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Original Article

Hyponatraemia is independently associated with in-hospital mortality in patients with pneumonia

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ABSTRACT

Background: Hyponatraemia on hospital admission has been shown to be a risk factor for illness severity in critically ill patients. The aim of the present study was to investigate whether hyponatraemia on emergency department (ED) admission independently influences in-hospital mortality, ICU admission, and/or length of hospitalisation in patients with pneumonia.

Methods: 610 patients (64.4% male, median 66 years) diagnosed with pneumonia were identified by retrospective screening of electronic admission data (06/2011–06/2013). Patients were admitted to the ED of Bern University Hospital, Switzerland. Patient characteristics, potential confounders, and patient-centred clinical outcomes, including mortality, ICU admission, and length of hospitalisation, were analysed. Multivariate logistic analysis adjusted for typical confounders was performed to analyse the association of hyponatraemia with clinical outcomes.

Results: In a large cohort of consecutive acutely admitted patients with pneumonia, the overall in-hospital mortality rate was 12.5%; 21.2% of patients required primary or secondary ICU admission, and the median length of hospital stay was 8 (IQR 5–13) days. At baseline, 47 patients (7.7%) were found to have concomitant hyponatraemia. Multivariate regression revealed a significant association between hyponatraemia and in-hospital mortality (adjusted OR: 2.7, 95% CI: 1.3–5.9, $p = 0.010$), but not with ICU admission (adjusted OR: 1.8, 95% CI: 0.9–3.6, $p = 0.103$) or length of hospitalisation ($p = 0.493$) after adjustment for age, neoplasia, COPD, suspected sepsis, and cardiac disease. The association was robust if controlled for other covariates, e.g. CRB-65 score.

Conclusions: Hyponatraemia on admission predicts poor outcome and is an independent risk factor for in-hospital mortality in admitted patients diagnosed with pneumonia.

1. Introduction

Pneumonia is a leading cause of death in Western Countries [1]. Hyponatraemia, i.e. low serum sodium concentration, is a common electrolyte disorder in hospitalized patients with a proportional incidence of up to 25–30% [2,3]. In critically ill patients, the incidence is even higher [4]. Hyponatraemia on hospital admission, irrespective of the initial underlying disease, has been identified as a risk factor for poor outcome in critically ill patients [2,5–7]. In addition, hyponatraemia is associated with increased hospital resource utilisation and health care costs [7–10]. The importance of hyponatraemia is also reflected by the inclusion of the presence of hyponatraemia in the Acute Physiological and Chronic Health Evaluation (APACHE) score, a routinely used classification system for disease severity in critically ill patients [11].

The underlying pathophysiology of hyponatraemia in pneumonia is not yet well understood, but the syndrome of inappropriate antidiuretic hormone secretion is thought to be an important component [12].

A few studies have previously focused on the association between hyponatraemia and mortality in pneumonia patients [5–13]. However, a formal confounder analysis has not yet been performed and evaluation of other poor outcome parameters is lacking. Thus, the aim of this study was to investigate the role of hyponatraemia in regard to relevant clinical outcomes, such as in-hospital mortality, ICU admission, and length of hospitalisation in patients with pneumonia, using an “every day” patient group and a broad set of clinically relevant confounding

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factors.

2. Methods

2.1. Setting

Bern University Hospital (Inselspital) is one of the largest hospitals in Switzerland with a catchment area of 2.5 million people [14].

2.2. Data collection and eligibility criteria

The medical reports in the Emergency Department (ED) are electronically stored in the patient database (*E*-Care, ED 2.1.3.0, Turnhout, Belgium). Patients' charts were retrospectively analysed using a keyword search approach. The key-word “pneumonia” (with different semantic combinations) was searched for, in an effort to identify all patients between 1 June 2011 and 31 May 2013 with the discharge diagnosis of pneumonia. Part of this database has already been published in a study evaluating qSOFA versus CURB-65 in regards to outcome [15].

All patients aged ≥16 years were eligible for inclusion. Exclusion criteria comprised duplicate records, missing data on sodium concentrations at ED admission, discharge diagnoses other than pneumonia and/or presence of moderate hypernatraemia on admission, defined as sodium concentration > 150 mmol/L (which was reported to be an independent risk factor for mortality in patients with pneumonia [16,17]).

2.3. Laboratory assessment of sodium

Serum samples were taken from each patient in S-Monovette® (Sarstedt, Germany) and sodium was determined with an ion-selective electrode system (Modular ISE®, Roche Diagnostics, Switzerland). As our laboratory automatically evaluated a lipid-index for each determination of sodium and results were only released below a specific threshold, pseudohyponatraemia due to high triglycerides was not possible. Sodium levels were not corrected for glucose values, as the proportion of glucose derailment was very low and hyponatraemia was not associated with hyperglycaemia in this study.

2.4. Study outcomes

The primary outcome was in-hospital mortality. Secondary outcomes were ICU admissions (primary and secondary admissions) and time of hospitalisation in days.

2.5. Data extraction

The following data were extracted from medical records and considered as potential confounders: i) demographic data (age, gender), ii) presence of risk factors for mortality or hyponatraemia in patients with pneumonia (i.e. chronic liver disease, kidney disease, severe cardiac disease, immunosuppression related to either medication or disease, malignancies, nicotine or alcohol abuse, diarrhoea, vomiting, current diuretic medication, chronic obstructive pulmonary disease, diabetes mellitus, and the diagnosis of hyperglycaemic derailment if present [18,19]), iii) type of pneumonia (community-acquired/nosocomial), days since symptoms had started, iv) presence of clinical symptoms (fever, altered mental status, limb pain, and clinically suspected sepsis), b) data to calculate CRB-65 score, i.e. respiratory rate, Glasgow Coma Scale, blood pressure, and age (see below), vi) microbiological sampling and results, vii) laboratory values (sodium), and viii) the outcome parameter: duration of hospitalisation in days, ix) intensive care unit (ICU) admission, and x) in-hospital mortality. Data were assessed and checked for quality by two members of the study team.

2.6. Definition of hyponatraemia

Hyponatraemia was defined as a serum sodium concentration of < 130 mmol/L, in accordance with the cut-off chosen in the APACHE II score [11].

2.7. Case definition of pneumonia

The diagnosis of pneumonia needed to be documented in the medical report. Furthermore, evidence of an infiltrate in radiography examination (X-ray or CT scan) had to be reported to fulfil the case definition of pneumonia.

Nosocomial pneumonia was defined as respiratory infection that developed after > 48 h of hospitalisation (hospital to hospital transfer, e.g. psychiatric hospital) or in patients who resided in a nursing home or other health care facility prior to ED admission [20].

2.8. Severity of pneumonia

Two different methods were used to control the association between hyponatraemia and in-hospital mortality for severity of pneumonia. Firstly, the variable “clinically suspected sepsis” was forced in the primary analysis as surrogate marker for pneumonia severity. “Clinically suspected sepsis” was assigned if the diagnosis or medical history field of the patients records contained the terms “sepsis” or “septic”.

Secondly, a subgroup analysis was performed, including all patients with sufficient data to calculate the CRB-65 score, a widely used marker for disease severity in pneumonia and which is associated with mortality [21]. To calculate the CRB-65 score for each of the following items, one point was assigned for: a Glasgow Coma Scale ≤ 14 as indication for confusion, respiratory rate ≥ 30/min, blood pressure of systolic ≤90 mm Hg or diastolic ≤60 mm Hg, and age ≥ 65 years.

2.9. Ethical considerations

The study was approved by the regional ethics committee of the Canton of Bern, Switzerland (KEK: 09-07-13). Individual informed consent was waived by the ethics committee.

2.10. Motivation of sample size/study period

In accordance with Kang, et al. [22], the ratio of the number of pneumonia patients with versus those without hyponatraemia (sodium concentration < 130 mmol/L) on admission to the ED was assumed to be 0.1 [22]. In order to detect an odds ratio of at least 3.5 with a power of 0.8 and alpha of 0.05, and assuming in-hospital mortality of 6% in patients without hyponatraemia [22], the sample size needed to be at least 542 pneumonia patients (including 50 patients with hyponatraemia). Based on the annual number of pneumonia cases of 300 at the ED, a study period of two years was sufficient to obtain the calculated sample size, assuming a dropout rate of 10% due to incomplete data.

2.11. Statistical analysis

Categorical variables were presented as frequency (proportion). The normal distribution of the continuous variables, i.e. age, duration of symptoms, and length of hospitalisation was tested using the Shapiro-Wilk test. Normally distributed continuous variables were presented with mean (standard deviation), non-normally distributed variables with median (interquartile range). Odds ratios (OR) to quantify the strength of association between two categorical outcomes were presented with 95% confidence intervals (CI). Associations between the categorical potential confounders with hyponatraemia (exposure) and in-hospital mortality (primary outcome), as well as ICU admission, were tested using chi-squared tests or exact Fisher's test, where appropriate; associations with the continuous variables – length of