Susceptibility to hyponatremia in the elderly: causes and consequences
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Citation for published version (APA):
Frenkel, W. J. (2014). Susceptibility to hyponatremia in the elderly: causes and consequences

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Chapter 4

The association between plasma sodium levels at time of admission and mortality and morbidity in acutely admitted elderly patients: a prospective cohort study


Adapted from Journal of the American Geriatric Society; 2010 Nov; 58(11):2227-8
ABSTRACT

Objectives: To assess whether or not plasma sodium levels at the time of hospital admission were associated with short-term mortality and morbidity in acutely admitted elderly patients

Design: Prospective cohort study

Setting: Internal Medicine department of a large university hospital.

Participants: 895 elderly patients >65 years of age who were acutely admitted.

Measurements: The in-hospital mortality and three-month mortality rates were assessed along patients’ functional status, living arrangements, and length of hospital stay.

Results: We enrolled 895 patients (mean age 78.0 (SD 8.7) years, 53.4% female). Their mean serum sodium concentration was 136 (SD 5.6) mmol/L. Patients with low plasma sodium levels (107-130 mmol/L) had an increased risk of mortality after 3 months as compared to the reference group (130-141 mmol/L), odds ratio (OR) of 1.5, 95% Confidence Interval (CI) 1.0-2.2. After correcting for possible confounders, the mortality rates did not differ between groups (OR 1.2, 95% CI 0.8-1.9). Patients with low plasma sodium levels had a longer hospital stay than those in the reference group (15.2 (SD 14.7) days versus 10.3 (SD 9.1) days; p<0.001). No differences were observed in functional status or living arrangements across the different groups.

Conclusion: Hyponatremia is common in acutely admitted elderly patients and is associated with an increased risk of mortality and an increased length of hospital stay. However, we were unable to demonstrate that plasma sodium level had an independent effect on mortality risk or functional status.
INTRODUCTION

Throughout life the plasma sodium level is maintained within narrow limits despite continuous variations in water and salt intake. Disturbances in water and sodium homeostasis are frequently observed in elderly patients and, when severe, may lead to loss of consciousness, coma or even death. Several age-related changes involving the hormonal, renal and thirst regulatory mechanisms that modulate these processes may explain the increased susceptibility that elderly patients have to disturbances in water and salt homeostasis. These changes may decrease an older person's ability to respond to alterations in their fluid and electrolyte balance. Difficulties in maintaining sodium and water balance may especially be unmasked by the presence of an underlying disease. This may result in an increased risk of hypo- or hypernatremia in susceptible patients.

Previous studies have reported that both hypo- and hypernatremia are associated with an increased risk of mortality in acutely admitted elderly patients. Many of these studies did not adjust for possible confounders that could be associated with abnormal plasma sodium levels, such as concomitant disease or medication. Recently a large prospective study showed that hyponatremia was associated with an increased risk of both in-hospital mortality and long-term mortality in hospitalized patients. This association was stronger in older patients admitted with cardiovascular disease and metastatic cancer as well as for those who were admitted for orthopedic procedures.

The presence of hyper- or hyponatremia, which is a manifestation of the body's inability to maintain water and salt homeostasis, may reflect the severity of a patient's underlying disease and may therefore be an indicator of mortality risk. However no studies addressed functional decline, a condition that often occurs after an acute illness and is associated with adverse outcome.

Based on the above, we hypothesized that disturbances in water and sodium homeostasis are associated with adverse hospital outcomes in acutely admitted elderly patients and that this association remains after adjusting for potential confounders. The aim of this study was to examine the relationship between deviations in sodium balance and short-term mortality, functional decline in acutely hospitalized elderly patients 65 years of age and older.

METHODS

We enrolled 945 consecutive patients >65 years, who were acutely admitted to the department of Internal Medicine of a large (1024-bed) university hospital (Academic Medical Centre, Amsterdam, the Netherlands) between November 2002 and July 2007. Patients were excluded if they were unable to speak or understand Dutch or English, if they or their relatives did not give permission for them to be included in the study, if they were primarily...
admitted to the intensive care unit or for cardiac monitoring, or if they were transferred to another ward, or left the ward within 48 hours. Patients who were admitted with a diagnosis of drug-induced hypo- or hypernatremia and had no evidence of concomitant disease were also excluded. The primary endpoints were in-hospital mortality and three-month mortality following admission. We chose to examine decline in functional status and living arrangements as secondary endpoints. The study was approved by the hospital’s Medical Ethics Committee. Before enrolment, informed consent was obtained from either the patient or their relatives. An initial multidisciplinary evaluation was completed for all study participants by members of the research team. First, patients, medical staff and nursing staff were interviewed by a research nurse to determine the study eligibility of the patients within 48 hours of admission. Eligible patients were then interviewed by research nurses who obtained social and demographic data concerning patients’ living arrangements, educational status, marital status and functional status (modified Katz ADL (activities of daily living) index) \(^{11}\). At discharge, additional data were obtained based on information derived from the discharge letter, the International Classification of Diseases (ICD-9) codes and the Charlson co-morbidity Index scores of all included patients \(^{12}\). The diagnoses at discharge were classified into the following disease categories: neurological disease, endocrine disease, infectious disease, malignancy, diseases of the digestive system, pulmonary disease and cardiovascular disease. Patients could be classified in multiple disease categories. Patients with conditions, known to be associated with hypo- or hypernatremia and increased mortality risk such as heart failure, liver disease and renal insufficiency, were separately assessed to study their possible relationship with plasma sodium levels and adverse outcomes. Heart failure was deemed to be present if patients were previously diagnosed with heart failure or if they had a combination of at least two of the following symptoms: peripheral edema, increased central venous pressure; dyspnoea, hypoxia with evidence of pulmonary edema on chest X-ray or diminished left ventricular ejection fraction (LVEF) (i.e., <45% as assessed by echocardiography prior to admission). Patients were considered to have liver disease if they had liver cirrhosis or chronic hepatitis and portal hypertension with or without a history of variceal bleeding. Renal insufficiency was defined as a plasma creatinine >150 µmol/L at the time of admission. Malignancy was defined as a solid tumor or hematological disease that was treated within five years preceding the study. Co-morbidity was defined as a combination of all medical conditions that were identified as predictors for an adverse outcome after assessing their association with mortality in univariate analysis. Information on prescription medication usage prior to hospital admission was obtained from patients’ medical charts. The number and type of prescribed drugs was assessed. Use of medications from the following drug classes was separately assessed because of their possible influence on plasma sodium levels: diuretics (loop diuretics, thiazide diuretics or potassium-sparing diuretics), antipsychotic drugs and antidepressants, corticosteroids, antiepileptic drugs, opioids and non-steroidal anti-inflammatory drugs \(^{13,14}\). Polypharmacy was defined as the use of five or more different drugs at time of admission. Laboratory analyses
were performed within 24 hours of admission using standard biochemical techniques. If these analyses were not obtained within 24 hours of admission they were classified as missing. Three months after hospital admission, we followed up on our patients by means of a telephone interview with patients or their relatives in order to assess survival, changes in living arrangement (which were defined as independent living or living under conditions in which the patients were dependent on help from others), and functional status (assessed by the modified Katz ADL (activities of daily living) Index). The modified Katz ADL Index is a 15-item scale that is used to measure functional status in the geriatric population and is calculated based on the number of disabilities as a patient has in performing his/her ADLs. A score of 0 denotes independence and a score of 15 were defined as severe functional impairment that interferes with patients’ daily functioning. A decline in functional status was defined as an increase of at least one point on the modified Katz ADL Index three months after admission as compared to the score two weeks prior to hospital admission.

**Statistical Analysis and sample size calculation**

Because of our interest in examining sodium disturbances as a potential predictor of mortality in acutely admitted elderly patients (a group that has been previously shown to have a high prevalence of hypo- and hypernatremia), we used the normal distribution of plasma sodium levels in the our population of interest and stratified them according to +/- 1 SD (standard deviation) around the mean plasma sodium level. Based on previous studies, we designed our study to detect a 10% in the three-month mortality rate with 80% and an alpha of 0.05 between the three groups.

Between-group-differences were assessed using analysis of variance (ANOVA) for continuous variables with a normal distribution and the Kruskal-Wallis test for variables with a non-normal distribution. $X^2$-statistics were used to assess between-group differences in the distribution of categorical variables. First, all variables with a p-value<0.20 were determined to be univariate predictors of mortality based in the results of logistic regression analysis. Next, these variables were retained and used in the multivariate model. To determine independent risk factors for short-term mortality, a decline in functional status, and a change in living arrangements, we performed logistic regression analysis after correcting for age, gender, co-morbidity status and polypharmacy.

Odds ratios (OR) were expressed with a 95% confidence intervals (95% CI). All p-value's <0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS statistical software (Statistics Package for Social Scientists, version 16.0).
RESULTS

Of the 945 eligible elderly patients who were acutely admitted to the department of Internal Medicine during the study period, 31 patients were excluded because plasma sodium was unknown at the time of admission, another 19 patients were excluded because they were admitted with medication-induced hypo- or hypernatremia, yielding a final population of 895 elderly patients with a mean age of 78 years (SD 8.7 years), 53.4% female and 87.0% native to the Netherlands. The mean plasma sodium level of the cohort was 136 mmol/L (SD 5.6 mmol/L). Based on the reference values used in our hospital 307 patients (34.3%) had hyponatremia (plasma sodium level (<135 mmol/L) and 22 patients (2.5%) had hypernatremia (>145 mmol/L). The plasma sodium levels of patients with values lower than 1 SD from the mean (low sodium group) ranged from 107-130 mmol/L, values in the reference group were 130-142 mmol/L, whereas values higher than 1 SD from the mean (high sodium group) were 142-162 mmol/L. Baseline characteristics of the patients stratified according to the groups with high and low plasma sodium are listed in Table 1. In the low sodium group, patients were more frequently female compared to the reference group (66% versus 51% respectively; p=0.04). The body weights of patients in the low sodium group (69.2 kg, SD 15.6) and the high sodium group (67.9 kg, SD 12.4) were lower than those of patients in the reference group (72.1 kg, SD 14.9) (p= 0.02). Patients in the low plasma sodium group had a higher Charlson co-morbidity Index score at time of hospitalization (3.9 SD 2.5) than patients in the reference group (3.4 SD 2.3; p=0.01). The low plasma sodium group contained more patients with renal insufficiency than the reference group, although this difference was not statistical significant (28% vs. 20%; p=0.07). The use of diuretics tended to be more frequent in the low plasma sodium group (61%, p=0.06). In the high sodium group, patients’ the functional status was more impaired according to their Katz ADL Index score (7.4 SD 5.3, p<0.01) and patients in this group were less likely to live independently (48%, p=0.02) or alone (61%, p<0.01) than patients in either the low sodium group or the reference group.

In-hospital mortality rates did not differ, whereas three-month mortality rates were significantly different between groups with higher mortality in patients with low plasma sodium levels (32.8 %) as compared to the reference group (24.7%, p=0.04). Kaplan-Meier curves are depicted in Figure 1. The in-hospital mortality rates are shown in Table 2.

The three-month mortality rate was higher in the low plasma sodium group as compared to the reference group [OR 1.5 (95% CI 1.0-2.2); p=0.05], whereas mortality rates in patients in the high plasma sodium group was comparable [OR 1.0 (95% CI 0.4-1.7); p= 0.7] (Table 3). History of malignancy within the five years preceding the study as well as renal failure, heart failure, liver failure and polypharmacy were identified as risk factors for three-month mortality. After adjusting for these comorbidities, the risk of three-month mortality of patients in the low sodium group was comparable to that of the reference group [OR 1.2 (95% CI 0.8-1.9); p=0.4]. Additional correction for polypharmacy did not significantly affect these findings.
Patients in the low sodium group had a longer hospital stay [15.1 days (SD 14.8)] as compared to the reference group [10.3 days (SD 9.1)] and the high plasma sodium group [8.4 days (SD 7.4)] (p <0.01). The Katz ADL Index scores at three months increased from baseline in all groups, implying a general decrease in functional status (p<0.01). The magnitude of changes the Katz ADL index scores from baseline did not differ across the plasma sodium groups (Table 4). Although 8.9% of the study population (n=80) lived less independently three months after admission than they did prior to admission, no significant inter-group differences could be demonstrated.
Figure 1. Kaplan-Meier curves for mortality 90 days after admission in acutely admitted elderly patients. A. Low plasma sodium group versus reference group (32.8% vs. 24.7%; p= 0.04). B. High plasma sodium group versus reference group (26.2% vs. 24.7%; p=0.65)

Table 2. Follow-up characteristics of all included acutely admitted elderly

<table>
<thead>
<tr>
<th></th>
<th>Low sodium</th>
<th>Reference group</th>
<th>High sodium</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma sodium level mmol/L</strong></td>
<td>107-130</td>
<td>130-142</td>
<td>142-162</td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay</strong>(days)</td>
<td>15.1(14.8)</td>
<td>10.3(9.1)</td>
<td>8.4(7.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td>14(10.4%)</td>
<td>42(6.4%)</td>
<td>4(3.9%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Katz ADL† Index score three months after admission</strong></td>
<td>10.2(5.1)</td>
<td>8.6(5.7)</td>
<td>10(5.4)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Change in Katz ADL Index score</strong></td>
<td>2.8(4.3)</td>
<td>3.4(4.8)</td>
<td>2.0(4.1)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Living arrangements (independently)</strong></td>
<td>35(54%)</td>
<td>208(66%)</td>
<td>16(48%)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Change in living arrangement</strong></td>
<td>13(10 %)</td>
<td>58(9%)</td>
<td>9(9%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*In hospital survivors only † ADL; activities of daily living
Table 3. Three-month mortality risk, stratified by plasma sodium level grouping. Logistic regression analysis (univariate and multivariate analysis)

<table>
<thead>
<tr>
<th>Reference group</th>
<th>Low sodium HR (95% CI)</th>
<th>p-value</th>
<th>High sodium HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>1.0</td>
<td>1.5 (1.0 - 2.2)</td>
<td>0.05</td>
<td>1.1 (0.7 - 1.7)</td>
</tr>
<tr>
<td>After adjustment for age and gender</td>
<td>1.0</td>
<td>1.5 (1.0 - 2.2)</td>
<td>0.05</td>
<td>1.0 (0.7 - 1.6)</td>
</tr>
<tr>
<td>After adjustment for age, gender and co-morbidity*</td>
<td>1.0</td>
<td>1.2 (0.8 - 1.9)</td>
<td>0.6</td>
<td>(0.7-1.8)</td>
</tr>
<tr>
<td>After adjustment age, gender and co-morbidity and polypharmacy†</td>
<td>1.0</td>
<td>1.0 (0.6 - 1.8)</td>
<td>0.8</td>
<td>(0.6 - 2.1)</td>
</tr>
</tbody>
</table>

* co-morbidity was defined as a history of malignancy in the preceding five years, renal-, heart- and liver failure † polypharmacy was defined as ≥5 prescription drugs before admission

Table 4. Decline in daily functioning three months after admission, stratified by plasma sodium level grouping. Logistic regression analysis (univariate and multivariate analysis)

<table>
<thead>
<tr>
<th>Reference group</th>
<th>Low sodium HR (95% CI)</th>
<th>p-value</th>
<th>High sodium HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>1.0</td>
<td>1.0 (0.6 - 1.6)</td>
<td>0.9</td>
<td>0.7 (0.4 - 1.1)</td>
</tr>
<tr>
<td>After adjustment for age and gender</td>
<td>1.0</td>
<td>0.9 (0.4 - 1.5)</td>
<td>0.7</td>
<td>0.7 (0.4 - 1.1)</td>
</tr>
<tr>
<td>After adjustment for age, gender and co-morbidity*</td>
<td>1.0</td>
<td>0.8 (0.4 - 1.5)</td>
<td>0.6</td>
<td>0.7 (0.4 - 1.2)</td>
</tr>
<tr>
<td>After adjustment age, gender and co-morbidity* and polypharmacy†</td>
<td>1.0</td>
<td>0.9 (0.5 - 1.4)</td>
<td>0.6</td>
<td>0.8 (0.4 -1.9)</td>
</tr>
</tbody>
</table>

* co-morbidity was defined as a history of malignancy in the last preceding years, renal-, heart- and liver failure † polypharmacy was defined as >5 prescription drugs before admission
DISCUSSION

In this study, we demonstrated that hyponatremia was a frequently observed condition in our population of acutely admitted elderly patients with 34.3% having plasma sodium levels <135 mmol/L at admission. Low plasma sodium levels (<130 mmol/L) at presentation were associated with a 50% increased risk of mortality. This association remained after adjustment for age and gender. However, hyponatremia was not found to independently increase mortality risk after adjustment for co-morbid conditions associated with low plasma sodium levels.

To the best of our knowledge this is the first large prospective cohort study that has included acutely admitted elderly medical patients and examined the association between abnormal plasma sodium levels and important outcome parameters, including mortality, functional status and living arrangements. Because we were interested in examining whether or not deviations in plasma sodium levels could be used to predict mortality in this particular group of patients, we stratified patients in three groups based on their plasma sodium level. Patients were included in the low sodium group if their plasma sodium level was <1 SD below the mean, the reference group if their plasma sodium level fell within +/-1 SD of the mean, and in the high sodium group if their plasma sodium level was >1 SD above the mean. The logistic regression we performed, using reference values utilized in our hospital, adjusting for age, gender and co-morbidity yielded similar results.

To assess whether or not plasma sodium levels and mortality were differ between patients who participated in the study and eligible patients who did not participate in the study due to refusal to provide informed consent, a sensitivity analysis was performed including all eligible patients >65 years of age and above who were acutely admitted to the department of Internal Medicine between October 2004 and July 2007. The characteristics of patients who did not participate were similar to those of participating patients with regard to age, gender, plasma sodium levels and three-month mortality rates compared to participating patients.

We found a relative high prevalence of hypo- and hypernatremia in our study compared to other reports that examined disturbances in plasma sodium levels in acutely hospitalized patients. This difference may be explained by the fact that we included only elderly patients (≥65 year old), which meant that the mean age of patients in our study was higher to that of previous studies. The observed increased prevalence of hyponatremia in elderly patients is likely explained by age-related changes in plasma sodium level. Although the plasma sodium level does not change with age in healthy older individuals, age-related physiological changes may increase the patients’ susceptibility of disturbances in water and salt balance in elderly persons. Deficits in both the intensity and threshold of the thirst response, a decreased extracellular volume and reduced renal function may reduce the elderly patients’ ability to respond to changes of in their fluid
and electrolyte balance. Therefore deviations in plasma sodium levels may occur more frequently in the setting of an intercurrent illness.

In our study, mortality risk at three months was 50% higher for patients with plasma sodium levels <1SD below the mean. However, after adjusting for discharge diagnosis the association between plasma sodium levels and mortality disappeared. This suggests that the effect of deviations in plasma sodium levels on mortality is associated with the patients’ underlying disease rather than deviations in plasma sodium per se. This finding is in contrast with several other reports that examined the association between hyponatremia and mortality risk in hospitalized patients. However, these studies did not adjust for potential confounders such as disease states that are commonly associated with hyponatremia-related increases in mortality risk such as malignancy and neurological conditions as well as heart, renal and liver failure. However, in a recent cohort study however, deviations in plasma sodium levels were associated with an increased risk of one-year mortality, which persisted after multivariable adjustment. The discrepancy between their results and our findings may be explained by several factors. First, the increased mortality risk observed in this study was confined to certain disease categories that are known to have a poor prognosis if patients develop hyponatremia, such as neurological conditions, heart failure and metastatic cancer. This confirms the importance of accounting for the underlying disease when determining the association between hyponatremia and mortality risk. Secondly, the association between hyponatremia and mortality risk appeared to have a U-shaped curve with patients in the lowest quintile (plasma sodium below 120 mmol/L) having an equal prognosis as compared to the reference group (plasma sodium 135-144 mmol/L). The better prognosis observed in patients with severe hyponatremia as opposed to milder hyponatremia might be explained by the fact that patients who presented with severe hyponatremia were not admitted because of their underlying disease, but rather because of the severity of the observed deviation in their plasma sodium level. To avoid confounding by indication, we excluded patients who were admitted with a diagnosis of medication-induced hypo- or hypernatremia without evidence of concomitant disease. Finally, previous reports have suggested that the development of hyponatremia during hospitalization (which may be due to inappropriate fluid management) is a more important risk factor for in-hospital mortality than the plasma sodium level at time of admission. The increased risk of in-hospital mortality associated with deviations in plasma sodium levels that was observed both in our study and in the study performed by Waiker et al. could be related to the complications of volume therapy that was instituted to correct abnormal plasma sodium levels, rather than to a direct detrimental effect of abnormal plasma sodium levels on in-hospital mortality. However, we could not observe any cumulative differences between in-hospital mortality and three-month mortality rates in our cohort, suggesting that the contribution of inappropriate fluid management on in-hospital mortality was limited.

In our study, plasma sodium levels were associated with a prolonged hospital stay. Because a deviation in plasma sodium level may be a reason for prolonged hospitalization
in itself, we also assessed differences in functional status (defined by changes in Katz-ADL Index score) and living arrangements as a measure of morbidity. Baseline Katz-ADL-Index scores were higher for patients in both the low and high plasma sodium group than for patients in the reference group both at baseline and three months after admission. We could not demonstrate significant inter-group differences in functional decline that occurred following admission as assessed by changes in the Katz ADL Index score or changes in patients’ living arrangements after admission. This suggests that a lower functional is associated with an increased risk of hypo- or hypernatremia than high-functioning patients, but we could not demonstrate an association between plasma sodium levels and decline in functional status. It is well-known that severe deviations in plasma sodium levels cause dysfunction of the central nervous system characterized by lethargy, disorientation, loss of consciousness and, ultimately, coma and death. Interestingly, several studies have also demonstrated an association between mild hyponatremia and neurological manifestations, loss of independence, and cognitive impairment. Whether functional decline is a consequence rather than a cause of abnormal plasma sodium levels remains unclear.

CONCLUSION

Hyponatremia is common in acutely hospitalized elderly patients and associated with a 50% increased mortality risk three months after acute hospitalization. This association remained after adjustment for age and gender. However, hyponatremia is not an independent risk factor for mortality, as the excess mortality risk disappeared after we adjusted for concomitant disease at time of admission. Furthermore, no independent effect of plasma sodium levels was observed with regard to functional status or living arrangements. Therefore, plasma sodium levels at time of admission were not found to be independently associated with adverse outcomes in this patient population.
REFERENCES