Challenge in hyponatremic patients – the potential of a laboratory-based decision support system for hyponatremia to improve patient’s safety

Abstract

Objectives: Hyponatremia is the most frequent electrolyte disorder in hospitalized patients with increased mortality and morbidity. In this study, we evaluated the follow-up diagnostic, the risk of inadequate fast correction and the outcome of patients with profound hyponatremia (pHN), defined as a blood sodium concentration below 120 mmol/L. The aim was to identify a promising approach for a laboratory-based clinical decision support system (CDSS).

Methods: This retrospective study included 378,980 blood sodium measurements of 83,315 cases at a German tertiary care hospital. Hospitalized cases with pHN (n=211) were categorized into two groups by the time needed for a follow-up measurement to be performed (time to control, TTC) as either <12 h (group 1: “TTC≤12 h”, n=118 cases) or >12 h (group 2: “TTC>12 h”, n=93 cases). Length of hospital stay, sodium level at discharge, ward transfers, correction of hyponatremia, and risk of osmotic demyelination syndrome (ODS) due to inadequate fast correction were evaluated with regard to the TTC of sodium blood concentration.

Results: pHN was detected in 1,050 measurements (0.3%) in 211 cases. Cases, in which follow-up diagnostics took longer (TTC>12 h), achieved a significantly lower sodium correction during their hospitalization (11.2 vs. 16.7 mmol/L, p<0.001), were discharged more frequently in hyponatremic states (<135 mmol/L; 58 (62.4%) vs. 43 (36.4%), p<0.001) and at lower sodium blood levels (131.2 vs. 135.0 mmol/L, p<0.001). Furthermore, for these patients there was a trend toward an increased length of hospital stay (13.1 vs. 8.5 days, p=0.089), as well as an increased risk of inadequate fast correction (p<0.001).

Conclusions: Our study shows that less frequent follow-up sodium measurements in pHN are associated with worse outcomes. Patients with a prolonged TTC are at risk of insufficient correction of hyponatremia, reduced sodium values at discharge, and possible overcorrection. Our results suggest that a CDSS that alerts treating physicians when a control time of >12 h is exceeded could improve patient care in the long term. We are initiating a prospective study to investigate the benefits of our self-invented CDSS (www.ampel.care) for patients with pHN.

Keywords: clinical decision support system (CDSS); control measurements; hyponatremia; patient safety; post-analytical.

Introduction

Hyponatremia, defined as a serum sodium concentration <135 mmol/L, is the most common fluid and electrolyte imbalance in hospitalized patients, with an incidence proportion between 15% [1] and up to 30% [2]. It is associated with prolonged hospital stays [1, 3, 4] and increased morbidity and mortality, especially in patients with heart failure [5] and liver cirrhosis [5, 6].

In patients with acute hyponatremia, i.e., a clinically relevant decrease in sodium levels within 48 h [7], symptoms
and severity of brain edema correlate with the degree of hyponatremia and the rapidity of sodium decrease [8, 9]. Symptoms in acute hyponatremia are nausea and vomiting, vertigo, and, in some cases, seizures, apathy, and coma [10].

However, chronic hyponatremia (≥48 h) [7] often presents with subtle or rather non-specific symptoms, such as headaches and cognitive and concentration deficits, as well as gait disturbances or falls in elderly patients [11, 12]. Although hyponatremia is a frequent laboratory finding, there are often subliminal or unspecific symptoms, as well as various etiologies with a wide spectrum of differential diagnoses and high relevance of acuteness or chronicity for outcome and therapy. These issues and the complexity of use of the existing diagnostic algorithms in hospital settings may result in often challenging and inadequate management of this disorder [13, 14].

Evidence-based recommendations on the frequency of blood sodium measurements are limited. Mainly, the suggestions of the guideline apply to acute or symptomatic hyponatremia [7]. In particular, there are no explicit recommendations for profound hyponatremia of unknown chronicity and with uncertain symptoms.

The aim of this study was to identify a promising approach for a laboratory-based clinical decision support system (CDSS) which identifies patients with profound hyponatremia at risk of delayed monitoring of blood sodium values.

A CDSS, which provides specific information to treating physicians, has great potential to improve attention and treatment adherence of treating physicians in line with guideline recommendations, and thus to improve patient care [15, 16].

Our study was part of the “AMPEL” CDSS project [17, 18], the primary objective of which is to improve patient care.

To evaluate our CDSS approach we compared retrospectively the sodium correction rate, hyponatremia at discharge, length of hospitalization, TTC in relation to type of ward, and risk of overcorrection of patients with profound hyponatremia (pHN) under consideration of the time to control (TTC) in a representative cohort of patients at a tertiary hospital of general care.

We analyzed ward transfers as one possible factor associated with increased TTC in patients with pHN.

**Materials and methods**

**Subjects and measurements**

We performed a retrospective, observational study of all laboratory and point-of-care (POC) sodium measurements (serum, plasma, and whole blood) carried out at the University of Leipzig Medical Center (ULMC) in 2018 (n=424,664).

After exclusion, n=6,677 measurements of n=211 cases with profound hyponatremia (pHN) remained as the database. Profound hyponatremia was defined as serum sodium concentrations below 120 mmol/L. We chose this threshold because of its immense clinical relevance for the development of severe symptoms [8, 19] and a higher risk of osmotic demyelination syndrome (ODS) [20].

Detailed information on data preparation and the inclusion and exclusion criteria are provided in Figure 1.

**Methods**

Serum and plasma sodium measurements were performed at the Institute of Laboratory Medicine on a Cobas 8000 Analyzer by Roche (Mannheim, Germany; ISE indirect Na-K-Cl for Gen. 2).

Whole blood point-of-care diagnostic was performed at the emergency department and intensive care units (ICUs) on an ABL 800 series and ABL 90 FLEX Analyzer by Radiometer (Copenhagen, Denmark).

For our analysis, we examined the measurement results for sodium concentrations from the laboratory information system (LabCentre by i-Solutions Health GmbH, Mannheim, Germany).

We used the variable of time to control (TTC) for further analyses. This was calculated as the time difference between one measurement result and its follow-up measurement result. Only a TTC within 168 h was considered a control measurement.

To examine the relevance of TTC for patient outcomes, we separated the cohort into two groups, the “WTH” or “Within Twelve Hours” group for cases where the pHN was controlled unexceptionally within twelve hours and the “OTH” or “Over Twelve Hours” group for cases where the TTC for at least one measurement of pHN was above 12 h. We investigated the following outcomes per group: sodium correction rate, hyponatremia at discharge, length of hospitalization, TTC in relation to type of ward, TTC in relation to ward transfer, and possible overcorrection with a risk of subsequent osmotic demyelination syndrome (ODS).

The few studies available suggest only specific control times for the active correction of hyponatremia [7, 20]. We chose the threshold of <12 h for the follow-up time of pHN based on expert consensus.

The significance of this chosen cut-off was confirmed by peer reviewing 21 randomly selected cases with at least one measurement of pHN (2–50 sodium measurements per case) in collaboration with two specialists from the clinic for endocrinology, nephrology, and rheumatology (Department of Internal Medicine) at ULMC.

We compared different cut-offs for maximal time of follow-up controls: <6 h, <12 h, and <36 h. Follow-up measurements within 6 h are recommended during active correction of asymptomatic hyponatremia [7], but both could not be determined from the blood sodium values alone in our study design. Furthermore, with this cut-off we detected too many patients which were considered to be adequately monitored by the specialists. In contrast, a high cut-off value (<36 h) identified fewer patients with a possible endangerment for patient safety. <12 h was a reasonable compromise between sufficient response time and maintaining safe patient care.

For further outcome investigations of patients with pHN, we automatically retrieved the times of hospital admission, within-hospital transfers, discharge, direction of transfer, and coded diagnosis according to ICD-10 from digital patient files.
Statistical analysis and ethical approval

The data processing and statistical analysis were performed using R 4.0.3 [21].

Categorical variables are summarized as frequencies and percentages; continuous variables are described by median and interquartile range. We used Pearson’s chi-squared test or, for smaller subcohorts \(n<40\), Fisher’s exact test to compare categorical data, and the Mann-Whitney U test to compare continuous parameters between two groups.

Group differences with p-values \(<0.05\) were considered statistically significant.

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ Institutional Review Board (Ethics Committee of the Medical Faculty of the University of Leipzig, Germany; No. 214/18-ek).

Results

General

All acquired measurements \(n=424,664\) were sampled in 2018 from 91,386 cases, of which 50.1% were female \(n=25,762\). Fourteen percent \(n=52,998\) of the measured sodium concentrations were below 135 mmol/L, and 0.3% \(n=1,154\) were below 120 mmol/L. Exclusion criteria were measurements from patients younger than 18 years, measurements below or above the detection limits, non-numerical or erroneous values, measurements from non-ULMC or study patients, measurements from cases with no measurement of profound hyponatremia \((<120 \text{ mmol/L})\) during hospitalisation \(n=366,836\), measurements from cases with implausible sudden decreases due to preanalytical disturbances \(n=5,387\), and measurements from outpatient cases (Figure 1). After exclusion, \(n=6,677\) sodium measurements with a proportion of 15.7% \(n=1,050\) measurements of pHN in 211 cases remained.

For further analysis, we used the time to control (TTC) to divide our cohort. TTC in patients with profound hyponatremia was lower when compared to all included sodium measurements \((3.8 \text{ vs. } 4.8 \text{ h}, p<0.001)\). No significant differences in median TTC for measurements of pHN between intensive care units (ICU) and non-ICUs could be observed \((3.8 \text{ vs. } 3.7 \text{ h}, p=0.33)\). Figure 2 shows the distribution of TTC in pHN differentiated by type of ward.

Figure 1: Inclusion and exclusion criteria for the study cohort. Detailed flowchart of the inclusion and exclusion criteria in the data preparation. Each transverse arrow symbolizes a criterion for the exclusion of measurements. \(n=\)total number of measurements.
Baseline characteristics

For further analysis of clinical indication and frequency of control measurements after detection of profound hyponatremia (<120 mmol/L), we divided the cohort into “WTH” (“Within Twelve Hours”, TTC for pHN≤12 h) and “OTH” cases (“Over Twelve Hours”, TTC for pHN>12 h). A TTC of 12 h for profound hyponatremia was exceeded in 185 measurements (17.6%) from 93 OTH cases (44.1%).

There were no significant differences in sex, age, or first measured sodium value at admission between OTH and WTH (Table 1). Possible causal comorbidities in profound hyponatremia, such as liver cirrhosis, underlying liver diseases, renal impairment, and heart failure, did not differ significantly between the two groups (Table 1). The last measured sodium value before discharge was lower for OTH (median 131.2 vs. 135.0 mmol/L, p<0.001).

OTH had a tendency for a longer hospitalization time (13.1 vs. 8.5 days, p=0.09), whereas WTH patients were more often treated in the ICU during their hospitalization (76.3 vs. 44.1%, p<0.001). Twenty-nine patients (13.7%) died during hospitalization, but no significant difference between

Table 1: Baseline characteristics and outcome measures in patients with profound hyponatremia.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>OTH (n=93)</th>
<th>WTH (n=118)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % female</td>
<td>55.9</td>
<td>55.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Age, years</td>
<td>67.0 (58.0–80.0)</td>
<td>69.0 (54.0–79.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>First measured sodium value, mmol/L</td>
<td>119.0 (115.0–125.4)</td>
<td>118.5 (115.0–120.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Comorbidities (ICD-10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis (K70, K71, K72, K74, K76)</td>
<td>20 (21.5%)</td>
<td>25 (21.2%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Acute renal failure or chronic kidney disease (N17, N18)</td>
<td>52 (55.9%)</td>
<td>59 (50.0%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Acute or chronic heart failure (I50)</td>
<td>20 (21.5%)</td>
<td>19 (16.1%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last measured sodium value, mmol/L</td>
<td>131.2 (124.7–135.7)</td>
<td>135.0 (130.1–138.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization time, days</td>
<td>13.1 (6.8–26.2)</td>
<td>8.5 (6.4–20.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stay at intensive care unit during hospitalization</td>
<td>41 (44.1%)</td>
<td>90 (76.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time in intensive care unit during hospitalization, days</td>
<td>1.9 (0.9–3.9)</td>
<td>2.8 (1.3–6.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Deceased during hospitalization</td>
<td>9 (9.7%)</td>
<td>20 (16.9%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Baseline data and outcome measures of patients in the “Over Twelve Hours” (“OTH”, Time to control>12 h) and “Within Twelve Hours” (“WTH”, Time to control≤12 h) groups. Categorical variables are summarized as frequencies and percentages, while continuous variables are described by median and interquartile range. Bold p-values are considered to be significant.
OTH and WTH was observed (9.7 vs. 16.9%, p=0.13). It is noticeable that no patient died while having profound hyponatremia.

Treatement of hyponatremia

Correction to normonatremia at discharge was not achieved in 125 cases (59.2%). OTH had an increased risk of failing to reach normalized sodium values at discharge (n=68, p<0.001; OR=2.90), although normonatremia may not necessarily be the goal of therapy for each patient. However, OTH had a significantly increased risk of being discharged with severe hyponatremia (<125 mmol/L) (n=24, p<0.001; OR=6.44). The median increase in serum sodium values between first measurement after admission and last measurement before discharge was significantly lower in OTH than WTH (11.2 mmol/L vs. 16.7 mmol/L, p<0.001) (Table 2). Figure 3 shows the comparison of the measured sodium values at admission and discharge for both groups. At admission, no significant difference between the groups was noticeable, whereas WTH cases had higher blood sodium levels than did OTH cases at discharge.

Transfers between general ward and ICU

To identify the possible causes for delayed sodium control measurements, ward transfers were investigated in more detail. We excluded all measurements from wards that were not ICUs or general wards, such as the emergency department (ER) or palliative care wards. The purpose of this procedure was to avoid bias in the TTC for non-ICU wards through either faster control measurements, such as after an admission through the ER, or slower follow-up requests by wards like the palliative care unit, in order to obtain a clear view of internal and surgical general wards and their controlling conduct.

Measurements of sodium concentration below 120 mmol/L were significantly more quickly controlled in the ICU than in general wards, irrespective of transfers before measurement (3.8 vs. 19.8 h, p<0.001). A similar difference was shown when patients were controlled at the same department (3.7 at ICU vs. 21.1 h at non-ICU, p<0.001).

If profound hyponatremia was detected before ward transfer, the TTC depended largely on the ward to which the patients were moved. Transfers from general wards to the ICU had a significantly shorter TTC than did transfers in the opposite direction (3.4 vs. 27.1 h, p<0.001). TTC for measurements at general wards was significantly increased for patients who were previously transferred from ICU (21.1 vs. 27.1 h, p=0.031) (Figure 4).

Risk of osmotic demyelinisation syndrome (ODS)

The correction of hyponatremia implies the inherent risk of facilitating ODS, caused by rapid correction in particular of chronic hyponatremia with a manifest deficit in intracellular osmolytes. To assess possible risks for ODS, we excluded all cases with implausible differences between the two measurements after a critical evaluation of each case (n=44). This resulted in n=167 remaining cases. To classify measurements as implausible, we reviewed each case individually by analyzing the graphically represented value development in relation to the time. Measurements were thereby considered as implausible when the value deviated widely from the expected value based on the course of the case.

For each included case, we determined the total maximum sodium delta in a 24-h period linked to the timely delta in which it was measured.

Forty-five cases (27.4%) had a possibly increased risk of ODS due to exceeding the correction limit of 10 mmol/L in 24 h. A correction of >10 mmol within 24 h was more frequently identified in WTH patients than in OTH patients (44.9 vs. 6.7%, p<0.001; OR=11.43). In 45 cases (26.9%), the maximum correction rate was <5 mmol/L per 24 h, or there was no control measurement within 24 h (Figure 5). OTH

Table 2: Correction of profound hyponatremia.

<table>
<thead>
<tr>
<th></th>
<th>OTH (n=93)</th>
<th>WTH (n=118)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value difference between last and first measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total difference, mmol/L</td>
<td>11.2 (3.0–18.1)</td>
<td>16.7 (9.1–22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>22 (23.7%)</td>
<td>12 (10.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;5 mmol/L</td>
<td>29 (31.2%)</td>
<td>16 (13.6%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Maximum value during hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;135 mmol/L</td>
<td>58 (62.4%)</td>
<td>43 (36.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;130 mmol/L</td>
<td>34 (36.6%)</td>
<td>19 (16.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;125 mmol/L</td>
<td>19 (20.4%)</td>
<td>3 (2.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Value at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;135 mmol/L</td>
<td>68 (73.1%)</td>
<td>57 (48.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;130 mmol/L</td>
<td>42 (45.2%)</td>
<td>29 (24.6%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>&lt;125 mmol/L</td>
<td>24 (25.8%)</td>
<td>6 (5.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Course of sodium concentration and correction rates of profound hyponatremia between “Over Twelve Hours” (Time to control>12 h) and “Within Twelve Hours” (Time to control≤12 h) groups. “Total difference” is given in median and interquartile range; the other results are given in total numbers and percentages. Bold p-values are considered to be significant.
patients were more frequently in this group than were WTH patients (50.7 vs. 7.9%, p<0.001; OR=11.82) (Table 3).

Discussion

To the best of our knowledge, this is the first study to examine the clinical importance of control measurements in profound hyponatremia (pHN) and to associate the time to control (TTC) with a worse outcome in these patients.

Only a small proportion of cases at the ULMC (University of Leipzig Medical Center) are affected by pHN<120 mmol/L (0.2%), which is comparable to the proportion of patients with pHN reported in other studies [1, 22]. The results of this retrospective study indicate the potential to increase the quality of care for these patients and encourage subsequent prospective analyses.

Our study shows that delayed control measurements (TTC>12 h) occurred at least once in nearly half of all cases with pHN. This finding was more often detected in general wards...
ICUs. Aplicable explanation of the more intensive care of patients in ICUs and the different staffing ratio, leading to closer monitoring and more frequent control measurements. The lower TTC in ICUs may also be independent of sodium blood levels because patients in ICUs are in a critical state, with the resulting need for closer evaluation in general. Patients with less frequent monitoring (TTC>12 h) had an increased risk of a worse outcome, including lower sodium concentration at discharge and an increased risk of not achieving sodium values above 130 mmol/L, with a high OR>2.5 and above. We suspected as a cause of this an accumulation of patients with chronic hyponatremia on general wards requiring slower and more careful correction. There are several frequent comorbidities that cause chronic hyponatremia, such as liver cirrhosis, heart failure, and renal insufficiency [23]. However, we found no increased frequency of these diagnoses in the OTH group. Hence, there seems to be no reason for a lower correction rate in consideration of comorbidities.

Patients with hyponatremia are at an increased risk of a wide spectrum of negative outcomes since they are associated with a prolonged length of hospital stay [3, 4, 9, 14, 24], higher readmission rates [3, 4], increased hospital mortality [25], and long-term mortality [5, 26]. Discharges in a hyponatremic state are associated with an increased risk of concentration disturbances [27], tendency to fall [12, 27–29], osteoporosis [29, 30], and fractures [28, 29, 31]. Further beneficial effects of appropriate compensation of hyponatremia are correction of neurological symptoms [11], lower readmission rate, and, most importantly, a decreased 60-day-mortality [5].

In the group with timely sodium controls (TTC≤12 h, “WTH”), we observed more patients from ICUs, which might also explain the increased hospital mortality of this group, as well as the more frequent control measurements in ICUs in general. A lower number of cases in general could be observed in the group with delayed sodium controls (TTC>12 h, “OTH”). Due to the increased control time, profound hyponatremia may be detected less frequently and therefore underdiagnosed [32].

Table 3: Increase in sodium concentration within 24 h after detection of profound hyponatremia.

<table>
<thead>
<tr>
<th>Delta Na in 24 h</th>
<th>OTH (n=75)</th>
<th>WTH (n=89)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta Na&gt;10 mmol/L in 24 h</td>
<td>5 (6.7%)</td>
<td>40 (44.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta Na≥5 mmol/L and ≤10 mmol/L in 24 h</td>
<td>32 (43.2%)</td>
<td>42 (47.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Delta Na&lt;5 mmol/L in 24 h</td>
<td>38 (50.7%)</td>
<td>7 (7.9%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Frequency of different correction rates within 24 h after detection of profound hyponatremia compared between the groups “Over Twelve Hours” (OTH, Time to control>12 h) and “Within Twelve Hours” (WTH, Time to control≤12 h). Results are given in total numbers and percentages. Bold p-values are considered to be significant.

Figure 5: Repeated sodium measurements within 12 h lead to an increased detection of patients at risk of ODS. The figure shows the maximum concentration difference of each case with profound hyponatremia within 24 h depending on the underlying time difference of each maximum concentration difference within 24 h, differentiated between the groups “Over Twelve Hours” (OTH, TTC>12 h, shape=black square) and “Within Twelve Hours” (WTH, TTC≤12 h, shape=white circle). n=total number of cases in each group. The diagram is separated into three sections by two lines: The diagonal line represents the extrapolated guideline requirement (limit of correction of 10 mmol/L in 24 h to avoid the risk of ODS). Below this line, cases have a low risk of ODS, whereas above the diagonal and under the horizontal line, cases have a moderate risk of ODS. The horizontal line at 10 mmol/L marks all cases with a definite excess of the limit value within 24 h, while all cases above the line in the darkest gray area have a high risk of potential ODS.
Patients from the WTH group also had a significantly higher median of the last measured sodium value. Considering the more frequent and longer treatments in ICUs in this group, there seems to be a positive effect of more intensive care on sodium levels. More frequent control measurements and closer monitoring seem to be beneficial with regard to treating hyponatremia.

Correction of severe hyponatremia according to the recommendations of the European Clinical Practice Guideline [7] remains challenging in the routine clinical scenario. Exceeding the correction limit of 10 mmol/L in 24 h was found more often in cases from the WTH group. This is associated with an increased risk of osmotic demyelinisation syndrome (ODS) [33] and can result in various severe neurological manifestations [34, 35].

In patients with a TTC above 12 h, we observed only a small proportion of overcorrections (6.7%). This may be due to the less frequent or complete absence of control measurements within 24 h, leading to a risk of overlooking possible severe courses. More frequent and timely control measurements could be useful here. Overall, the incidence and outcomes of ODS in association with different sodium correction regimes need to be evaluated in prospective studies. Our current approach can be used in a CDSS to screen at-risk patients and to improve patient care.

Patient transfers are another explanatory risk factor for delayed controls. In-hospital transfers from ICUs to general wards increased the risk of delayed control measurements. We recommend further investigation of transfers as a risk factor and of ways to minimize the increased TTC in this regard in clinical practice. Further studies are needed to detect other risk factors for late controls and to differentiate clinically reasonable from unreasonable late controls.

**Limitations**

One limitation of our study is the retrospective character of the analysis and the classification of life-threatening hyponatremia based primarily on the measured value, in which the clinical condition of the patients could not be considered. The diagnosis and therapy of hyponatremia are mainly oriented toward the manifestation of symptoms, which depend not only on the severity but also on the rapidity of the decrease.

Our study does not account for methodical differences between serum and whole blood measurements. One possible bias is pseudohyponatremia: A relevant part of the included sodium measurements were performed with the analytical method of an indirect ion-selective electrode (ISE) (n=2,006, 30.0%). A dilution before measurement (1:31) leads to the possibility of falsely low sodium concentrations in cases of very high protein or lipid concentrations. This can occur in patients with severe hyperlipidemia or gammopathy. However, relevant biases are rare: Even a severe hyperproteinemia of 110 g/L leads only to a moderate sodium bias of about −5 mmol/L [36].

The definition of our thresholds, especially the TTC, was challenging due to the sparse literature. To the best of our knowledge, there are no other studies that address the conduct of blood measurements in the context of outcomes for patients with hyponatremia. The chosen temporal inclusion criteria allow for only a limited assessment of chronicity, previous episodes of hyponatremia, and performed therapies.

Indications for sodium control measurements could not be determined. Thus, indication-related controls and routine blood collections could not be analyzed in a differentiated manner. Due to the available data, we included only inpatient cases. Hence, an assessment of morbidity and mortality outside of the hospital or further general development of the patients was not possible.

From a clinical and laboratory perspective, we could only determine the risk of ODS in our specific cohort. The high proportion (27.4%, 45/164 included cases) detected may not be comparable to other studies [35, 37]. Further studies involving other parameters, such as a patient’s clinical appearance or radiological imaging, are needed to determine the incidence of ODS.

**Conclusions**

We have shown that patients with pHN and prolonged TTC have an increased risk of worse clinical outcomes.

More frequent controls have a potentially positive effect on an appropriate correction rate, increased sodium values during hospitalization and at discharge, and detection of patients at risk of ODS.

This study was part of the AMPEL CDSS project. Our results suggest the need for a hyponatremia framework that monitors pHN and its correction rate and prevents possible oversight of this severe electrolyte imbalance. The data form the basis for the clinical implementation and creation of further variants of other CDSSes currently part of a prospective randomized controlled trial.

**Highlights**

- Hyponatremia is the most common fluid and electrolyte disorder in hospitalized patients and associated with increased mortality and morbidity.
More frequent control measurements in patients with hyponatremia are associated with increased correction rates, reduced length of hospitalization and decreased risk for overcorrection.

Hyponatremia, its control measurements and correction rates could be monitored with a CDSS, which could improve outcome and patient care.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors’ Institutional Review Board (Ethics Committee of the Medical Faculty of the University of Leipzig, Germany; No. 214/18-ek).

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