Review Article

Prognostic importance of deranged sodium level in critically ill patients: A systemic literature to review

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Abstract

It is common upon admission or during stay at a hospital or intensive care unit (ICU) for patients to present with or acquire a serum sodium abnormality. Hyponatremia, serum sodium level less than 135 mmol/L, frequently associated with critical illnesses such as heart failure and liver cirrhosis, is an indicator of disease severity as well as a risk factor for poor prognosis. Hypernatremia, serum sodium level greater than 145 mmol/L, results due to any ailment disabling a patient's modality of thirst or the ability to relieve it once sensed. Hypernatremia has a more frequent iatrogenic component than hyponatremia. It can develop insidiously among patients through IV fluid administration of saline; both its presentation upon admission and development during stay is associated with mortality. Hyponatremia is associated with increased mortality and its treatment with morbidity as it carries a risk of overcorrection and consequently the development of central pontine myelinolysis. This review article covers the findings, and subsequent correlation between findings sought, of six articles catering to underscore the correlation between sodium disorders and prognosis of hospitalized or critically ill patients. PubMed search engine was utilized to select articles befitting the purpose of this review. Cumulatively, this review article substantiates the need to diligently evaluate and treat serum sodium disorders in hospitalized patients to achieve better prognosis.

Keywords: Importance, patients, prognostic, systemic

Introduction

Dysnatremias (variation of the sodium level from normal limit) pose as common finding both on admission and during stay amongst patients in ICUs.[1,2] Upon admission, hyponatremia prevail more than other, with 13.7-15% patients being hyponatremic, and 2-9% patients being hypernatremic.[2] It is quite opposite in patient's physician-induced sodium abnormalities, hypernatremic is twice more common than the other.[1]

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Defined as a serum sodium level less than 135 mmol/L, hyponatremia is the most common electrolyte disorder.[2,3] Mostly asymptomatic, a rapid decline in sodium levels can be fetal.[3] A patient suffering from symptomatic hyponatremia may present with headaches, falls, confusion, muscle cramps, polydipsia, altered mental status, status epilepticus, obtundation or even coma.[3] Not only is hyponatremia consequential for the brain, many studies confirmed sodium disorder to be an independent predictor for mortality and morbidity.[1,2]

Its counterpart, hypernatremia, defined to be sodium level greater than 145 mmol/L, is also an independent indicator of morbidity and mortality.[2,3] As with hyponatremia, an acute change can lead to symptoms irrespective of its level. As the

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sodium concentration increases, symptoms can vary from mild, being muscle weakness, nausea, vomiting, restlessness, to severe, being, tachypnea, muscle weakness, insomnia, and coma.[3]

Fluctuations in sodium levels can both be an indicator of disease severity and an independent factor for prognosis in the critically ill.[2] In this article, we will be reviewing findings of six different literature which gathered data to elucidate the prognostic importance of serum sodium levels in patients admitted to the hospital or ICU.

Objectives

The objective of this article is to highlight the importance of derangement of the sodium levels on both extremes, which can determine, mortality, morbidity and length of hospital stay of the patient who gets admitted with either hyponatremia or hypernatremia in patient admitted to the intensive care unit.

Methods

PubMed, Medline, Embase and Scopus search engine were used to extract the pertinent data. Studies from 2006 till present were included in literature review. Keywords such as "sodium disorder, dysnatremia, hyponatremia, hypernatremia, prognosis, outcome, critically ill, hospitalized patients, and ICU" were used as keywords, Major Topic to retrieve studies discussing the role, sodium disorders play in the prognosis of hospitalized or critically ill patients. Articles to be reviewed were selected based on its content largely discussing sodium disorders, their risk factors, and their outcomes on the patients studied in each selected study. For each study, reviewed in this article, a general blueprint of the study conducted was outlined as well as their conclusive findings, results, and inferences. Lastly, conclusions drawn from each study were analyzed and discussed for the purpose of enabling an overall understanding of the effect of sodium disorders on in-patient prognosis. Ethical approval was taken before the extensive literature review was started.

Stelfox HT *et al.*[1]

This observational cohort study covering a large Canadian health region examined the incidence of ICU acquired Dysnatremias at three medical-surgical ICUs as well as their outcomes on critically ill patients admitted over a span of 7 years. Of the 8142 patients, having normal sodium levels upon admission, 11% acquired hyponatremia and 26% acquired hypernatremia during stay at an ICU. Sodium levels analyzed accounted for the first episode of development of a dysnatremia in patients with a stay more than 1 day. Patients acquired moderate levels of hyponatremia or hypernatremia at a median of 2 days after admission. Either sodium disturbance was associated with longer ICU stays, higher APACHE II scores and body temperature fluctuations presenting as hypothermia or fever. ICU acquired hyponatremia was associated with patients admitted upon a surgical or neurological/trauma diagnosis as well as factors such as age, serum glucose and level of consciousness. On the other hand, level of care, mechanical ventilation, and a baseline creatinine were associated with ICU acquired hypernatremia. In comparison to patients with normal serum sodium levels, patients with an acquired dysnatremia experienced a greater length of stay and higher mortality. Duration of the acquired sodium disturbance and its daily rate of change contributed to ICU mortality. Even slight deviations from normal sodium levels indicated a worse prognosis. After adjustment, hyponatremia or hypernatremia acquired during ICU stay remained as independent risk factors for mortality. The development of ICU acquired hypernatremia was twice as common as the development of hyponatremia in the patients observed and a dose-response relation was seen between the degree of serum sodium deviation and mortality.

Funk GC *et al.*[2]

Incorporating data from 77 medical and surgical ICUs in Austria over a period of ten years, this retrospective audit studied associations of serum sodium deviations upon admission with raw and risk-adjusted mortality in 151486 patients admitted between 1998 and 2007, 75.4% patients had normal sodium levels on admission. The frequency of dysnatremias in the remaining 24.6% were as follows: 13.8% had borderline hyponatremia (130 to 135 mmol/L), 2.7% had mild hyponatremia (125 to 130 mmol/L) 1.2% had severe hyponatremia (serum sodium level less than 125 mEq/L) 5.1% had borderline hypernatremia (145 to 150 mmol/L) 1.2% had mild hypernatremia (150 to 155 mmol/L) and 0.6% had severe hypernatremia (serum sodium level greater than 155 mmol/L). Raw and risk-adjusted mortality had a direct relationship with hyponatremia and hypernatremia; it increased with an increase in severity of dysnatremia. Sensitivity analysis within subgroups demonstrated a U-shaped curve for high-risk patients and for lower aged patients. While both older and younger patients had an increased mortality, risk associated with severe hypernatremia, an accentuated U-shaped curve for the younger age group indicated a higher mortality risk. Affirming that varying degrees of hyponatremia may be a surrogate for underlying disease severity, a multivariate analysis adjusting for co-morbidities, severity of illness and diagnosis upon admission highlighted hyponatremia as an independent risk factor for mortality. Even slight decrease in serum sodium levels were independently associated with a poor prognosis in this study. The association of abnormal sodium concentrations and mortality results from both an effect of the sodium disorder itself and underlying organ dysfunction. Both acute and chronic hyponatremia as well as hypernatremia can potentiate cerebral damage of varying degrees. The treatment for hyponatremia itself can lead to worsening impact on brain tissue. Although a correction rate of up to 12 mmol/day is known to be safe in treatment protocol, depending on how long a patient has had low serum sodium levels, a correction rate even below 12 mmol/day can result in osmotic demyelination. In tangent to this, if the time period is known, it is recommended to not treat hyponatremia if the deviation in serum sodium concentration has taken place for more than 48 hours. Hypernatremia, caused by any impairment that deficits the patient from adequate

water intake or occurs in an inpatient setting as an iatrogenic component or due to malpractice, not only causes neurological impairment itself but also disrupts peripheral insulin resistance, left ventricular contractility, and hepatic gluconeogenesis. The treatment of chronic hypernatremia can also worsen neurological findings; a rapid correction can result in cerebral edema. Standing as risk factors for ICU acquired delirium, this association further correlates hyponatremia and hypernatremia with increased morbidity and mortality. This study demonstrated hyponatremia and hypernatremia to be independently associated with mortality, with increases in sodium concentration posing a greater risk for mortality than decreases in sodium concentration of the same degree.

Tokgöz Akyil F *et al.*[4]

Correlations between dysnatremias and community-acquired pneumonia are necessary to be investigated as while CAP is the most common infectious cause of mortality worldwide, hyponatremia is most frequent finding in pneumonia patients. An association of in-hospital mortality and pneumonia with hypernatremia has also been noted. Henceforth, this bi-centric retrospective cross-sectional study analyzed factors related to baseline dysnatremias as well as outcomes of the sodium disorders in CAP patients with respect to length of hospital stay, 30-day mortality and 1-year mortality. Among 471 patients included in this study with CAP, 25.3% had hyponatremia and 5.3% had hypernatremia. Findings for hyponatremia indicated a correlation between higher leukocyte count and lower albumin levels. Lower serum sodium levels prolonged hospital stays and were associated with long-term mortality noted in this study as 1-year mortality. Duration of treatment for hyponatremia as well as higher baseline CRP levels were conjectured to also be responsible for the increase in length of stay in the hyponatremic patients. Advanced age and female gender were correlated to CAP cases with hypernatremia. A higher leukocyte count and urea levels frequented with an increase from the normal range of sodium levels. Hypernatremia presented with significantly higher short-term mortality noted as 30-day mortality and long-term mortality. Not only did patients with hypernatremia survive significantly less than patients with hyponatremia but also hypernatremia weighed as a better predictor of mortality than hyponatremia in patients with CAP.

Sim JK *et al.*[5]

Previous studies have observed that 1 in 9 of the critically ill patients acquire hyponatremia during stay at an ICU. Hyponatremia usually presents at the time of admission while hypernatremia is mostly iatrogenic,. Thus, this retrospective cohort-based on a prospective registry aimed to demonstrate the frequency of hyponatremia in admitted patients to a medical ICU of a tertiary referral hospital in Seoul, South Korea. This study was conducted on 1342 eligible patients admitted over 3 years from January 2015 to December 2018. 217 (16.2%) acquired hyponatremia within 48 hours after ICU admission. The median SOFA score and SAPS3 was significantly higher on admission of those who acquired hyponatremia than others. Co-morbidities were similar in both the groups. Use of dobutamine and vasopressin was also seen more often in patients with low sodium levels. Net volume balance was the only management variable that was significantly higher among the hyponatremic patients. Hematological malignancy and potassium concentrations on admission were baseline characteristics independently correlating to the development of hyponatremia. An inverse relationship was detected with potassium concentration and sodium concentration. An initial finding of high potassium levels was common in patients with ICU acquired hyponatremia. Length of stay, ICU mortality, and 28-day mortality remained similar between patients who developed hyponatremia and patients who didn't. 12.7% of patients from the total placement count were supported by renal replacement therapy; among those patients, a consistently higher risk of undergoing RRT was seen in the hyponatremic group.

Linder G *et al.*[6]

Patients admitted to a medical ICU of a university hospital in Vienna over the span of 35 months were studied in this retrospective analysis to assess the prevalence and outcomes of hypernatremia present on admission and hypernatremia acquired during ICU stay. Noted as a serum sodium level greater than 149 mmol/L, hypernatremia was found in 2% of patients upon admission and developed during stay in 9% of patients from the 981 patients' data studied. Compared to a morality rate of 24% in patients without hypernatremia, patients who acquired hypernatremia had mortality rates of 43% and 39% respectively, indicating a higher mortality rate for hyper-natremic patients overall. A decreased length of stay (LOS) of 8 ± 10 days was noted in patients without hypernatremia, in comparison to a LOS of 20 ± 16 days in patients with hypernatremia. Significantly increased SAPS II scores and significantly less patients with a surgical type of admission correlated to patients with high serum sodium levels upon admission. ICU acquired hypernatremia was analyzed via univariate cox regression analysis to have a significant influence on mortality. A multivariable analysis performed indicated hypernatremia as an independent risk factor for 28-day hospital mortality. Hypernatremia has a strong iatrogenic component in the ICU as physicians are mostly responsible for water and electrolyte balance among patients. The longer a patient remains in intensive care unit, the greater the risk of acquiring hypernatremia develops. The severity of disease in patients admitted to the ICU renders them susceptible to acquiring hypernatremia as well. Thus, given the impact of hypernatremia on length of stay and mortality it is necessary to monitor fluid and electrolyte balances prudently to detect early recognition of this sodium disturbance. Monitoring of renal electrolyte losses add to a better evaluation of electrolyte and fluid balance in the body.

Chi C *et al.*[7]

Over a period of one year, 2015, dysnatremias upon admission in patients presenting to a quaternary referral hospital, were

analyzed to ascertain prognosis in terms of length of stay, in hospital mortality, and a combined outcome of in hospital mortality or consecutive ICU admission.

Among 6447 patients, documented dysnatremia range was extended from as low as 110 mmol/L to as high as 175 mmol/L was identified. Irrespective of the sodium level, 190 patients died during there hospital stay. In comparison to patients with normal serum sodium levels, patients with severe hypernatremia (Na > 155 mmol/L) had the highest odds ratio of 11.1 for in hospital mortality followed by the odds ratios of mild hypernatremia (Na 146 - 155), severe hyponatremia (Na < 125), and mild hyponatremia (Na 125-134). 15.2% of the patients admitted were further admitted to the ICU. Abnormal sodium concentration resulted to be an independent prognostic factor for the combined outcome of in-hospital mortality or ICU admission, on multivariate analysis. Both hyponatremic and hypernatremia patients had a longer length of stay than patients with normal sodium levels. From 74 patients who had severe hyponatremia, 7 patients were administered hypertonic saline. All 7 of these patients had symptomatic hyponatremia and experienced symptoms such as decreased level of consciousness, an acute confused state, and seizures. 1 patient received 20% saline and the remaining 6 received 3% saline. With infusion rates varying between 16 and 50 mL/h over a mean duration of 20 ± 15 h, 3 of the 7 patients experienced rapid correction of sodium concentration by more than 10 mmol/L over a 24-hour period. 1 patient who was administered 20% hypertonic saline experienced a fluctuation in level of consciousness; however, this patient was in a confused state prior to administration of the hypertonic saline as well. Rate of administration of hypertonic saline was noted to be faster in those who experienced overcorrection. While overcorrection of hyponatremia is associated with an increased mortality as well as the development of central pontine myelinolysis, no such findings were encountered in this study.

Discussion

Dysnatremias in the ICU or hospital setting manifest as surrogates for disease severity as well as independent predictors for mortality and length of stay.[2,7] In the ICU alone, hyponatremia and hypernatremia are prevalent in 20%–30% of the patient population.[8] Individual patient characteristics, underlying disease and comorbidities, the type of intravenous fluid administered during in-hospital or ICU stay and fluid and electrolyte losses throughout admission, all contribute to prognosis of patients with abnormal serum sodium levels.

Development of hyponatremia before, upon, or during admission indicates worse prognosis in any given patient.[1,2,4,5] Gauged as a marker of disease severity in patients with chronic organ dysfunction such as heart failure or liver cirrhosis, hyponatremia stands alone as a predictor of mortality with adjustment for these comorbidities on multivariate analysis.[2] For example, hyponatremia not only communicates severity of disease in liver cirrhosis patients but also it contributes to the development of hepatic encephalopathy. Although hyponatremia can be asymptomatic, cerebral consequences may result due to its development or treatment; symptoms can include headache, nausea, or vomiting. Worsening of symptoms represented by a deceased mental status, seizures, coma, brainstem herniation, respiratory arrest, or death are more likely to occur in ICU patients as progression of symptoms cannot be apparently observed or communicated by these patients.[8] As brain cells require time to adjust to changes in the osmotic environment, rapid correction of hyponatremia can result in osmotic demyelination syndrome of pons leading to quadriparesis. Thus though a valuable treatment of severe hyponatremia, rapid correction via 3% hypertonic saline should remain limited for those with an acute onset of severe hyponatremia within a 48-h range as risk for ODS upon rapid correction increases with an increasing duration of hyponatremia particularly that of greater than 48 hours.[2,7,8] Additive factors for the development of hyponatremia especially during hospitalization are stimuli for the release of arginine vasopressin. Non-osmotic factors responsible for AVP release include nausea, pain, narcotics, stress, and volume depletion. Thus in regards to release or suspension of AVP stimulus, the amount of water excretion with an emphasis on urine diluting capacity should be noted while administrating intravenous fluids as hyponatremia and its resulting consequences can develop in an in-hospital setting with the administration of hypotonic or isotonic fluids.[8]

Known as a geriatric disease due to prevalence of an impaired thirst mechanism or the inability of acquiring water for one's own self in the elderly, hypernatremia is also common in the critically ill patients.[2] In fact, Funk GC and colleagues noted an increased risk for mortality in the younger patients than the older ones with severe hypernatremia on admission to an ICU. Increased length of stay is both an etiology and outcome of hypernatremia.[6-8] Often iatrogenic, hypernatremia may result from inadequate water distribution or an excess administration of hypertonic fluids in patients who acquire this sodium disturbance upon stay at a hospital or ICU.[2] Other predisposing factors for hypernatremia include a renal concentrating defect through either renal disease or use of diuretics, solute diuresis in a hypermetabolic state or from glucose and urea via a high protein food regime, water losses, and sepsis.[4,8] Older age, comorbidities, a lower estimated glomerular filtration rate, ACPACHE II scores, SAPS II scores, level of in-patient care, mechanical ventilation, and length of stay are factors associated with an increased risk for the development of hypernatremia.[1,4,6] As hypernatremia indicates a worse short-term and long-term survival, it is crucial to recognize at-risk patients and prevent elevations in serum sodium concentration.[4] Patients with concurrent hypernatremia and hypovolemia, as is often the case, should be administered isotonic saline prior to adequate water administration. Urine concentrating ability and electrolyte-free water losses should be monitored alongside intravenous fluids administered for hypernatremia correction. A rising serum sodium as per consecutive laboratory values obtained is an indicator for cessation of saline administration and for resumption of a hypotonic intravenous solution to correct a possible water deficit and electrolyte disturbance. Even slight

elevations in serum sodium urge a prompt correction as they too are associated with a poor prognosis in the critically ill patients.[2,8] This study is an extensive literature review of the tenure of 15 years from 2006 till present concluding that sodium level is crucial in both the directions and small but acute change in its level in critically ill patient might lead to increase mortality or morbidity, increased stay at the hospital and increase cost of management as well.

Key points

As per the studies reviewed, dysnatremias are a common finding in the critically ill and hospitalized patients. Hyponatremia and hypernatremia are independent risk factors for worse prognosis and mortality. They are associated with increased morbidity, length of in-hospital or ICU stay, and cost of care. Deviations in sodium concentration are a surrogate for underlying disease severity as well as markers for a longer duration of treatment and higher mortality. Identification of at-risk patients and efficient monitoring of serum sodium levels can allow for appropriate timely treatment and reduce the risk for mortality and poor outcomes. Treatment for hyponatremia should be executed with caution due to the risk of overcorrection and a subsequent osmotic demyelination syndrome.

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Conflicts of interest

There are no conflicts of interest.

References

1. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Crit Care 2008;12:R162. doi: 10.1186/cc7162.
2. Funk GC, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, *et al.* Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med 2010;36:304-11.
3. Braun MM, Barstow CH, Pyzocha NJ. Diagnosis and management of sodium disorders: Hyponatremia and hypernatremia. Am Fam Physician 2015;91:299-307.
4. Tokgöz Akyil F, Akyil M, Çoban Ağca M, Güngör A, Ozantürk E, Söğüt G, *et al.* Hyponatremia prolongs hospital stay and hypernatremia better predicts mortality than hyponatremia in hospitalized patients with community-acquired pneumonia. Hastanede tedavi edilen toplumda gelişen pnömonide hiponatremi hastane yatışını uzatır ve hipernatremi mortalite için hiponatremiden daha güçlü bir belirteçtir. Tuberk Toraks 2019;67:239-47.
5. Sim JK, Ko R-E, Na SJ, Suh GY, Jeon K. Intensive care unit-acquired hyponatremia in critically ill medical patients. J Transl Med 2020;18:268.
6. Lindner G, Funk GC, Schwarz C, Kneidinger N, Kaider A, Schneeweiss B, *et al.* Hypernatremia in the critically ill is an independent risk factor for mortality. Am J Kidney Dis 2007;50:952-7.
7. Chi C, Patel S, Cheung NW. Admission sodium levels and hospital outcomes. Intern Med J. 2021 Jan;51(1):93-98. doi: 10.1111/imj.14777. PMID: 32043721.
8. Rosner MH, Ronco C. Dysnatremias in the intensive care unit. Contrib Nephrol 2010;165:292-8.