ORIGINAL ARTICLE

The Association of Hyponatremia, Risk of Confusional State, and Mortality

A Prospective Controlled Longitudinal Study in Older Patients

Tania Zieschang, Marcia Wolf, Tinu Vellappallil, Lorenz Uhlmann, Peter Oster, Daniel Kopf

SUMMARY

Background: Hyponatremia and delirium are frequent problems in older hospitalized patients. Although confusional states are considered to be a possible complication of hyponatremia, there has been no systematic study to date of the precise prevalence of delirium among patients with hyponatremia and its effect on long-term outcomes.

Methods: In a 13-month period in 2009/2010, all patients with a serum sodium level less than or equal to 130 mmol/L (the hyponatremia group) in a cohort of hospitalized older patients were studied and compared to a normonatremic control group of patients who were matched for age, sex, and diagnosis group. The prevalence of delirium was determined by two-stage examination. In-hospital mortality, mortality six months after initial examination, and functional status were prospectively analyzed.

Results: 179 patients were identified whose serum sodium level was less than or equal to 130 mmol/L (7.9% of all treated patients), of whom 141 were included in the hyponatremia group. The mean age of the participants was 83 (range, 63–102), and 84% were women. Patients with hyponatremia suffered more often from delirium (22.7% versus 8.5%; $p = 0.002$) and had a higher in-hospital mortality (10.6% versus 2.1%; $p = 0.005$). The mortality six months after initial examination was 31.9% versus 22.7% ($p = 0.080$). 59.7% of patients in the hyponatremia group and 49% in the control group ($p = 0.146$) needed a higher level of chronic care after discharge than they had needed before the hospitalization.

Conclusion: Hyponatremia in hospitalized older patients is associated with a higher likelihood of delirium and an elevated in-hospital mortality.

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With a prevalence of 15–30%, hyponatremia is the most common electrolyte abnormality in hospital inpatients (1–3). Geriatric patients are a high-risk group because of their changed physiology, multimorbidities, and polypharmacy (4). In older persons, hyponatremia is usually mildly to moderately pronounced, with a serum sodium (SNa) concentration of 130–134 mmol/L and 125–129 mmol/L, respectively, as well as chronic—that is, the hyponatremia developed within a time period of more than 48 hours (5). Hyponatremia has a negative effect on a multitude of clinical parameters, among these several functional aspects that are reflected in the basic geriatric assessment (6, 7), and on cognitive performance. Even a mildly to moderately lowered sodium concentration is associated with cognitive impairment (8), which may improve again once the sodium concentration has been balanced (9). In contrast to acute hyponatremia, which results in cerebral edema (10), the mechanisms that lead to cognitive impairment in chronic hyponatremia remain unclear (4). The few studies on the effect of chronic hyponatremia on cognition described in an undifferentiated way cognitive impairments that had been recorded by means of screening instruments for dementia (6, 8) or an attention test (9). None of the studies documented whether participants were subject to delirium. The prevalence of delirium in older patients in general medical or geriatric wards is 29–64% (11). It constitutes a severe complication of the inpatient stay, with mortality 1.5 times higher in the first year after hospital admission (11), poorer long-term outcomes in terms of cognition (12), a reduction in functional performance, and a rate of institutionalization of 33.4% in patients with delirium, compared with 10.7% in patients without delirium (13).

Our study was the first to investigate the association of hyponatremia with delirium in a cohort of geriatric hospital inpatients compared with a carefully matched control group without hyponatremia. Subsequently we prospectively described the effects of hyponatremia and delirium on mortality and independent living in follow-up examinations during the inpatient stay and after six months.

Geriatric Centre at the University of Heidelberg, Agaplesion Bethanien Hospital Heidelberg:
Dr. med. Zieschang, Prof. Dr. med. Oster

SLK-Kliniken Heilbronn GmbH: Dr. med. Wolf

Department of Anesthesiology and Intensive Care, Evangelische Diakonissenanstalt Karlsruhe-Rüppurr:
Dr. med. Vellappallil

Institute for Medical Biometry and Informatics (IMBI), University of Heidelberg: Lorenz Uhlmann

Geriatric Hospital, Katholisches Marienkrankenhaus Hamburg, gGmbH: PD Dr. med. Kopf

TABLE 1

Comparison of baseline data

	HNG N = 141	CG N = 141	P value*
Age in years, median (range)	83 (63–102)	84 (65–98)	0.249
>85 years, n (%)	43 (30.5)	53 (37.6)	
Rehab ward, n (%)	39 (27.7)	52 (36.9)	0.058
Acute ward, n (%)	102 (72.3)	89 (63.1)	
Deterioration of orientation/memory in the preceding 5 years (IQCODE) n (%) n = 109	37 (33.9)	23 (21.1)	0.031
Deterioration of orientation/memory in the preceding 14 days (IQCODE) n (%) n = 111	44 (39.6)	27 (24.3)	0.011
Social situation before admission			
– Independent, n (%)	86 (61.0)	86 (61.0)	0.724
– Living with relatives at home, n (%)	19 (13.5)	15 (10.6)	
– Receiving nursing care at home, n (%)	7 (5.0)	14 (9.9)	
– Sheltered housing, n (%)	5 (3.5)	9 (6.4)	
– Care home, n (%)	24 (17.0)	16 (11.3)	
MMSE T1 (points), median (range) n = 96	23 (0–30)	24 (2–30)	0.087
Barthel index at admission (points) median (range)	50 (0–100)	50 (0–100)	0.639
POMA at admission (points) median (range) n = 121	9 (0–27)	8 (0–25)	0.227
CIRS (points), median (range)	35 (23–48)	35 (24–53)	0.934
Number of drugs, median (range)	6 (0–15)	7 (0–14)	0.027
Loop diuretics, n (%)	43 (30.5)	74 (52.5)	<0.001
Thiazide diuretics, n (%)	36 (25.5)	19 (13.5)	0.017

We used the McNemar test to conduct a comparison between the groups for all administered drugs and medication groups; the table lists only those where the difference between groups reached significance.

* Wilcoxon signed rank test for continuous variables, McNemar test for categorical variables

Barthel index, maximum achievable score of 100 (16); CIRS, Cumulative Illness Rating Scale (18); HNG, hyponatremia group; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly (informant questionnaire for relatives, as the affected patient cannot be questioned) (14) (compared with 5 years previously/14 days previously, how is this person at memory/orientation: much improved [1], a bit improved [2], not much change [3], a bit worse [4], much worse [5]); CG, control group, matched by sex, age, and diagnosis at admission; MMSE, Mini Mental State Test according to Folstein, maximum achievable score of 30 points (15); POMA, performance oriented mobility assessment, maximum achievable score of 28 points (17); n, number of pairs with available data if these are not available for all patients;

Methods

Study design

We planned a prospective observational study with paired controls and a follow-up data collection six months later over the telephone. Heidelberg University's ethics committee approved the study protocol (application number S-224/2009). The study was registered with the German Clinical Trials Register (*Deutsches Register Klinischer Studien*, DRKS), registration number DRKS00004280.

Setting and participants

Study participants were consecutively recruited at AGAPLESION Bethanien Hospital Heidelberg, the university's geriatric center, in the acute geriatric ward and the inpatient geriatric rehabilitation ward from May 2009 to June 2010.

On each working day, the laboratory variables of all patients with hyponatremia ($\text{SNa} < 135 \text{ mmol/L}$) that had been measured on that day were recorded.

Hyponatremia group (HNG): All patients with moderately severe or severe hyponatremia ($\text{SNa} \leq 130 \text{ mmol/L}$) were eligible for inclusion in the study. We excluded patients whom we had not been able to examine within 24 hours or who refused participation in the study. If patients had cognitive impairment, their legal representatives agreed to participation; where necessary, where necessary, guardianship was instituted by local authorities. Each patient was included in the study only once. The treatment of hyponatremia was the responsibility of the treating physicians. The study did not affect the frequency of laboratory tests nor the treatment of hyponatremia.

Control group (CG): Each patient in the hyponatremia group was matched with a suitable patient with a serum sodium concentration that was consistently in the normal range. To this end, we selected for every case the patient who next received hospital treatment, who was comparable in terms of sex, age group (65–80 years or ≥ 80), and main diagnosis, and who gave

written consent. The main diagnoses were combined into groups according to the codes of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), following the chapter structure of the ICD-10. ICD-subgroups with disease symptoms such as cirrhosis of the liver, in whom hyponatremia typically occurs more often, were documented as independent groups (*eTable*).

We used the routine data shown in *Table 1* to check the comparability of the groups. All drugs were recorded as possible risk factors.

Cross-sectional study: delirium examination (T1)

All patients in both groups were examined for delirium within 24 hours after inclusion in the study (T1 examination). This was done in two stages: the mini mental state examination (MMSE; 15) confirmed cognitive impairment, and the confusion assessment method (CAM; 19, 20) confirmed delirium. In order to do justice to the potential fluctuation of the symptoms of delirium, we searched the documentation kept by the nursing staff and doctors for indications of delirium. Where this was suspected, we questioned nurses and doctors accordingly. In the second step, medical specialists ascertained the diagnosis on the basis of the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The screening examinations were not blinded regarding the patients' group allocation, but the subsequent investigations were. In a small number of cases however, the investigators were also the responsible treating physicians, so that complete blinding was not guaranteed. In order to distinguish delirium and dementia, or delirium in dementia, family members were surveyed in a standardized manner about the cognitive status five years earlier and 14 days earlier, by using Jorm's (14) Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) questionnaire.

Prospective studies

After seven days, the same standardized two-step diagnostic test for delirium was undertaken (T2 examination). Hospital mortality was determined after discharge.

A follow-up study took place six months after inclusion into the study. The long term effects of hyponatremia and delirium on mortality (primary analysis), housing situation, and level of care ('*Pflegestufe*', a four-step grading system provided by the German Social Security system) (secondary analysis) were documented by means of a questionnaire-supported, semistructured telephone survey of patients and/or their relatives. If it was not possible to reach these people then we interviewed their general practitioners. The investigation was blinded with regard to group allocation.

Statistical methods

Sample size calculation: We calculated the sample size for the primary endpoint rate of delirium. The risk of delirium in patients with hyponatremia was esti-

Flow chart of study recruitment

All patients with hyponatremia were consecutively recorded over a time period of 13 months. Controls were matched by sex, age, and diagnosis at admission. HNG, hyponatremia group; CG, control group

mated on the basis of a previously conducted pilot study, in which 10 out of 27 patients had delirium. In a more conservative calculation we assumed a rate of 35% for the sample size calculation. For the control group we used as our basis a study of delirium conducted in 2003/2004 in our hospital, in which 12 out of 50 patients with dementia had delirium. As dementia increases the risk of delirium, we estimated a rate of 20%. On the assumption of an α error of 5% and a statistical power of 80%, a sample of 109 cases per group was required in order to prove statistically significant differences. In order to be able to compensate for a dropout rate of 20% we attempted to recruit 137 patients per group.

Analysis of results: For categorical variables we presented absolute and relative frequencies. When comparing categorical variables between groups we used the McNemar test for paired samples, and for continuous variables we used the Wilcoxon test. We used the χ^2 test to compare categorical variables of non-paired subgroups. We used the t test for dependent variables to test the development over time of the sodium concentrations. Patients who had died in hospital were categorized as deceased in the follow-up examination. We assigned a higher level of care to deceased patients in order to avoid survivorship bias. The secondary endpoints (mortality, institutionalization, level of care) were evaluated in a purely

TABLE 2

Prevalence of delirium

	HNG N = 141	CG N = 141	P value*	Subgroup HNG with moderate hyponatremia N = 121	Subgroup CG paired with moderate hyponatremia N = 121	P value*
Delirium T1 n (%)	32 (22.7 %)	12 (8.5 %)	0.002	25 (20.7 %)	9 (7.4 %)	0.005
Delirium e T2 n (%)	15 (14.3 %) n = 105	7 (6.7 %) n = 105	0.088	12 (12.9 %) n = 93	6 (6.5 %) n = 93	0.157

The prevalence of delirium at T1 is the study's primary endpoint, the rate of delirium in the examination one week later (T2) is a secondary endpoint.

In a secondary analysis we compared the subgroup with moderate hyponatremia (n = 121) with the CG.

* McNemar test for paired samples, comparison between HNG and CG or comparison between subgroup with moderate hyponatremia and the paired subgroup of the CG.

HNG, hyponatremia group; CG, control group, matched for sex, age, and diagnosis at admission; moderate hyponatremia, serum sodium concentration 125–130 mmol/L; n, number of pairs with available data, if these were not available for all patients at T2

TABLE 3

In-hospital mortality, results of 6-month follow-up examination

	Died in hospital n (%)	P	Died after 6 months n (%)	P	Died after 6 months/ institutionalized n (%)	P	Higher level of care n (%)	P
HNG	15/141 (10.6)	0.005	45/141 (31.9)	0.080	65/140 (46.4)	0.067	83/139 (59.7)	0.146
CG	3/141 (2.1)		32/141 (22.7)		49/140 (35.0)		65/132 (49.2)	
Delirium	6/44 (13.6)	0.032	19/44 (43.2)	0.010	24/44 (54.5)	0.042	35/44 (79.5)	<0.001
No delirium	12/238 (5.0)		58/238 (24.4)		90/236 (38.1)		113/227 (49.8)	
HNG and delirium	5/32 (15.6)	0.298	13/32 (40.6)	0.229	16/32 (50.0)	0.645	25/32 (78.1)	0.016
HNG without delirium	10/109 (9.2)		32/109 (29.4)		49/108 (45.4)		58/107 (54.2)	
CG and delirium	1/12 (8.3)	0.119	6/12 (50.0)	0.018	8/12 (66.7)	0.016	10/12 (83.3)	0.013
CG without delirium	2/129 (1.6)		26/129 (20.2)		41/128 (32.0)		55/120 (45.8)	
HNG and delirium	5/32 (15.6)	0.530	13/32 (40.6)	0.576	16/32 (50.0)	0.323	25/32 (78.1)	0.703
CG and delirium	1/12 (8.3)		6/12 (50.0)		8/12 (66.7)		10/12 (83.3)	
HNG without delirium	10/109 (9.2)	0.007	32/109 (29.4)	0.099	49/108 (45.4)	0.036	58/107 (54.2)	0.208
CG without delirium	2/129 (1.6)		26/129 (20.2)		41/128 (32.0)		55/120 (45.8)	

In the secondary data analysis of the follow-up examination 6 months after inclusion in the study, we recorded by means of a telephone interview with patients and/or relatives or general practitioners mortality, institutionalization, and an increase in the level of care compared with before patients' inpatient stay.

We defined delirium according to the criteria of the DSM-IV. We used the McNemar test for paired samples to compare HNG versus CG. For our other calculations we used a mixture of matched and unmatched pairs and therefore used the χ^2 test for our calculation for unpaired samples.

DSM, Diagnostic and Statistical Manual of Mental Disorders; HNG, hyponatremia group; CG, control group, matched by sex, age, and diagnosis at admission.

FIGURE 2

Secondary endpoints in-hospital mortality and mortality after six months as %

- a) group comparison between hyponatremia group (HNG) versus control group (CG); for mortality after six months, subgroups with and without delirium are also shown; P values: as the groups were matched, we used the McNemar-Test for paired samples.
 b) Mortality comparison for patients with and without delirium; for mortality after six months, the subgroups from the HNG and CG are shown separately; P values: As the groups were not paired we used the χ^2 test.

descriptive way. The significance level was defined as $P = 0.05$. We used the software packages SPSS (Statistical Package for the Social Sciences, version 21) and R (23) for our analyses.

Results

Patient characteristics

In the study period, a total of 2267 patients (excluding patients with repeated admissions received inpatient treatment in the AGAPLESION Bethanien Hospital Heidelberg. The prevalence of serum sodium concen-

trations <135 mmol/L was 20.7% (470 out of 2267), seen in 22.7% (356 of 1566) of women and in 16.3% (114 of 701) of men. A serum sodium concentration of ≤ 130 mmol/L was seen in 179 patients; the prevalence was 7.9% (9.5% in women and 4.4% in men). Each group included 141 patients (118 women, 23 men) (Figure 1). The distribution of main diagnoses is shown in the eTable.

The groups did not differ with regard to social situation, independence, comorbidities, and mobility (Table 1). Because of work flow planning, we

conducted the T1 examination in the control group at a later date during their inpatient stay (a median of 8 days later). According to family members, patients in the hyponatremia group had experienced cognitive deterioration significantly more often, in the preceding five years as well as in the preceding 14 days. Patients in the hyponatremia group took thiazide diuretics significantly more often and loop diuretics significantly less often. The difference in the consumption of other drugs did not reach statistical significance.

A comparison of baseline data of patients with or without delirium showed the following results for those with delirium:

- A higher comorbidities index (18) (39.1 ± 5.9 versus 34.6 ± 5.6 points, $P < 0.001$)
- Greater dependency in activities of daily life (Barthel index [16]: 27.9 ± 24.2 versus 49.7 ± 26.2 points, $P < 0.001$)
- Higher rates of cognitive deterioration (over five years: 84.2 % versus 17.1 %, $P < 0.001$; over 14 days: 76.9 % versus 23.2 %, $P < 0.001$)
- No difference regarding age, sex distribution, and proportion of nursing/care home residents.

Progression of hyponatremia

In 79.4% of cases, patients had hyponatremia at the time of their admission to the hospital. The average sodium concentration rose from 127.0 ± 3.9 mmol/L (T1) to 133.0 ± 4.6 mmol/L (T2) ($P < 0.001$) within a week.

Occurrence of delirium

Delirium was significantly more common in the hyponatremia group (22.7 % versus 8.5 %, $P = 0.002$), and the same was true for the subgroup with moderate hyponatremia (20.7 %, $P = 0.005$). Seven days later, differences between the groups did no longer reach significance (Table 2). In the hyponatremia group, the delirium went into remission in 12 of 28 patients, in the control group in only 2 of 11 patients.

Follow-up examinations

In-hospital mortality was five times higher in patients in the hyponatremia group than in those in the control group. After six months, the outcomes seen in the hyponatremia group were worse (mortality 32% versus 23%, $P = 0.080$; mortality or institutionalization 46% versus 35%, $P = 0.067$), especially for the subgroup without delirium (45 % versus 32 %, $P = 0.036$) (Table 3, Figure 2).

In the total population, delirium was associated with a 2.5-fold increase in in-hospital mortality. Mortality after 6 months rose in patients with delirium in the total population as well as in the control group (Table 3, Figure 2).

An increased need for care, determined on the basis of the level of care, in both groups was associated with delirium. Hyponatremia, however, did not seem to have any relevant effect on the level of care (Table 3).

Discussion

The present study of geriatric patients showed a strong association of hyponatremia—even moderate hyponatremia—with delirium.

The prevalence of hyponatremia (SNa concentration < 135 mmol/L in 20.7% and $131\text{--}118$ mmol/L in 6.0%) was higher than in the geriatric cohort studied by Gosch et al. (6) (16.7% and 4.5%). The prevalence of milder forms was similar to the values in a review (5) for geriatric wards (SNa concentration < 135 mmol/L: 20.7% versus 22.2%; SNa concentration < 130 mmol/L: 4.7% versus 7.5%). The prevalence of severe hyponatremia was much lower (SNa concentration < 125 mmol/L: 0.9% versus 4.5%). As described earlier (25), the prevalence in women was higher than in men (9.5% versus 4.4%).

The prevalence of delirium was clearly higher in the hyponatremia group than in the control group. Earlier studies, mostly retrospective observational studies, showed that attention and cognitive performance are impaired in hyponatremia, which was interpreted as a causal association (4, 6, 8, 9). Notably, however, hyponatremia and delirium have important risk factors in common, especially age and underlying conditions. Conclusions about causality are therefore difficult to confirm on the basis of retrospective or uncontrolled studies. Furthermore, monocausal associations seem fundamentally unlikely in a multimorbid patient population. In the present study, the researchers were able to rule out important confounding variables because of comparisons with a matched control group. This adds support to the hypothesis that hyponatremia, even when less pronounced, may be regarded as a relevant cofactor in the pathogenesis of delirium. However, the fact that the hyponatremia group included a higher proportion of patients in whom relatives reported having observed cognitive deterioration before hospital admission illustrates the complexity of the association between hyponatremia and delirium. Factors that cause cognitive deterioration may also facilitate hyponatremia.

In-hospital mortality was five times higher in the hyponatremia group, even without a diagnosis of delirium. This means that in our study, mortality was higher than in a recent study (7) in patients who were younger (median 71 years) and in whom hospital mortality was 4%. In patients without delirium, the long-term study found a poorer prognosis for hyponatremia. Earlier studies identified hyponatremia as an independent risk factor (25, 26). The comparison with a matched control group with comparable comorbidities in our study supports the hypothesis that hyponatremia directly contributes to mortality.

Our study confirms that the administration of thiazide diuretics is a relevant risk factor for hyponatremia in older patients (27, 28). The fact that guidelines still recommend thiazide diuretics as the first-line medication for the treatment of arterial hypertension should be subject to critical revision in the light of these data.

An earlier study identified delirium as an independent risk factor for mortality and admission to institutionalized care (30). Accordingly, in the control group, delirium was associated with an increase in long-term mortality from 20% to 50% compared with patients without delirium. In the total cohort, mortality after delirium was slightly higher—at 43.2%—than in other geriatric cohorts with death rates of up to 40% (30).

Limitations and strengths

Our data cannot describe the causes of hyponatremia or the volume status with any certainty, but this is a fundamental difficulty in the geriatric population (4). Screening for delirium was not undertaken every day but only twice, at a week's interval. Furthermore, the patients in the control group were examined at a later time during their inpatient stay. We therefore cannot rule out the possibility that the delirium had already subsided. Thorough review of the documentation and discussion with the staff treating the patients did, however, enable us to include indications of delirium at other time points. As the precise onset of hyponatremia cannot be defined in most patients, no conclusions can be drawn regarding the sequence in which hyponatremia and delirium occurred. In order to ensure as much objectivity in the diagnostic evaluation of delirium, standardized approaches were used in the first stage, and in the second stage, the researchers were not informed about patients' sodium status. Complete blinding was, however, impossible in the clinical setting, which may have affected the assessment/evaluation in spite of the careful approach. The follow-up examination was completely blinded. The power analysis related to the prevalence of delirium depending on hyponatremia. The study was not adequately powered for the purposes of subgroup comparison regarding long term mortality.

The study had the following strengths:

- Consecutive inclusion of all patients with hyponatremia in a sample that was typical of geriatric inpatients
- First ever comparison of hyponatremia patients with a matched control group
- Standardized diagnostic evaluation of delirium
- Prospective follow-up.

Conclusions

Our results allow us to draw conclusions about the treatment of geriatric patients and further research in this area. Hyponatremia is common in older patients and is a risk factor for delirium even when mild. Furthermore, our study indicates that hyponatremia increases in-hospital mortality even in the absence of delirium and leads to poor long-term outcomes. The study did not show any increases in long-term mortality. Thiazide diuretics seem to constitute a crucial, avoidable risk factor. In view of its high prevalence, the absence of an algorithm for the diagnostic evaluation of hyponatremia deserves criticism, as does the fact that the existing guidelines are still based largely on expert recommendations, owing to lacking evidence (31).

KEY MESSAGES

- In a cohort of geriatric inpatients, the prevalence of hyponatremia (serum sodium concentration <135 mmol/L) was 20.7%, and of moderate to severe hyponatremia (serum sodium concentration ≤130 mmol/L), 7.9%.
- An important, avoidable risk factor seems to be therapy using thiazide diuretics.
- Even mild hyponatremia is associated with delirium. 22.7% of hyponatremia patients had delirium, compared with 8.5% in a comparable, matched control group.
- Even without delirium, hyponatremia was associated with increased in-hospital mortality.
- Delirium was not only associated with a higher in-hospital mortality of 14%; after 6 months, 43% of patients with delirium had died compared with 24% of patients without delirium.

Conflict of interests statement

The authors declare that no conflict of interest exists.

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Corresponding author

Dr. med. Tania Zieschang
Geriatrisches Zentrum an der Universität Heidelberg
Agaplesion Bethanien Krankenhaus Heidelberg
Rohrbacher Str. 149
69126 Heidelberg, Germany
tzieschang@bethanien-heidelberg.de

[Supplementary material](#)
eTable:
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Supplementary material to:

The Association of Hyponatremia, Risk of Confusional State, and Mortality

A Prospective Controlled Longitudinal Study in Older Patients

by Tania Zieschang, Marcia Wolf, Tinu Vellappallil, Lorenz Uhlmann, Peter Oster, and Daniel Kopf

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eTABLE

Groups of admission diagnoses

Diagnosis code ICD-10	Disorders	Number of pairs	Proportions
All A and B	Infectious and parasitic diseases	5	3.5 %
All C	Malignant neoplasms	16	11.3 %
D10–D48	Other neoplasms	1	0.7 %
D50–D90	Anemia, etc	3	2.1 %
E00–E03	Hypothyroidism	0	0 %
E04–E16, E50–E90	Other disorders of thyroid gland, pancreas	20	14.2 %
E20–E35	Disorders of other endocrine glands	0	0 %
F00–F09	Dementia, delirium	3	2.1 %
F30–F39	Mood (affective) disorders	3	2.1 %
Other F	Schizophrenia, alcoholism	1	0.7 %
G40–G41	Epilepsy	3	2.1 %
Other G, I60–I69	Stroke, TIA	13	9.2 %
I50	Heart failure	6	4.3 %
Other I, R55	Hypertension, coronary heart disease (CHD), syncope	9	6.4 %
All J	Lung diseases	9	6.4 %
K70–K77	Liver diseases	1	0.7 %
Other K	Diseases of the digestive system	6	4.3 %
All M, all S, R29	Diseases of the musculoskeletal system and connective tissue, fractures, falls	26	18.4 %
All N	Diseases of the genitourinary system	3	2.1 %
I62	Subdural hematoma	2	1.4 %
	Other diagnoses	11	7.8 %

Distribution of pairs into the groups of the International Statistical Classification of Diseases and Related Health Problems (ICD)-10: We matched control patients to hyponatremia patients by age, sex, and ICD-10 group of the admission diagnosis. TIA, transient ischemic attack.