Long-term outcome of profound hyponatremia: a prospective 12 months follow-up study

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Abstract

Background: Hyponatremia is the most common electrolyte abnormality in hospitalized patients and given its impact on mortality and morbidity, a relevant medical condition. Nevertheless, little is known about factors influencing long-term outcome.

Methods: This is a prospective observational 12-month follow-up study of patients with profound hyponatremia (≤ 125 mmol/L) admitted to the emergency department of two tertiary care centers between 2011 and 2013. We analyzed the predictive value of clinical and laboratory parameters regarding the following outcomes: 1-year mortality, rehospitalization and recurrent profound hyponatremia.

Results: Median (IQR) initial serum sodium (s-sodium) level of 281 included patients was 120 mmol/L (116–123). During the follow-up period, 58 (20.6%) patients died. The majority (56.2%) were rehospitalized at least once. Recurrent hyponatremia was observed in 42.7%, being profound in 16%. Underlying comorbidities, assessed by the Charlson Comorbidity Index, predicted 1-year mortality (odds ratio (OR) 1.43, 95% confidence interval (CI) 1.25–1.64, $P < 0.001$). Furthermore, 's-sodium level at admission' (OR 1.14, 95% CI 1.01–1.29, $P = 0.036$) and 'correction of hyponatremia' defined as s-sodium ≥ 135 mmol/L at discharge were associated with mortality (OR 0.47, 95% CI 0.23–0.94, $P = 0.034$). Mortality rate fell with decreasing baseline s-sodium levels and was lower in the hyponatremia category ≤ 120 mmol/L vs > 120 mmol/L (14.8% and 27.8%, $P < 0.01$). Patients with s-sodium level ≤ 120 mmol/L were more likely to have drug-induced hyponatremia, whereas hypervolemic hyponatremia was more common in patients with s-sodium > 120 mmol/L.

Conclusion: Hyponatremia is associated with a substantial 1-year mortality, recurrence and rehospitalization rate. The positive correlation of s-sodium and mortality emphasizes the importance of the underlying disease, which determines the outcome besides hyponatremia itself.

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Introduction

Hyponatremia is the most common electrolyte abnormality in hospitalized patients (1). Prevalence for mild hyponatremia is up to 30–42%, depending on the health care setting and the patient population studied (2). Profound hyponatremia, defined as a serum sodium

(s-sodium) level < 125 mmol/L, is less common with a prevalence of 2–3% (3, 4).

Hyponatremia is associated with an increased in-hospital, short-, and long-term mortality both in hospitalized (5, 6, 7) and ambulatory patients (8, 9).

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An increased morbidity and mortality rate was shown especially in hyponatremic patients with medical conditions such as heart failure (10), myocardial infarction (11), liver cirrhosis (12), cancer (13), pneumonia (14) and stroke (15, 16).

Given the poor prognosis linked to hyponatremia, identification of modifiable factors in this context is of great interest. As highlighted by previous studies, hyponatremia per se may contribute to adverse outcome, which is reflected by a positive correlation of mortality and severity of hyponatremia (17, 18, 19, 20). Conversely, other studies observed a paradoxical fall in mortality rate as s-sodium values decreased below a certain level (e.g. <120mmol/L) (5, 19, 21). This indicates the presence of factors other than hyponatremia itself affecting mortality, e.g. etiology of hyponatremia, comorbidities or therapeutic issues. So far, in previous publications, these possible outcome parameters have not been precisely assessed and studied in a prospective manner, and especially in profound hyponatremia, data are scarce and controversial (7, 19, 21, 22).

The aim of this study was to prospectively explore the predictive value of different clinical, laboratory and therapeutic parameters regarding outcome in a broad, well-defined cohort of hospitalized patients with profound hyponatremia.

Methods

Study design

From June 2011 to August 2013, 298 patients with profound hyponatremia presenting to the medical emergency department of the University Hospital Basel and the University Medical Clinic Aarau in Switzerland were included in a prospective observational study, which as a primary endpoint aimed to evaluate plasma copeptin as a diagnostic marker in the differential diagnosis of profound hyponatremia. As a predefined secondary endpoint, we aimed to explore clinical outcome and outcome predictors of patients with profound hyponatremia after 12 months of study entry. Inclusion criteria were full legal age, initial s-sodium level ≤ 125 mmol/L and a serum osmolality below 280 mmol/kg. Patients with hyponatremia due to hyperglycemia or with age <18 years were excluded from the analysis. Study protocol was approved by the Ethics Committee of Basel and Aarau, and informed consent was obtained from all patients or in case of impaired mental state from their relatives.

Baseline data collection

Collected baseline data contained medical history, clinical examination (especially volume status) and specific laboratory testing including plasma and urine electrolytes, creatinine, osmolality, urea and uric acid. Furthermore, blood glucose, as well as thyroid-stimulating hormone and cortisol levels in unclear cases, were routinely measured.

Diagnostic and therapeutic approach

Initial diagnostic adjudication and treatment decisions were completely up to the attending physician and not influenced by the study team. Symptomatic hyponatremia was treated with hypertonic sodium chloride (3% NaCl) infusion irrespective of the underlining cause. Oligo- or asymptomatic patients were treated with either fluid restriction or fluid administration (0.9% NaCl infusion) according to the cause of hyponatremia. Vaptans were not used, as they are not approved in Switzerland.

The final classification of hyponatremia was done by experienced board-certified endocrinologists (not involved in patients' treatment and care) in a standardized fashion using the above-mentioned data collected at admission. Moreover, information regarding management during hospitalization and treatment response was also included in the final diagnosis.

Follow-up

Follow-up was done by a structured telephone interview 12 months after study entry. Interviews were performed by study doctors, study nurses or students. Patients and/or their respective family doctors were asked regarding rehospitalization and recurrent hyponatremia. Clinical report including laboratory findings was requested from every single rehospitalization to objectify information from phone interview and to get detailed information about circumstances of rehospitalization or eventually death.

Outcome measures and analyzed outcome predictors

We analyzed the influence of different laboratory and clinical parameters on three main outcomes: overall mortality, rehospitalization and recurrent profound hyponatremia. Besides 's-sodium level at admission', the following therapy-associated predictors were evaluated: 'ICU admission', 's-sodium correction rate' defined as

delta s-sodium from admission to 24 h later, 'correction of hyponatremia' defined as s-sodium level ≥ 135 mmol/L at discharge, 'hospital aggravated hyponatremia' defined as decrease in s-sodium level ≥ 2 mmol/L during the first 48 h after hospital admission, and 'overly rapid correction' as a s-sodium increment >12 mmol/L during first 24 h respectively >18 mmol/L during first 48 h. Furthermore, we analyzed whether etiology of hyponatremia or comorbidities assessed by the Charlson Comorbidity Index (CCI) were outcome predictors. The CCI is a comorbidity scoring system counting from 0 to 37 points, which allows to weigh disease severity according to the ICD-9-CM system (23, 24).

Because of controversial data regarding mortality according to hyponatremia severity, patients were divided in two categories (initial s-sodium level $\leq$ and >120 mmol/L) and were characterized in view of hyponatremia cause, therapy and outcome.

Statistics

For statistical analysis, all relevant clinical and laboratory parameters obtained by interview, clinical testing and reviewing of medical records were entered

Table 1 Baseline characteristics of 281 patients. Data are presented as % (n) and median (IQR: 25th–75th).

Characteristics	Values
Age (years)	72 (61–80)
Female	66.5% (187)
Systolic blood pressure (mmHg)	136 (119–155)
Heart rate (per minute)	80 (68–90)
Body temperature (°C)	37 (36.5–37.5)
GCS (Glasgow Coma Score)	15 (15–15)
BMI (kg/m ²)	23.8 (20.8–27.4)
Charlson Comorbidity Index	2 (1–5)
Etiology of hyponatremia	
Malignant SIAD	7.1% (20)
Non-malignant SIAD	54.1% (152)
SIAD drugs/diuretics	40.2% (113)
SIAD idiopathic	4.6% (13)
SIAD lung	3.2% (9)
SIAD cns	6% (17)
Hypervolemic hyponatremia	11.4% (32)
Heart failure	5.3% (15)
Liver failure	4.3% (12)
Kidney failure	1.8% (5)
Hypovolemic hyponatremia	19.9% (56)
Primary polydipsia	7.5% (21)
Laboratory findings	
S-sodium at hospital admission (mmol/L)	120 (116–123)
Plasma glucose (mmol/L)	6.6 (5.7–8.1)

BMI, body mass index.

into an Excel database. Data were analyzed using STATA (12.1, Texas 77845, USA) and GraphPad Prism 6.00 for Windows (San Diego, California, USA). Discrete variables are expressed as frequency (percentage), continuous variables as mean with standard deviation (s.d.) and non-continuous variables as medians with interquartile range (IQR). For data not normally distributed, Mann–Whitney *U* test was used for two-group comparison. Univariate and multivariate logistic regression analyses with two different models were performed. Both models were adjusted for age, CCI and s-sodium level at hospital admission. Model 1 was calculated for s-sodium ≥ 135 mmol/L at

Table 2 Follow-up and outcome data. Data are presented as % (n) and median (IQR: 25th–75th).

Therapeutic findings during initial hospitalization	
Delta s-sodium 24 h (mmol/L)	5 (2–8)
Overly rapid correction	7.1% (20)
Hospital aggravated hyponatremia	8.5% (24)
ICU admission	36.7% (103)
Laboratory findings at discharge	
S-sodium (mmol/L)	134 (130–137)
S-sodium ≥ 135 mmol/L	49.1% (138)
Outcome	
Overall mortality	20.6% (58)
In-hospital-mortality	3.9% (11)
30-day-mortality rate	31% (18)
Time to rehospitalization (days)	75 (21–206)
30-day-rehospitalization rate	18.5% (52)
Rehospitalization rate	56.2% (158)
- with hyponatremia during first rehospitalization	60.8% (96)
Recurrent rehospitalization	28.5% (80)
Recurrent hyponatremia	42.7% (120)
Recurrent profound hyponatremia (Na ≤ 125 mmol/L)	16% (45)
Cause of Mortality (n=58)	
Malignant disease	32.8% (19)
Unknown	24.1% (14)
Respiratory insufficiency	12.1% (7)
Heart failure	10.3% (6)
Septic shock	8.6% (5)
Liver failure	8.6% (5)
Renal failure	3.4% (2)
Cause of first rehospitalization (n=158)	
Infectious	18.4% (29)
Orthopedic/surgery	17.7% (28)
Hematological/oncological	11.4% (18)
Others	10.8% (17)
Neurologic	10.1% (16)
Gastrointestinal	9.5% (15)
Cardiovascular	7.6% (12)
Hyponatremia	6.3% (10)
Psychiatric	5.7% (9)
Pulmonary	2.5% (4)

BMI, body mass index.

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Table 3 Univariate analysis.

Predictors	Outcome 1 Mortality		Outcome 2 Rehospitalization		Outcome 3 Recurrent profound hyponatremia	
	ODDS (95% CI)	P value	ODDS (95% CI)	P value	ODDS (95% CI)	P value
Laboratory parameters						
S-sodium at admission	1.17 (1.05–1.3)	0.005	0.98 (0.90–1.07)	0.694	0.83 (0.73–0.95)	0.005
Etiology of hyponatremia						
Malignant SIAD	4.4 (1.73–11.15)	0.002	4.89 (1.4–17.1)	0.013	5.07 (1.96–13.1)	0.001
Non-malignant SIAD	0.43 (0.24–0.77)	0.005	1.00 (0.62–1.61)	0.998	0.95 (0.5–1.79)	0.866
Hypervolemic hyponatremia	3.07 (1.41–6.67)	0.005	0.58 (0.27–1.21)	0.144	0.5 (0.15–1.73)	0.278
Hypovolemic hyponatremia	0.79 (0.37–1.69)	0.546	0.74 (0.41–1.34)	0.320	0.45 (0.17–1.2)	0.109
Primary polydipsia	0.7 (0.2–2.48)	0.580	1.38 (0.53–3.62)	0.512	1.42 (0.45–4.51)	0.547
Therapeutic parameters						
S-sodium correction rate first 24 h	0.93 (0.87–1.00)	0.058	1.04 (0.98–1.09)	0.222	0.98 (0.91–1.06)	0.646
Hospital-aggravated hyponatremia	1.65 (0.65–4.18)	0.294	0.53 (0.23–1.25)	0.146	1.41 (0.5–4.01)	0.514
Correction of hyponatremia (≥ 135 mmol/L)	0.46 (0.25–0.84)	0.011	0.59 (0.36–0.94)	0.028	0.4 (0.2–0.79)	0.009
Comorbidities						
Charlson Comorbidity Index	1.49 (1.33–1.68)	<0.0001	1.07 (0.98–1.16)	0.157	1.1 (0.99–1.22)	0.087

Bold values indicate statistically significant values.

discharge, Delta s-sodium 24 h and ICU admission and Model 2 for s-sodium ≥ 135 mmol/L, Delta s-sodium 24 h, ICU admission, hypervolemic hyponatremia and malignant SIAD. All tests were two-tailed, and P values less than 0.05 were considered to indicate statistical significance.

Results

From the initial 298 patients, complete follow-up data were available for 281 patients. Seventeen patients were

excluded because of loss of follow-up ($n=8$), withdrawal of informed consent ($n=3$) or insufficient data ($n=6$).

Baseline characteristics and follow-up data

Median age of the 281 analyzed patients (66.5% females) was 72 (IQR 61–80). SIAD was the most common cause of hyponatremia (61.2%), especially drug-induced SIAD was very frequent (40.2%). Other etiologies of hyponatremia were as follows: hypovolemic hyponatremia (gastrointestinal losses and loss in the third space) 19.9%,

Table 4 Multivariate analysis.

	Model 1*		Model 2**	
	ODDS (95% CI)	P value	ODDS (95% CI)	P value
Outcome 1: Mortality				
S-sodium at admission	1.15 (1.01–1.32)	0.04	1.15 (0.10–1.32)	0.05
Correction of hyponatremia (≥ 135 mmol/L)	0.48 (0.24–0.97)	0.039	0.47 (0.23–0.94)	0.034
Charlson Comorbidity Index	1.48 (1.31–1.68)	<0.0001	1.44 (1.27–1.65)	<0.0001
Outcome 2: Rehospitalization				
S-sodium at admission	0.94 (0.85–1.04)	0.216	0.95 (0.86–1.06)	0.368
Correction of hyponatremia (≥ 135 mmol/L)	0.56 (0.34–0.92)	0.022	0.57 (0.35–0.95)	0.030
Charlson Comorbidity Index	1.07 (0.98–1.18)	0.148	1.05 (0.94–1.16)	0.391
Outcome 3: Recurrent profound hyponatremia				
S-sodium at admission	0.74 (0.63–0.87)	<0.0001	0.75 (0.64–0.89)	0.001
Correction of hyponatremia (≥ 135 mmol/L)	0.38 (0.18–0.79)	0.010	0.39 (0.19–0.81)	0.012
Charlson Comorbidity Index	1.1 (0.98–1.24)	0.104	1.06 (0.93–1.22)	0.364

*Model 1 adjusted for age, Charlson Comorbidity Index, s-sodium at hospital admission, s-sodium ≥ 135 mmol/L at discharge, Delta s-sodium 24 h, ICU admission. **Model 2 adjusted for age, Charlson Comorbidity Index, s-sodium at hospital admission, s-sodium ≥ 135 mmol/L at discharge, Delta s-sodium 24 h, ICU admission, hypervolemic hyponatremia, malignant SIAD.

hypervolemic hyponatremia (liver, heart and kidney failure) 11.4% and primary polydipsia 7.5%.

Median s-sodium level at hospital admission was 120mmol/L (IQR 116–123) and was raised by a median of 5 mmol/L (IQR 2–8) during the first 24 h. Half of the patients (49.1%) reached normal s-sodium levels (≥ 135 mmol/L) at discharge. During hospitalization, 36.7% of patients were admitted to the intensive care unit (ICU) and 8.5%

were treated with 3% NaCl infusion. Hospital aggravated hyponatremia occurred in 8.5% of patients. Overly rapid correction was seen in 20 (7.1%) patients, whereby nine of them received 0.9% NaCl infusion, six 3% NaCl infusion and five patients were treated with fluid restriction. No patient developed osmotic demyelination syndrome (ODS) during the observation phase. Detailed baseline characteristics are shown in Table 1 and follow-up data in Table 2.

Table 5 Characteristics of patients with initial s-sodium level of ≤ 120 mmol/L and > 120 mmol/L. Data are presented as % (n) and median (IQR: 25th–75th).

Characteristics	S-sodium ≤ 120 mmol/L (n = 155)	S-sodium > 120 mmol/L (n = 126)	P value
Age (years)	73 (62–81)	70 (58–79.3)	0.0769
Female	65.8% (102)	67.5% (85)	0.7712
Systolic blood pressure (mmHg)	139 (120–159)	135 (114–153)	0.0811
Heart rate (per minute)	76 (65.8–88)	84 (70–97)	0.0008
Charlson Comorbidity Index	2 (1–4)	2 (1–5.3)	0.0436
Etiology of hyponatremia			
Malignant SIAD	7.7% (12)	6.3% (8)	0.6533
Non-malignant SIAD	62.6% (97)	43.7% (55)	0.0016
SIAD drugs/diuretics	49% (76)	29.4% (37)	0.0008
SIAD idiopathic	5.2% (8)	4% (5)	0.6379
SIAD lung	3.2% (5)	3.2% (4)	0.9826
SIAD cns	5.2% (8)	7.1% (9)	0.4903
Hypervolemic hyponatremia	7.7% (12)	15.9% (20)	0.0333
Heart failure	3.9% (6)	7.1% (9)	0.2265
Liver failure	1.9% (3)	7.1% (9)	0.0323
Kidney failure	1.9% (3)	1.6% (2)	0.8290
Hypovolemic hyponatremia	15.5% (24)	25.4% (32)	0.0390
Primary polydipsia	6.5% (10)	8.7% (11)	0.4718
Medication			
Diuretics	64.5% (100)	54% (68)	0.0736
Thiazide diuretics	50.3% (78)	37.3% (47)	0.0293
Loop-diuretics	16.1% (25)	19.8% (25)	0.4199
Potassium-sparing diuretics	12.3% (19)	11.9% (15)	0.9292
Antihypertensives	54.2% (84)	45.2% (57)	0.1363
NSAID	11% (17)	15.1% (19)	0.3068
Neuroleptics	10.3% (16)	7.9% (10)	0.4941
Opioids	7.7% (12)	11.9% (15)	0.2404
Laboratory findings			
S-sodium at hospital admission (mmol/L)	117 (113–120)	123 (122–124)	<0.0001
S-sodium at discharge (mmol/L)	135 (131–137)	134 (129–137)	0.2306
S-sodium ≥ 135 mmol/L at discharge	52.3% (81)	45.2% (57)	0.2429
Therapeutic findings			
Delta s-sodium 24 h (mmol/L)	5 (2–9)	4.5 (1–6)	0.0163
Delta s-sodium 48 h (mmol/L)	11 (7–15)	8 (3.5–11)	<0.0001
Overly rapid correction	11.6% (18)	1.6% (2)	0.0012
ICU admission	48.4% (75)	22.2% (28)	<0.0001
3% NaCl infusion	12.3% (19)	4% (5)	0.0136
Outcome			
Overall mortality	14.8% (23)	27.8% (35)	0.0078
In-hospital mortality	1.3% (2)	7.1% (9)	0.0121
Rehospitalization rate	56.1% (87)	56.3% (71)	0.9712
Recurrent hyponatremia	45.8% (71)	38.9% (49)	0.2449
Recurrent profound hyponatremia	21.3% (33)	9.5% (12)	0.0076

BMI, body mass index.

Outcome measures

Mortality

Overall mortality was 20.6%, whereof 3.9% died during the initial hospital stay and 31% within the first 30 days after discharge. Leading causes of death were malignant disease (32.8%), respiratory (12.1%) respectively cardiac arrest (10.3%), or unspecified polymorbidity (24.1%) (Table 2). In none of these patients, death could directly be attributed to hyponatremia, as suggestive hyponatremia complications (e.g. brain edema, epileptic seizure) were not recorded.

Mortality risk was significantly higher in patients with multiple comorbidities expressed by a high CCI both in univariate and multivariate analysis (OR 1.49, 95% CI 1.33–1.68, $P < 0.001$ and OR 1.45, 95% CI 1.27–1.65, $P < 0.001$).

A significant correlation with mortality was shown for 's-sodium level at admission', whereby higher values were associated with a higher mortality rate (OR 1.17, 95% CI 1.1–1.3, $P = 0.005$). This association was also present in multivariate analysis (OR 1.14, 95% CI 1.01–1.29, $P = 0.036$).

Single therapeutic factors, such as 'correction rate', 'ICU admission' or 'hospital aggravated hyponatremia', were not associated with mortality. However, correction of hyponatremia (s-sodium level ≥ 135 mmol/L) was significantly associated with a lower mortality rate (OR 1.09, 95% CI 1.01–1.18, $P = 0.02$ and OR 0.46, 95% CI 0.3–0.8, $P = 0.011$), even after multivariate adjustment (OR 0.47, 95% CI 0.23–0.95, $P = 0.034$).

Concerning etiology of hyponatremia, higher mortality rates were found for hypervolemic hyponatremia and malignant SIAD (OR 3.07, 95% CI 1.4–6.7, $P = 0.005$ and OR 4.4, 95% CI 1.7–11.2, $P = 0.002$ respectively). On the contrary, non-malignant SIAD was associated with a lower mortality rate (OR 0.45, 95% CI 0.24–0.77, $P = 0.005$). However, after multivariate analysis, etiologies of hyponatremia lost significance as outcome markers (data not shown). Detailed results for univariate and multivariate analyses are shown in Tables 3 and 4.

Rehospitalization and recurrent hyponatremia

Thirty-day rehospitalization rate was 18.5%, but 56.2% of patients were rehospitalization at least once in 12 months, 28.5% repeatedly. During follow-up, recurrent hyponatremia was observed in 42.7% of patients, being profound (s-sodium level ≤ 125 mmol/L) again in 16% (Table 2).

'S-sodium level at admission' was not linked to an increased rehospitalization rate, but showed a significant association with recurrent profound hyponatremia, after multivariate adjustment (OR 0.75, 95% CI 0.64–0.89, $P = 0.001$) also.

The risk of rehospitalization and recurrent profound hyponatremia was lower in patients who reached eunatremia at discharge ('correction of hyponatremia'), both in univariate and multivariate analysis (OR 0.57, 95% CI 0.35–0.95, $P = 0.03$ and OR 0.39, 95% CI 0.19–0.81, $P = 0.012$ respectively).

'Malignant SIAD' was a risk factor for rehospitalization (OR 4.89, 95% CI 1.4–17.1, $P = 0.013$) and recurrent profound hyponatremia (OR 5.07, 95% CI 1.96–13.1, $P = 0.001$) in univariate but not in multivariate analysis.

All other variables were not significantly associated with the outcomes of rehospitalization and recurrent profound hyponatremia (Tables 3 and 4).

Patients characteristics according to hyponatremia categories: s-sodium $\leq$ and > 120 mmol/L

Characteristics of patients with initial s-sodium level $\leq$ vs > 120 mmol/L revealed several differences (Table 5).

In-hospital and overall mortality was higher in patients with initial s-sodium levels > 120 mmol/L (7.1% vs 1.3%, $P = 0.0121$ vs 27.8% vs 14.8%, $P = 0.0078$). Figure 1 shows Kaplan–Meier survival curves for both subgroups. Concerning etiology of hyponatremia patients with a s-sodium level > 120 mmol/L more

Figure 1

Kaplan–Meier curve. Survival rate in patients with initial s-sodium level ≤ 120 mmol/L and > 120 mmol/L.

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often suffered from hypervolemic or hypovolemic hyponatremia (15.9% vs 7.7%, $P=0.0333$ and 25.4% vs 15.5%, $P=0.039$ respectively). With 62.6%, non-malignant SIAD – especially due to drugs/diuretics – was the most frequent etiology in the lower s-sodium subgroup (49% vs 29.4%, $P=0.0008$).

Initial s-sodium correction rate was higher when hyponatremia was more pronounced: 5 mmol/L during the first 24h compared with 4.5 mmol/L ($P=0.0163$) in the subgroup with initial s-sodium level >120 mmol/L. Furthermore, ICU admission and treatment with 3% NaCl infusion was more common in patients with initial s-sodium ≤ 120 mmol/L (48.4% vs 22.2%, $P<0.0001$ and 12.3% vs 4%, $P=0.0136$ respectively).

During follow-up, patients in the lower hyponatremia category recurred more often with profound hyponatremia (21.3% vs 9.5%, $P=0.0076$). On the contrary, rehospitalization rate was comparable between the two groups (56.1% vs 56.3%, $P=0.97$).

Discussion

We herein confirm the adverse outcomes linked to hyponatremia. As a key finding, we observed a highly significant association of the CCI and death, meaning that mortality in hyponatremia is mainly influenced by comorbidities. Besides CCI, we identified two other important predictors of long-term survival: 's-sodium level at admission' and 'correction of hyponatremia'.

The mortality rate in our cohort of hyponatremic patients was 20.6%, which is well within the published range of 5–50% (5, 19, 2). Supposing that hyponatremia itself is causing death, an inverse relationship between s-sodium and mortality would be expected. In contrast, we found a strong, positive association between initial s-sodium concentration and mortality; thus, mortality rate was lower in patients with lower s-sodium levels. This is in contrast with a recently published meta-analysis indicating that hyponatremia-related risk augments with decreasing s-sodium level (6). In this meta-analysis, only 5 of 81 analyzed studies used a s-sodium cutoff of <125 mmol/L as was used in our study, thus supporting an inverse correlation of hyponatremia level and death in mild but not in profound hyponatremia. Indeed, similar to our data, other studies observed a paradoxical fall in mortality rate in profound hyponatremia (5, 19, 21, 25). In two large prospective studies, one-year mortality rate was highest in patients with a s-sodium between 120 and 129 mmol/L and lower in patients with a s-sodium

>130 mmol/L or <120 mmol/L respectively (5, 19). As a possible explanation for the lower mortality rate in patients with lower s-sodium levels, we found a lower CCI and in line with a previous study, significantly more cases with non-malignant (mainly drug induced) SIAD in the lower hyponatremia category (19, 21). Thus, etiologies of hyponatremia may vary according to its degree and notably drug-induced SIAD seems to predispose to very low s-sodium levels (26). We assume that hyponatremia – being a marker of disease severity and outcome in heart failure or liver cirrhosis – might not be similarly linked to mortality in other conditions like drug-induced SIAD.

An alternative rationale for the lower mortality in patients with s-sodium <120 mmol/L may be a different therapeutic approach in very profound vs milder hyponatremia. Indeed, we observed a higher percentage of ICU admission and of hypertonic saline administration as well as a more rapid initial sodium correction rate in patients with s-sodium of ≤ 120 vs >120 mmol/L. Furthermore, in patients with s-sodium levels >120 mmol/L, hospital-aggravated hyponatremia tended to be more frequent suggesting a delayed or inadequate management of hyponatremia. This is in accordance with the recently published Hyponatremia Registry showing that active treatment significantly depends on hyponatremia severity (27). However, the hypothesis that modality and velocity of hyponatremia treatment influences outcome could not be strengthened by our data: besides hyponatremia correction, we did not find a significant association of single therapeutic factors and mortality – probably because of insufficient power.

Hyponatremia correction was reached in 49.1% of our patients and strongly correlated with a lower mortality rate. This is in agreement with a recent meta-analysis, finding a reduced risk of death for any degree of hyponatremia improvement (28). One might postulate that patients who reach normonatremia are generally healthier, and their condition is more often attributable to a transient etiology of hyponatremia (e.g. drug-induced SIAD, pulmonary infection) (26). However, when looking at patients in the hyponatremia category ≤ 120 mmol/L – harboring a lower CCI and often a transient hyponatremia cause – we did not find a higher percentage of hyponatremia correction. This is probably explained by an 'earlier' hospital discharge of healthier patients (before reaching an s-sodium level of ≥ 135 mmol/L).

In the aforementioned meta-analysis, comorbidities were not considered as confounders due to insufficient data. In our study, data were adjusted for age, comorbidities

Clinical Study	B Winzeler, N Jeanloz, N Nigro and others	Outcome in hyponatremia	175:6	506
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(CCI) and cause of hyponatremia, but ‘correction of hyponatremia’ remained significantly associated with a reduced mortality rate. This underscores the significance of hyponatremia correction across different clinical conditions, which could play an important role in preventing mortality.

The 1-year readmission rate in our study was very high (56.2%). Not surprisingly, malignant SIAD turned out to be a predictor of both rehospitalization and rehyponatremia. Reasons for rehospitalization were various, but hyponatremia itself was only rarely indicated as the main cause. However, many patients presented with accompanying hyponatremia, and it is tempting to speculate that it was a contributing factor for rehospitalization. This is supported by the fact that CCI was not a predictor of readmission, whereas correction of hyponatremia was significantly associated with a lower rehospitalization rate even after multivariate adjustment.

Interestingly, there was a significant association of hyponatremia severity and recurrent profound hyponatremia; patients with initial s-sodium level ≤ 120 mmol/L recurred more often compared with those with initial levels above 120 mmol/L. In these patients with mainly drug-induced SIAD, this may be explained by a restart of predisposing drugs after normalization of hyponatremia.

Our study has the following strengths. Aside from large-scale epidemiologic studies, it is the largest reported series of prospectively enrolled patients with profound hyponatremia. The prospective study design with specific testing allowed us to carefully categorize patients into diagnostic groups. Excluding patient with hyperglycemia-induced hyponatremia eliminated an important and frequent confounder in hyponatremia studies. However, some limitations should be considered. First, this is a predefined secondary analysis of a prospective study. Thus, there was no power calculation specific to this paper, what may weaken our findings. Secondly, when focusing on the subgroups on initial s-sodium level $\leq$ or > 120 mmol/L, the primary endpoint death was reached in ‘only’ 23 and 35 patients respectively. Thus, caution is needed when interpreting results according to these hyponatremia categories. Furthermore, although in line with previous studies, the division into these two categories at a cutoff of 120 mmol/L is somehow arbitrary.

In conclusion, we confirm the impact of profound hyponatremia in daily clinical practice, with a high 1-year mortality, recurrence and rehospitalization rate. The positive correlation of the CCI and initial s-sodium level with mortality emphasizes the importance of the underlying disease, which seems to particularly impact

on prognosis. But still, hyponatremia of any degree is associated with poor outcome, and our data suggest that a particular attention should be paid to hyponatremia itself as a therapeutic target – irrespective of etiology and severity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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