Research Article

Sodium Fluctuations and Mortality in a General Hospitalized Population

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Keywords

Hyponatremia · Hypernatremia · Hospital mortality · Retrospective study · Survival analysis

Abstract

Background/Aims: Aim of our study was to describe the association between natremia (Na) fluctuation and hospital mortality in a general population admitted to a tertiary medical center. **Methods:** We performed a retrospective observational cohort study on the patient population admitted to the Fondazione Policlinico A. Gemelli IRCCS Hospital between January 2010 and December 2014 with inclusion of adult patients with at least 2 Na values available and with a normonatremic condition at hospital admission. Patients were categorized according to all Na values recorded during hospital stay in the following groups: normonatremia, hyponatremia, hypernatremia, and mixed dysnatremia. The difference between the highest or the lowest Na value reached during hospital stay and the Na value read at hospital admission was used to identify the maximum Na fluctuation. Cox proportional hazards models were used to estimate hazard ratios (HRs) for in-hospital death in the groups with dysnatremias and across quartiles of Na fluctuation. Covariates assessed were age, sex, highest and lowest Na level, Charlson/Deyo score, cardiovascular diseases, cerebrovascular diseases, dementia, congestive heart failure, severe kidney disease, estimated glomerular filtration rate, and number of Na measurements during hospital stay. **Results:** 46,634 admissions matched inclusion criteria. Incident dysnatremia was independently associated with in-hospital mortality (hyponatremia: HR 3.11, 95% CI 2.53, 3.84, $p < 0.001$; hypernatremia: HR 5.12, 95% CI 3.94, 6.65, $p < 0.001$; mixed-dysnatremia: HR 4.94, 95% CI 3.08, 7.92, $p < 0.001$). We found a higher risk of in-hos-

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pital death by linear increase of quartile of Na fluctuation (p trend <0.001) irrespective of severity of dysnatremia (HR 2.34, 95% CI 1.55, 3.54, p < 0.001, for the highest quartile of Na fluctuation compared with the lowest). **Conclusions:** Incident dysnatremia is associated with higher hospital mortality. Fluctuation of Na during hospital stay is a prognostic marker for hospital death independent of dysnatremia severity.

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Introduction

Dysnatremia is the most common electrolyte disorder in hospitalized patients; it encompasses hyponatremic and hypernatremic conditions. Hyponatremia is a pathological condition defined as a serum sodium <135 mmol/L. Epidemiological studies report a prevalence in the general population between 1 and 10% [1, 2] and between 15 and 20% in the hospital setting [3].

Hypernatremia is defined as a serum sodium >145 mmol/L. It is generally related to water losses with increase of plasma osmolality. It is less frequent than hyponatremia [4] with a reported in-hospital prevalence of up to 7.7% [5].

Serum sodium is the main cation of extracellular fluid and plays a key role in serum osmolality.

Although generally asymptomatic, dysnatremia may develop to a severe condition with high morbidity and mortality [6–8]. Severe hypernatremic conditions can lead to brain shrinkage potentially associated with cerebral bleeding, subarachnoid hemorrhage, and death [9].

Hyponatremic encephalopathy with brain injury is one of the most serious diseases following electrolyte disturbance. By contrast, mild to moderate chronic hyponatremia is considered a non-severe disease [6]. However, recent literature suggests that even mild hyponatremia and hypernatremia may have a considerable burden on patient outcomes, being associated with significantly higher mortality and length of hospital stay [10].

Although several studies evaluated the association between dysnatremia and in-hospital death, only a few reported on the association between incident in-hospital dysnatremia and mortality [11–15] and described the relation between sodium variations and patient outcomes [12, 14, 15].

The aim of our study was to report the incidence of dysnatremia and to analyze the association between development of dysnatremia, magnitude of sodium fluctuations, and in-hospital mortality in a general medical-surgical inpatient population admitted to a tertiary medical center.

Materials and Methods

Study Population

We performed a retrospective single-center observational study on the patient population admitted between January 1, 2010, and December 31, 2014, to the Fondazione Policlinico A. Gemelli IRCCS, a tertiary care academic medical center in Rome (Italy). Data extraction and analysis included only adult patients (≥ 18 years) admitted to the hospital during the period of interest with at least 2 sodium measurements available and with a normonatremic condition (sodium values between 135 and 145 mmol/L) at hospital admission. All patients admitted to the intensive care units (ICU) during hospital stay were excluded.

Data Source and Data Collection

Data were extracted from the Hospital's central electronic database using a specific website interface. We retrospectively collected demographic data including sex and age, clinical data, vital status at hospital

discharge, primary and secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD 9 CM) codes at discharge, and laboratory parameters (serum sodium, serum glucose). If a patient had multiple hospital admissions, all of them were included in the analysis.

Definitions

Hyponatremia was defined as a sodium level <135 mmol/L. Hypernatremia was defined as a sodium level >145 mmol/L. Patients were categorized according to all sodium values recorded during hospital stay in the following dysnatremic groups: hyponatremia (lowest/highest sodium values during hospital stay <135 and ≤ 145 mmol/L, respectively), hypernatremia (lowest/highest sodium values ≥ 135 and >145 mmol/L), mixed dysnatremia (lowest/highest sodium values <135 and >145 mmol/L), normonatremia (lowest/highest sodium values ≥ 135 and ≤ 145 mmol/L). The difference between the highest or lowest sodium value reached during hospital stay and the sodium value at hospital admission was used to identify the sodium fluctuation.

Sodium levels were corrected for the dilutional effect associated with hyperglycemia using validated methods [16, 17].

Outcomes and Covariates

The outcome of interest was in-hospital mortality. Our exposures of interest were the groups of dysnatremia and quartiles of sodium fluctuation. Covariates assessed to control confounding were age, sex, highest and lowest sodium level reached during hospital stay, cardiovascular diseases, cerebrovascular diseases, diabetes, severe kidney disease, dementia, congestive heart failure, estimated glomerular filtration rate (eGFR), malignancies, number of measurements, and Charlson/Deyo comorbidity index score [18]. ICD 9 CM codes were used to identify all comorbid conditions (diabetes: ICD 9 CM 250.1–250.7; cardiovascular diseases: ICD 9 CM 390–459; cerebrovascular diseases: ICD 9 CM 430–438; dementia: ICD 9 CM 290; malignancies: ICD 9 CM 140–239; liver diseases: ICD 9 CM 571.2, 571.4–571.6, 572.2–572.8). Severe kidney disease was identified at hospital admission as an eGFR <15 mL/min/1.73 m². eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation [19].

Statistical Analysis

Continuous variables were described using means (SDs) or medians (interquartile ranges) and categorical variables as counts (percentages). Categorical variables were compared using the chi-square test. Continuous variables were compared using Student *t* test or Mann-Whitney test as appropriate. The normality of the data distribution was assessed by visually inspecting the histograms and Q-Q plots.

Cox proportional hazards models were used to estimate unadjusted and adjusted hazard ratios (HRs) and 95% CIs for in-hospital death among the groups of dysnatremias (with the normonatremic group used as the reference) and across quartiles of sodium fluctuation (expressed as percentage and absolute values; the lowest quartile was used as the reference). Time at risk was calculated from the date of hospital admission up to the date of in-hospital death or discharge. All hospitalizations were censored at 60 days of hospital stay.

We assessed nonlinear relationships as well as the potential effect of the velocity (rate) of sodium changes by calculating the rate of change in mmol/L per 24 h and performing an analysis of the sodium slope and in-hospital death in the dysnatremic groups using restricted cubic splines (R studio, “rms” package [20]). Four knots were used at 5th, 25th, 75th, and 95th percentiles of the sodium fluctuation rate distribution. The sodium slope was calculated from an ordinary least-square regression model using all available sodium measurements for each patient between the sodium value at hospital admission and the highest or lowest sodium value reached during hospital stay.

All analyses incorporated standard errors clustered by patient identity to account for within-patient correlations.

A *p* value <0.05 was considered as statistically significant in all analyses.

All analyses were conducted using R version 3.4.4 (R Foundation for Statistical Computing, Vienna University of Economics and Business).

Fig. 1. Flowchart of the study.

Table 1. Demographic and clinical characteristics of study cohort at first hospital admission by serum sodium status

	Normonatremic group	Dysnatremic group	p value
Number	31,425	5,022	
Age, years	59.8 (17.8)	67.0 (16.3)	<0.001
Gender, males	13,883 (44.2)	2,436 (48.5)	<0.001
Charlson score			<0.001
0	25,045 (79.7)	3,449 (68.7)	
1	4,073 (13.0)	925 (18.4)	
2	1,299 (4.1)	327 (6.5)	
>2	1,008 (3.2)	321 (6.4)	
Charlson score	0.3 (0.9)	0.6 (1.2)	<0.001
Diabetes	307 (1.0)	63 (1.3)	0.060
Cardiovascular disease	10,485 (33.4)	2,090 (41.6)	<0.001
Congestive heart failure	1,126 (3.6)	316 (6.3)	<0.001
Malignancies	10,898 (34.7)	2,096 (41.7)	<0.001
Cerebrovascular disease	2,037 (6.5)	440 (8.8)	<0.001
Liver disease	673 (2.1)	203 (4.0)	<0.001
Dementia	133 (0.4)	50 (1.0)	<0.001
Severe kidney disease	412 (1.3)	173 (3.4)	<0.001
eGFR	79.7 (27.2)	70.7 (29.6)	<0.001

Values are presented as mean (SD) or *n* (%).

eGFR, estimated glomerular filtration rate.

Results

Demographics

Between January 1, 2010, and December 31, 2014, 338,754 adult patients were admitted to the hospital. Overall, 46,634 admissions from 36,447 unique patients matched inclusion criteria (Fig. 1). There were 6,848 incident dysnatremic admissions (14.7%). The baseline characteristics of the cohort (referred to the first hospital admission for each patient) are shown in Table 1. As expected, compared with normonatremic patients, dysnatremic patients were older and had higher prevalence of comorbidities (mean Charlson/Deyo score comorbidity index: 0.6 [SD 1.2] vs. 0.3 [SD 0.9], $p < 0.001$). Specifically, we found a higher prevalence of cardiovascular diseases (41.6 vs. 33.4%, $p < 0.001$), cerebrovascular diseases (8.8 vs. 6.5%, $p < 0.001$), severe kidney diseases (3.4 vs. 1.3%, $p < 0.001$) in the dysnatremic groups. The characteristics of the entire cohort stratified by quartiles of percentage sodium fluctuation are reported in Table 2.

Outcomes

Incident Dysnatremia and In-Hospital Death

Incident dysnatremia was associated with increased risk of in-hospital death (Table 3): the incidence of in-hospital death among dysnatremic patients was 4.6% (subgroup analysis: incident hyponatremia 3.9%; incident hypernatremia 5.4%; mixed-dysnatremia mortality of 14.2%) compared with 0.5% in patients who did not develop dysnatremia during hospital stay.

In multivariate analysis, incident dysnatremia was independently associated with in-hospital death (hyponatremia HR 3.11, 95% CI 2.53, 3.84, $p < 0.001$; hypernatremia: HR 5.12, 95% CI 3.94, 6.65, $p < 0.001$; mixed-dysnatremia: HR 4.94, 95% CI 3.08, 7.92, $p < 0.001$). Patients with hypernatremia showed increased risk for in-hospital death compared with hyponatremic patients (HR 1.64, 95% CI 1.27, 2.12, $p < 0.001$).

Table 2. Demographic and clinical characteristics of study cohort at first hospital admission by quartile of sodium fluctuation

	1st quartile (<0.7%)	2nd quartile (0.7–2.1%)	3rd quartile (2.1–2.9%)	4th quartile (>2.9%)
Number	9,841	9,667	8,420	8,519
Age, years	58.3 (17.9)	60.5 (17.7)	60.5 (17.8)	64.1 (17.2)
Gender, males	4,266 (43.3)	4,336 (44.9)	3,773 (44.8)	3,944 (46.3)
Charlson score				
0	8,015 (81.4)	7,620 (78.8)	6,599 (78.4)	6,289 (73.8)
1	1,252 (12.7)	1,324 (13.7)	1,145 (13.6)	1,295 (15.2)
2	321 (3.3)	391 (4.0)	388 (4.6)	501 (5.9)
>2	253 (2.6)	332 (3.4)	288 (3.4)	434 (5.1)
Charlson score	0.3 (0.8)	0.4 (0.9)	0.4 (0.9)	0.5 (1.0)
Diabetes	78 (0.8)	93 (1.0)	93 (1.1)	113 (1.3)
Cardiovascular disease	3,202 (32.5)	3,357 (34.7)	2,862 (34.0)	3,098 (36.4)
Congestive heart failure	261 (2.7)	369 (3.8)	335 (4.0)	421 (4.9)
Malignancies	3,164 (32.2)	3,353 (34.7)	3,071 (36.5)	3,508 (41.2)
Cerebrovascular disease	643 (6.5)	633 (6.5)	490 (5.8)	692 (8.1)
Liver disease	191 (1.9)	232 (2.4)	221 (2.6)	236 (2.8)
Dementia	29 (0.3)	44 (0.5)	34 (0.4)	62 (0.7)
Severe kidney disease	66 (0.7)	124 (1.3)	136 (1.6)	235 (2.8)
eGFR	82.1 (25.6)	78.9 (27.0)	78.5 (27.9)	73.8 (29.3)

Values are presented as mean (SD) or *n* (%).

eGFR, estimated glomerular filtration rate.

Table 3. Association between serum sodium status and in-hospital death

	Normonatremia	Hyponatremia	Hypernatremia	Mixed dysnatremia
Admissions, <i>n</i>	39,786	4,827	1,881	140
Patients, <i>n</i>	31,425	3,466	1,450	106
In-hospital death, <i>n</i> (%)	144 (0.5)	135 (3.9)	79 (5.4)	15 (14.2)
Univariate HR (95% CI)	1.00	3.93 (3.21, 4.80)	7.04 (5.48, 9.05)	8.73 (5.63, 13.54)
<i>p</i> value	Reference	<0.001	<0.001	<0.001
Multivariate HR (95% CI)*	1.00	3.11 (2.53, 3.84)	5.12 (3.94, 6.65)	4.94 (3.08, 7.92)
<i>p</i> value	Reference	<0.001	<0.001	<0.001
Multivariate HR (95% CI)*	0.32 (0.26, 0.40)	1.00	1.64 (1.27, 2.12)	1.59 (0.99, 2.54)
<i>p</i> value	<0.001	Reference	<0.001	0.056
Multivariate HR (95% CI)*	0.20 (0.15, 0.25)	0.61 (0.47, 0.78)	1.00	0.96 (0.59, 1.58)
<i>p</i> value	<0.001	<0.001	Reference	0.886
Multivariate HR (95% CI)*	0.20 (0.13, 0.32)	0.63 (0.39, 1.01)	1.04 (0.63, 1.69)	1.00
<i>p</i> value	<0.001	0.056	0.886	Reference

*Adjusted for baseline covariates (age, sex, Charlson/Deyo Score, diabetes, cardiovascular disease, congestive heart failure, malignancies, eGFR, severe kidney disease, cerebrovascular disease, dementia, liver diseases, number of sodium measurements).

HR, hazard ratio; eGFR, estimated glomerular filtration rate.

Table 4. Association between quartiles of sodium fluctuation (expressed as percentage) and in-hospital death

	1st quartile (<0.7%)	2nd quartile (0.7–2.1%)	3rd quartile (2.1–2.9%)	4th quartile (>2.9%)	<i>p</i> value trend
Admissions, <i>n</i>	12,109	12,165	10,890	11,470	
Patients, <i>n</i>	9,841	9,667	8,420	8,519	
In-hospital death, <i>n</i> (%)	22 (0.2)	33 (0.3)	55 (0.7)	208 (2.4)	
Univariate HR (95% CI)	1.00	1.22 (0.77, 1.92)	1.88 (1.24, 2.83)	4.72 (3.28, 6.78)	<0.001
<i>p</i> value	Reference	0.396	0.003	<0.001	
Multivariate HR (95% CI)*	1.00	1.03 (0.65, 1.63)	1.51 (0.99, 2.31)	2.34 (1.55, 3.54)	<0.001
<i>p</i> value	Reference	0.899	0.057	<0.001	

* Adjusted for baseline covariates (age, sex, Charlson/Deyo Score, diabetes, cardiovascular disease, congestive heart failure, malignancies, eGFR, severe kidney disease, cerebrovascular disease, dementia, liver diseases, the lowest and the highest serum sodium levels reached during hospital stay, number of sodium measurements).

HR, hazard ratio; eGFR, estimated glomerular filtration rate.

Table 5. Association between quartile of sodium fluctuation (expressed as absolute value) and in-hospital death

	1st quartile ≤1 mmol/L	2nd quartile 1–3 mmol/L	3rd quartile 3–4 mmol/L	4th quartile >4 mmol/L	<i>p</i> value trend
Admissions, <i>n</i>	12,590	17,388	5,790	10,866	
Patients, <i>n</i>	10,205	13,727	4,443	8,072	
In-hospital death, <i>n</i> (%)	28 (0.3)	56 (0.4)	29 (0.7)	205 (2.5)	
HR crude (95% CI)	1.00	1.29 (0.88, 1.88)	1.34 (0.85, 2.10)	4.08 (2.93, 5.69)	<0.001
<i>p</i> value	Reference	0.189	0.207	<0.001	
HR adjusted (95% CI)*	1.00	1.08 (0.74, 1.59)	1.01 (0.64, 1.61)	1.93 (1.30, 2.85)	<0.001
<i>p</i> value	Reference	0.685	0.965	0.001	

* Adjusted for baseline covariates (age, sex, Charlson/Deyo Score, diabetes, cardiovascular disease, congestive heart failure, malignancies, eGFR, cerebrovascular disease, dementia, liver diseases, the lowest and the highest serum sodium levels reached during hospital stay, number of sodium measurements).

HR, hazard ratio; eGFR, estimated glomerular filtration rate.

Sodium Fluctuation and Mortality

Tables 4 and 5 report the association between quartiles of sodium fluctuation and in-hospital death.

There was a higher risk of in-hospital death among increasing quartiles of sodium fluctuation (*p* value for trend <0.001).

Multivariate analysis revealed a HR of 2.34 (95% CI 1.55, 3.54, *p* < 0.001) for in-hospital death in the highest quartile of percentage sodium fluctuation compared with the lowest (Table 4).

Similar results were found when absolute values of sodium fluctuation were used (Table 5).

Figure 2 shows the association between the sodium slope and in-hospital death in incident hyponatremic and hypernatremic patients. Using restricted cubic splines, we found a nonlinear (*p* < 0.001) increase in the risk of in-hospital death with increasing sodium slope.

Fig. 2. Association between sodium slope and in-hospital death. Multivariate HRs (95% CI) of in-hospital death associated with sodium slopes using restricted cubic splines, adjusted for age, sex, Charlson/Deyo Score, diabetes, cardiovascular diseases, congestive heart failure, malignancies, eGFR, severe kidney disease, cerebrovascular disease, dementia, liver diseases, the lowest and the highest serum sodium level reached during hospital stay, number of sodium measurements. HR, hazard ratio.

Discussion/Conclusion

In this study, we describe the association between incident dysnatremia and in-hospital death and, to the best of our knowledge for the first time, the association between sodium fluctuation and in-hospital death in a general medical-surgical non-ICU hospitalized population. Incident dysnatremia is confirmed to be an independent risk factor for in-hospital death and sodium fluctuations are associated with increased in-hospital death independent of the severity of dysnatremia.

Dysnatremia is the most common electrolyte disorder. To date, a variety of studies evaluated its epidemiology in hospital patients reporting a quite varied incidence and prevalence especially because it is strongly influenced by the study population (ICU vs. non-ICU). The prevalence of hyponatremia in the hospital setting has been described to range between 12 and 17% [5, 11, 21–23] and 40% in the hospitalized population [24]. Similarly, several studies demonstrated that hypernatremia appeared also to be common at hospital admission ranging from 0.5 to 7.7% [5, 25–28]. However, most of these studies focused on critically ill ICU patients or analyzed community-acquired dysnatremia observed at hospital admission. Conversely, few studies have investigated hospital-acquired dysnatremia and its incidence during hospital stay. The incidence of in-hospital hyponatremia and hypernatremia has been described ranging from 9.0 to 13.6% [11, 12] and from 1.0 to 9.1% [11, 12], respectively.

In order to describe the incidence of dysnatremia during hospital stay, we considered only normonatremic patients at hospital admission. Here we reported one of the largest retrospective studies focusing on hospital-acquired dysnatremia, with an incidence of hyponatremia and hypernatremia of 10.7 and 4.3%, respectively (Table 3).

Explanations for differences in dysnatremia epidemiology compared with previous works include study design (retrospective vs prospective), sample sizes, differences in study population, and in cutoff levels used to define dysnatremia.

Medical interest in dysnatremic conditions is justified by the burden of morbidity and mortality associated with its development. Adverse consequences following dysnatremic conditions have been widely reported in the scientific literature. The association between dysnatremia and mortality is well known in clinical practice and documented in medical literature. Waikar et al. [22] showed that 98,411 prospective patients with hyponatremia had higher in-hospital, 1-year, and 5-year mortality rates than patients without hyponatremia. Hu et al. [11] demonstrated that all kinds of dysnatremia were independently associated with in-hospital mortality, and mixed dysnatremia (especially “hypo- to hyper”) and hypernatremia (especially hospital-acquired and persistent hypernatremia), were strong predictors of mortality. Recent scientific literature suggests also a possible role of borderline or mild forms of dysnatremia on patient outcomes [5, 12, 13, 22, 29, 30].

In our cohort, 4.6% of all patients who developed a dysnatremic condition died during hospital stay. In survival analysis, incident dysnatremia was associated with increased in-hospital mortality both in incident hyponatremic and hypernatremic patients. Worthy of notice, the hypernatremic groups had higher risk of death compared with the hyponatremic group.

Our study focused also on sodium fluctuations and mortality. According to data an increase of the blood sodium concentration $>2.9\%$ from its baseline value is associated with in-hospital death independently of severity of dysnatremia. Furthermore, as expected, a fluctuation occurring too quickly was associated with increased risk of in-hospital death, regardless of sodium value (Fig. 2).

Investigations into sodium fluctuation are still lacking. In particular, the link between sodium fluctuations and in-hospital death is poorly characterized. Until now, this issue has been investigated only in 3 other works [12, 14, 15]. However, those studies were set in ICU in critically ill patients rather than general population patients. Here, focusing on a mixed medical-surgical non-ICU population, we provide increased generalizability to our results, underlining the importance that mild sodium fluctuations ($>2.9\%$ or 4 mmol/L from baseline value) and incident dysnatremia carry on patient outcomes.

Similar to previous works, we found a significant association between severity of dysnatremia and mortality. However, while the link between the most severe forms of dysnatremia and mortality has a strong rationale, data on the risk associated with small sodium fluctuations are lacking and the mechanism leading to higher mortality are still unclear. According to our data, a sodium fluctuation just a bit over 4 mmol/L from baseline was significantly associated with higher in-hospital death. As recently elucidated by a consensus statement from the Italian Society of Endocrinology, Italian Society of Nephrology and the Italian Association of Medical Oncology electrolytes disorders (especially in hyponatremic status) are frequently associated with cardiovascular, liver, malignancies, renal diseases (as well as showed in our study) [31]. It is possible that sodium fluctuation is a potential marker of underlying disease severity. In fact, in our data, we report a higher baseline prevalence of cerebrovascular, renal, and cardiovascular diseases in the highest quartile of sodium fluctuation, all conditions characterized by deranged osmolality control. A direct effect of dysnatremia and mild sodium fluctuations on mortality could also be hypothesized. Sodium is not only the main determinant of plasma osmolality [32] but it also plays a key role in several biochemical and electrical processes within the body [33]. However, our study was not designed to elucidate a possible causal relationship between sodium fluctuations and in-hospital death. Because of the retrospective observational study design, here we can only document an association between exposures and outcomes and only speculate on potential mechanisms.

Our work has several limitations. First, it is a retrospective study conducted on a single hospital center; hence, generalizability of our results could be limited. However, we could include in our analysis admissions from all kinds of medical and surgical wards, which in part improves external validity of our findings. We have no information on causes of dysnatremia and treatments administered during hospital stay, so we could not correct our outcomes for different causes of dysnatremia. Furthermore, we used administrative codes for identification of all comorbid conditions; however, to account for comorbidities, we used the Charlson/Deyo score, a validated method of categorizing comorbidities of patients based on the ICD diagnosis codes from administrative data.

Regarding the strengths of our study, to date this is one of the largest retrospective works on the epidemiology of incident dysnatremia and in-hospital death and, to the best of our knowledge, our work describes for the first time the impact of sodium fluctuations on in-hospital death in a general hospitalized population.

What we would emphasize with our study is the importance that even mild variations in sodium levels have on patient outcomes. It is necessary to pay attention to both small and rapid sodium fluctuations, even when in a normonatremic range.

In summary: (i) incident dysnatremia is associated with increased in-hospital death; (ii) incident hypernatremia is associated with higher mortality than hyponatremia; (iii) sodium fluctuations during hospital stay is a potential predictor of in-hospital death independent of dysnatremia severity.

Statement of Ethics

The Ethics committee of Fondazione Policlinico Universitario A. Gemelli IRCCS approved the research protocol.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

G.G., P.M.F., and G.L. contributed to the research idea and study design. G.L. contributed to data acquisition. G.G., P.M.F., and G.L. contributed to data analysis/interpretation. P.M.F. and G.L. contributed to statistical analysis. G.L. and L.C. drafted the paper. G.G., P.M.F., A.N., and S.D.A. contributed to supervision. Each author contributed important intellectual content during manuscript drafting for the overall work.

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