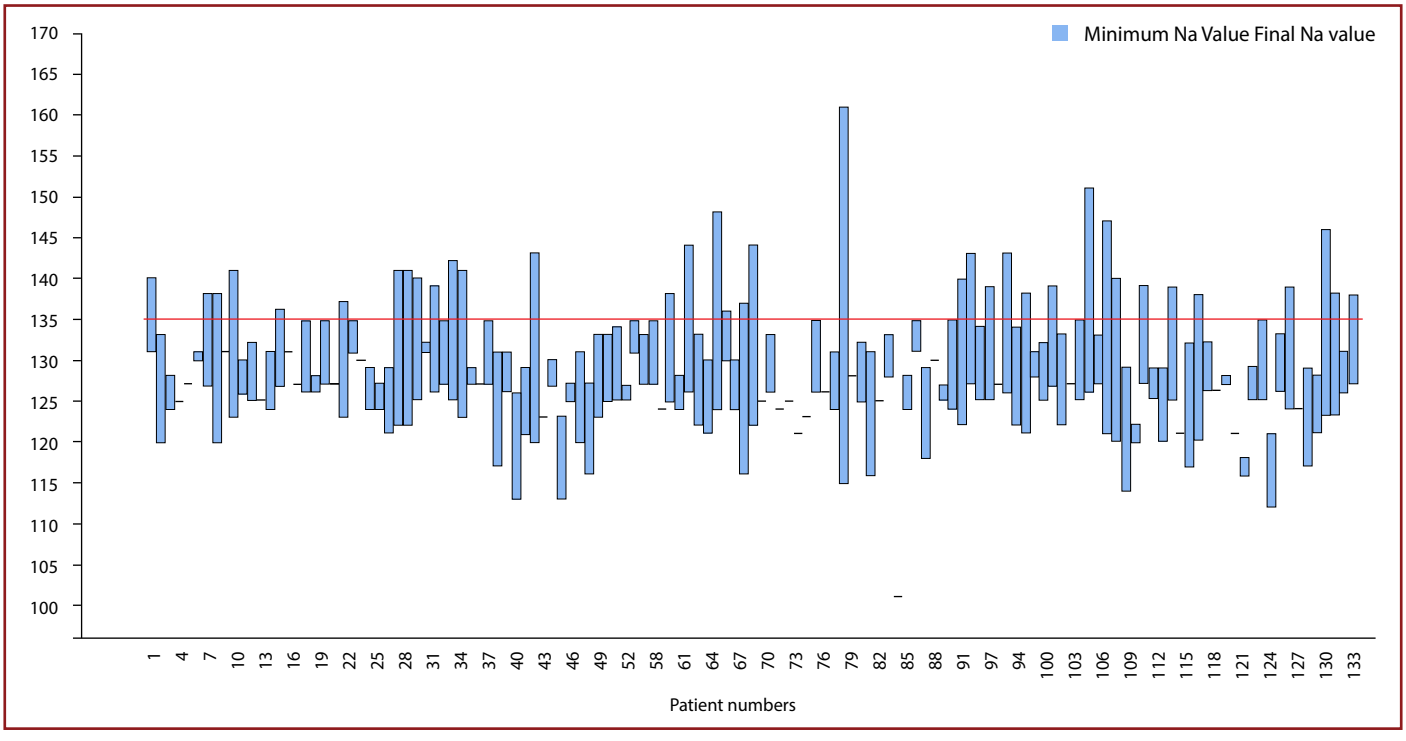

Figure 3. The lowest and the final control values of blood sodium.

Table 4. Relationship between mortality rates, clinical characteristics and risk factors

	Total (n=133) n (%)	Mortality absence (n=95) n (%)	Mortality presence (n=38) n (%)	p
		General Characteristics		
Age, med (range)	69.0 (76)	69.0 (76)	69.5 (62)	[a]0.913
Hospital stay, med (range) (days)	21.0 (148)	21.0 (148)	24.5 (91)	[a]0.790
The lowest Na value, med (range) mEq/L	125.0 (30)	125.0 (18)	125.0 (30)	[a]0.863
M/F	64/69	42/53	22/16	[a]0.217
		Symptoms		
Nausea	27 (20.3)	21 (77.8)	6 (22.2)	[b]0.562
Vomiting	20 (15.0)	16 (80.0)	4 (20.0)	[b]0.514
Confusion	20 (15.0)	12 (60.0)	8 (40.0)	[b]0.338
Coma	6 (4.5)	1 (16.7)	5 (83.3)	c0.007*
Asymptomatic	88 (66.2)	63 (71.6)	25 (28.4)	[b]1.000
		Comorbid Diseases		
Hypertension	57 (42.9)	45 (78.9)	12 (21.1)	[b]0.142
Diabetes Mellitus	42 (31.6)	29 (69.0)	13 (31.0)	[b]0.836
Malignancy	39 (29.3)	25 (26.3)	14 (36.8)	[b]0.320
Chronic Renal Failure	36 (27.1)	28 (77.8)	8 (22.2)	[b]0.440
Heart Failure	20 (15.0)	14 (70.0)	6 (30.0)	[b]1.000
Coronary Artery Disease	16 (12.0)	14 (87.5)	2 (12.5)	[c]0.153
Previous CVE	15 (11.3)	8 (53.3)	7 (46.7)	[c]0.129
Dementia	7 (5.3)	2 (28.6)	5 (71.4)	[c]0.020*
Hypothyroidism	6 (4.5)	6 (100.0)	0 (0.0)	[c]0.182
Nephrotic Syndrome	6 (4.5)	6 (100.0)	0 (0.0)	[c]0.182
COPD	5 (3.8)	5 (100.0)	0 (0.0)	[c]0.321
Cirrhosis	4 (3.0)	1 (25.0)	3 (75.0)	[c]0.070

[a]Mann-Whitney U Test; [b]Yates Cotinuity Test; [c]Fisher's Exact Test.

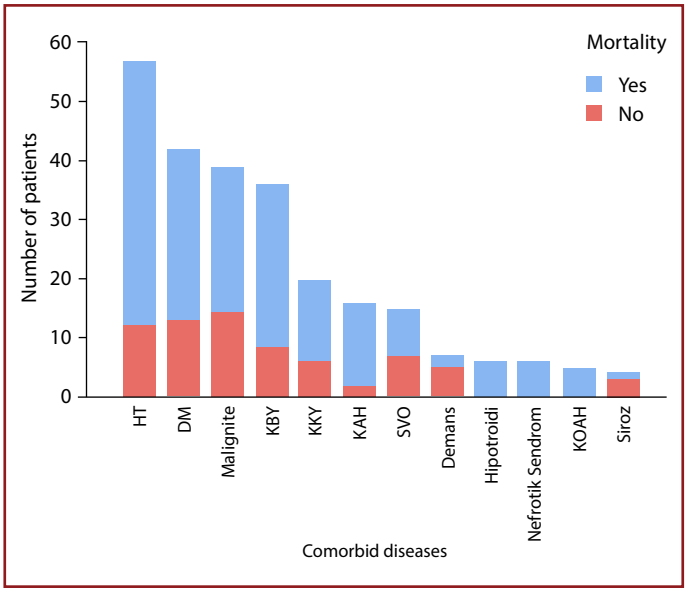

Figure 4. Relationship between comorbid diseases and mortality.

Compared to this study, the mortality rate is quite low in other studies. This condition may be partly and appropriately explained with the mean age of the patients in the study by Beukhof et al., the upper limit of sodium and rates of comorbid diseases in the study of Wald et al., and the limited number of patients and comorbid disease rates in Hoorn's study. However, explaining the differences in mortality rates may not be possible with these data alone. As previously mentioned in the editorial letter of Ewout J. Hoorn and Robert Zietse, the relationship between hyponatremia and mortality is more complex than a simple cause-effect relationship [13], and its explanation may only be possible in prospective and case-controlled studies to be conducted with a greater number of patients. On the other hand, hyponatremia increases the mortality rates for some comorbid diseases both by adversely affecting the course of the disease and by various conditions caused by it. The most important of these are heart failure, coronary

Table 5. Studies where patients with hospital-acquired hyponatremia were included, and comparative characteristics of this study

	Index	Wald	Beukhoff	Hoorn
Years	2014	2010	2007	2006
Study type	Retrospective	Retrospective	Prospective	Prospective
Control	No	Yes	Yes	No
Number of patients	133	10662	50	36
Hospital stay (mean) (days)	21	7.6	-	30.7
Age (mean) (years)	69	69	57	64
Upper limit of Na (mean) mEq/L	135	138	136	125
F/M (%)	52/48	50/50	46/54	46/54
Symptomatic (%)	18.7	-	-	33
Mortality (%)	28.6	2.9	12	14
Diabetes mellitus (%)	31.6	17.2	32	-
Coronary artery disease (%)	12	13.8	-	-
Heart failure (%)	15	21.7	12	17
Cerebrovascular event (%)	11.3	4.7	12	-
COPD (%)	3.8	21.5	-	-
Chronic renal failure (%)	27.1	3.6	-	33
Hepatic failure (%)	3.0	1.7	10	11
Malignancy (%)	29.3	7.0	38	-
Dementia (%)	5.3	1.1	-	-

artery disease, cirrhosis and malignancy.

In a subanalysis of the OPTIMIZE-HF study, Mihai Gheorghiade et al. [14] demonstrated that hyponatremia prolonged hospitalization and increased early mortality rates in inpatients treated for heart failure after hospitalization and after discharge. Goldberg et al. [15] reported that hyponatremia in the early phase of ST-elevation myocardial infarction is a predictor of both long-term mortality and admission with post-discharge heart failure. Kim et al. [16] demonstrated that hyponatremia is an important indicator of survival in a study of liver transplant candidates.

Sersté et al. [17] found that severe hyponatremia was a better predictor of mortality than the MELDNa score in patients with cirrhosis or treatment- refractory ascites. Doshi showed that hyponatremia prolongs hospitalization and increases mortality in cancer patients in a study performed in 3357 cancer patients [18]. In light of all this information, any statistically significant relationship between the above-mentioned comorbid diseases and mortality could not be detected in this study. However, in the studies reported above, not all of the patient groups are composed of patients with hospital-acquired hyponatremia.

To our knowledge, this is the first study that revealed that mortality rates were higher in patients with hyponatremic and patients with dementia, which has not been reported so far in any study.

When the relationship between symptoms and mortality is considered, it is not surprising that all patients with coma in this study were in the severe hyponatremia group, or the mortality rate was very high in these patients. Although HGDG has identified severe symptoms associated with mortality in its most current guideline as hyponatremia, vomiting, cardiopulmonary stress, abnormal and severe drowsiness, seizures and coma [19].

The information retrospectively obtained in this study about the symptoms does not include the findings listed above. Inclusion of the patients followed up in the intensive care unit and the difficulty of detecting the presence of mild symptoms in these patients are among the limitations of this study. In addition, these findings may not be attributed to hyponatremia in patients with many comorbidities and it is also difficult to make a differential diagnosis.

Because no signs of hyponatremia are specific, a prospective study without comorbid factors will determine the range of symptoms more clearly and perhaps increase the prognostic value of hyponatremia.

In this study, the findings showed that moderate hyponatremia group was significantly asymptomatic. In fact, the concept of "symptomatic" in this study included only four findings included in this study and patients who did not show any of these findings were evaluated in the asymptomatic group. However, as mentioned in the latest HGDG guideline, there is no "asymptomatic" hyponatremic patient in the full sense of the word [19]. Benoit Rennoboug et al. demonstrated the presence of concentration disorders

even at the mildest levels of hyponatremia [20].

In conclusion, it is thought that the results of this study shed light on the future concerning identifying patients at risk for hyponatremia and determining appropriate approaches for treatment and follow-up, shortening hospitalization times and preventing hospital-acquired hyponatremia-related deaths.

Conclusion

In a retrospective study of the etiology and clinical course of hospital-acquired hyponatremia, data from 133 patients were evaluated and the following conclusions were reached in the present study:

In this study, the mortality rate observed in patients with hospital-acquired hyponatremia was found to be higher than the relevant previous studies. The reason for this may be the differences in study designs and the characteristics of the patient populations.

It was observed that all patients with hyponatremic coma were in severe hyponatremia group and had a very high mortality rate.

Mortality rates were found to be significantly increased in the presence of hospital-acquired hyponatremia in dementia patients. However, to fully explain the relationship between comorbid diseases and hyponatremia, conduction of case-controlled, prospective studies with larger-scale patient populations may be guiding.

In the light of these results, it has been concluded that appropriate and individual treatment approaches, and especially avoiding hypotonic fluids will be guiding for future medical applications in the prevention of hospital-acquired hyponatremia and its complications.

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: G.S., R.D.; Design: G.S., K.K.; Data Collection or Processing: Z.E.D., M.T.; Analysis or Interpretation: G.S., Z.E.D.; Literature Search: Y.Ö., S.T.; Writing: Z.E.D., Y.Ö., S.T.

Conflict of Interest: None declared.

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