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Original Article

Hyponatremia, all-cause mortality, and risk of cancer diagnoses in the primary care setting: A large population study

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ABSTRACT

Background: Hyponatremia has been associated with increased all-cause mortality in hospitalized individuals. In this study we examine the risk of all-cause mortality in primary care subjects with hyponatremia, while also exploring the association with subsequent diagnosis of cancer.
Methods: Retrospective cohort study on subjects who underwent blood tests, consulting their general practitioner 2000–2012 in Copenhagen, Denmark. Reference range for sodium was 135–145 mmol/L, and mild, moderate, and severe hyponatremia were defined as 130–135, 125–129, and <125 mmol/L, respectively. Primary outcome was all-cause mortality, and secondary outcomes overall and specific types of cancer diagnoses.
Results: Among 625,114 included subjects (mean age 49.9 [SD ± 18.4] years; 43.5% males), 90,926 (14.5%) deaths occurred. All-cause mortality was increased in mild, moderate, and severe hyponatremia (age-adjusted mortality rates [IRs, incidence rates] 26, 30, and 36 per 1000 person-years (py), respectively and incidence rate ratios [IRRs] 1.81 [95% CI: 1.76–1.85], 2.11 [2.00–2.21], and 2.52 [2.26–2.82], respectively) compared with individuals with normonatremia (IR 14 per 1000 py). For the secondary endpoint an increased level-dependent risk was found with lower sodium levels in relation to cancer overall, head and neck cancers, and pulmonary cancer, with severe hyponatremia associated with the highest IRRs (1.77 [1.39–2.24], 5.24 [2.17–12.63]), and 4.99 [3.49–7.15], respectively).
Conclusions: All levels of hyponatremia are associated with all-cause mortality in primary care patients and hyponatremia is linked to an increased risk of being diagnosed with any cancer, particularly pulmonary and head and neck cancers.

1. Introduction

Hyponatremia in hospitalized patients is very common, and studies on newly hospitalized patients have shown a strong association between hyponatremia and an increased risk of death, as recently reviewed in a meta-analysis on 81 studies including 850,222 patients total (17.4% with hyponatremia) [1,2]. In this analysis, hyponatremia was associated with 2.5–3.5 times increased mortality during the hospital stay largely independent of the underlying disease. However, the majority of these studies were based on selected cohorts known to have increased mortality, and most of them were relatively small. In a recent Danish cohort study of 279,508 individuals with a first-time acute admission to a medical department, the 30 day and 1 year mortality were increased 1.7 and 1.4 times in hyponatremia, respectively [3]. It is unclear whether this association is caused by hyponatremia itself or it is caused by increased vulnerability due to underlying medical conditions or concomitant medications.

Hyponatremia is often seen among patients with active cancer in 5–30% of patients [4–6]. When looking at subtypes of cancers, there is an increased prevalence of hyponatremia especially in lung cancer, but also upper respiratory tract and gastrointestinal cancers [7]. In both untreated cancer and later during treatment, several chemotherapeutics,

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nausea, vomiting, and pain seem to induce hyponatremia. This is most often due to the syndrome of inappropriate anti-diuretic hormone (vasopressin) (SIADH) [8]. Thus, hyponatremia reflects the presence of active cancer tissue and is also a response to treatment. With the recent development of selective vasopressin receptor antagonists for treatment of hyponatremia, it is important to study the impact of hyponatremia in patients evaluated in primary care [9,10].

Only a few studies have been carried out on primary care patients; however, recently Hoorn et al. reported an increased risk of all-cause mortality in 5208 elderly subjects, 399 with hyponatremia, from the Rotterdam Study [11]. With the present large-scale study, we evaluated if hyponatremia in the primary care setting was a predictor for all-cause mortality, as well as for the diagnosis of several clinically overt cancer types including lung, gastrointestinal, and urogenital. We performed extensive sensitivity analyses to examine the temporal importance of hyponatremia, followed by spontaneous normalization.

2. Materials and methods

2.1. Study setting

In Denmark, each resident has a permanent and unique civil registration number, enabling individual level-linkage between nationwide administrative registers on healthcare usage [12]. Since 1978, the Danish National Patient Registry has registered all hospital contacts in Denmark [13]. Each admission is registered with one primary and, if appropriate, one or more secondary diagnoses according to the World Health Organization International Classification of Diseases 10th revision (ICD-10). The Danish Register of Medicinal Product Statistics holds information regarding all claimed prescriptions (coded according to the international Anatomical Therapeutic Chemical [ATC] classification) in Denmark since 1995 [14]. The registry also includes information on the date of dispensation, strength, and quantity dispensed. Due to partial reimbursement of drug expenses by the Danish healthcare authorities, all pharmacies are required to provide information that ensures complete and accurate registration [15]. Vital status was obtained from the Central Population Register, which records all deaths within 14 days [12]. Specific causes of death were obtained from the Danish Register of Causes of Death [16]. Annual incomes were retrieved from the Integral Database for the Danish Labour Market [17], and socioeconomic status was defined by the average yearly gross household income in a 5-year period prior to inclusion in the study. We conducted and reported this study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative guidelines [18].

2.2. Population

The study cohort comprised citizens of Copenhagen (the capital of Denmark), aged 18 years or older, who had serum sodium analyzed in the period from 1 January 2000 to 31 December 2012. Each subject entered the cohort at the first known assessment of serum sodium and was followed until 31 December 2012, migration, or death. The Copenhagen General Practitioners Laboratory analyses tests from primary care physicians in the Copenhagen area, except for the municipality of Frederiksberg. This corresponded to approximately 1.17 million inhabitants in 2009. Serum sodium concentrations were determined using the commercially available ADVIA Centaur System (Bayer/Siemens, Tarrytown, NY), according to the instructions of the manufacturer. Individuals where categorized according to their sodium levels at the time of first testing into three levels of hyponatremia. The normal reference range for serum sodium was 135–145 mmol/L, and mild, moderate, and severe hyponatremia were defined as 130–135, 125–129, and <125 mmol/L, respectively.

2.3. Co-morbidity and concomitant medical therapy

We identified co-morbidities from the Danish National Patient Registry using the ICD-10 diagnosis codes for e.g. heart failure, adrenal insufficiency, and renal failure (Supplementary Table A) [19,20]. The Charlson Comorbidity Index was based on 16 pre-specified diagnoses up to five years prior to cohort entry [21,22]. We identified all claimed prescriptions of commonly used medications known to potentially cause disturbances in serum sodium from the Danish Register of Medicinal Product Statistics [23].

2.4. Outcomes

The primary outcome was all-cause mortality. Secondary outcomes included the diagnoses of head and neck, pulmonary, gastrointestinal, urogenital, hematological, and other cancers.

2.5. Statistical analysis

Baseline characteristics are presented as numbers with percentages for categorical variables and as means (±SD) for continuous variables. Median follow-up time was reported with the interquartile range (IQR). Incidence rates (IRs) were the number of events per 1000 person-years (py), stratified by sodium-level. We constructed age-adjusted Kaplain Meier curves for the primary endpoint of all-cause mortality. We assessed cumulative incidence proportion curves for any cancer at all levels of hyponatremia using a competing risk model to adjust for all-cause mortality in the cohort [24]. We constructed time-dependent Poisson regression models to estimate incidence rate-ratios (IRRs, with 95% confidence intervals [CIs]) for each study outcome. The Poisson regression models were adjusted for age, sex, and calendar year; therefore, they included two time scales: Calendar time with bands split in 1-year periods after 1st of January 2000, and duration time since first serum sodium measurement. Age was calculated at the beginning of each interval. Individuals were censored at the time of death, the end of the follow-up period (31st of December 2012), or at migration. The significance level was set at 5% in all analyses, including testing for interactions.

We validated our primary findings with several sensitivity analyses. First, we stratified all results by sex and age. Second, we stratified whether a second serum sodium testing demonstrated a normalized or a continued state of hyponatremia. Third, we adjusted for baseline covariates including medication. Fourth, we limited the follow-up time to only 6 months to assess the short-term outcome following a single measurement of serum sodium. Within this 6-month follow-up period, we also limited the cohort to patients treated with diuretics only, patients treated with Selective Serotonin Reuptake Inhibitors (SSRI) only, and patients treated with neither diuretics nor SSRI. Finally, we looked at the full follow-up period under three special circumstances: 1) including only SSRI treated individuals with no diuretics use; 2) introducing a 30-day grace period (postponing the follow-up period by 30 days) in the analysis to assess the potential issue of confounding by indication; and 3) adjusting the main model for the Charlson Comorbidity Index and use of SSRI and diuretics; 4) adjusting for hypothyroidism at time of sodium evaluation defined as thyroid-stimulating hormone (TSH) >4.5; 5) regrouping hyponatremia using frequency groups. All statistical analyses were performed with the SAS Statistical Software package version 9.2 (SAS Institute Inc., Gary, NC, USA) and Stata Software version 11 (StataCorp, College Station, TX, USA).

3. Results

A total of 625,114 individuals were included (Fig. 1) at the first serum sodium testing from 2000 to 2012. Baseline characteristics of the cohort are presented in Table 1. The study cohort comprised more

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