Original article

Journal of INDEPENDENT MEDICINE

Impact of Acquired Hypernatremia in the ICU on Mortality in Patients with Acute Respiratory Failure: A Retrospective Analysis from the NIS Database

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Abstract

Introduction: Hypernatremia is a critical condition frequently present in critically ill patients. In patients with acute respiratory failure, studies have shown that it worsens patients' condition and prolongs the time for mechanical ventilation, leading to adverse outcomes, yet in-hospital mortality is not completely acknowledged.

Methodology: Analyzing data from the National Inpatient Sample database (2018–2021), a retrospective analysis was conducted using proper ICD-10 codes to identify patients with acute respiratory failure, then dividing them into two groups: with and without hypernatremia. Primary outcome assessed in-hospital mortality, while secondary outcomes were length of stay (LOS) and demographics.

Results: Out of 153,840 hospitalized patients that met our criteria (median age 64, 56% male), 76,950 (50%) were selected for the hypernatremia group. Hypernatremic patients (median age 66, 57.5% male) had higher mortality (28.2% vs. 18.9%, OR=1.489, CI=1.432–1.548, p<0.001) and longer LOS (11 vs. 5 days). Hypernatremia increased mortality risk (OR=1.522, CI=1.480–1.564), especially with diabetes insipidus (OR=11.664), dementia (OR=2.192), and acute kidney injury (OR=1.630). Hypernatremic patients had more illness severity (OR=1.273, CI=1.225–1.323) and fewer routine discharges (OR=0.814, CI=0.783–0.846).

Discussion: Hypernatremia increased mortality (28.2% vs. 18.9%, OR=1.522) and length of stay (11 vs. 5 days) in this population, particularly in patients with comorbidities like diabetes insipidus, dementia, and acute kidney injury. Routine ICU monitoring of blood gases facilitates the detection and the opportunity to create a proper management plan to improve the outcomes. Racial differences and different clinical courses were identified, requiring more research.

Conclusion: Hypernatremia is an independent mortality risk factor in this population; it can be worsened and altered by other subsequent factors of patients' conditions, like comorbidities. Proper management of hypernatremia is needed to avoid the worst outcomes and should be personalized depending on each specific patient. Acknowledging patient-acquired hypernatremia in the ICU in this population is an opportunity in healthcare for prevention, and management serves to boost patients' survival.

Keywords: Hypernatremia, acute respiratory failure, intensive care unit, in-hospital mortality, National Inpatient Sample (NIS)

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Introduction

Hypernatremia is defined as an elevated concentration of sodium in the blood, usually over 145 mmol/L. Sodium levels are normally regulated between 135 and 145 mmol/L, and any disturbance of these values could lead to life-threatening electrolyte imbalance outcomes. This imbalance typically occurs due to water loss, such as dehydration, but can also result from excessive intake or retention of sodium. (1–3)

In the intensive care unit (ICU), hypernatremia is an important challenge due to a wide variety of causes, including restrictive access to free water (mechanical ventilation, sedation, or altered mental status), excessive water loss (diarrhea, polyuria, or osmotic diuresis), iatrogenic sodium obtention, and a decrease in renal function, usually exacerbated in catabolic states. (4–7) Hypernatremia is an independent factor associated with ICU and in-hospital mortality, prolonged length of stay, and has been proven to worsen neurologic outcomes. The risk of this is directly proportional to the severity of the hypernatremia, and the disorder often reflects the underlying disease severity, catabolic stress, and other subsequent factors. Hypernatremia can cause altered mental status, neuromuscular irritability, seizures, and, in rapidly severe developing cases, can cause vascular rupture and intracerebral hemorrhage. (4,7–9)

Acute respiratory failure is a clinical syndrome caused by a drop in the respiratory system's function, leading to inadequate gas exchange, eventually leading to low oxygenation levels (hypoxemia), lack of CO2 elimination (hypercapnia), and the onset of symptoms caused by this imbalance. Hypoxemic respiratory failure (ARDS, pneumonia, pulmonary embolism, pulmonary edema) is designated by PaO_2 <60 mm Hg or SaO_2 <88%; on the other hand, hypercapnic respiratory failure (COPD, CNS depression, opioid overdose, obesity, hypoventilation syndrome) is designated by $PaCO_2 \geq 45$ mm Hg with a pH less than 7.35. All these alterations lead patients to ICU settings, mechanical ventilation, inflammation processes, and water loss that, if not properly managed or identified, can lead to hypernatremia. (10,11)

In patients with acute respiratory failure, especially in the ICU, the incidence of hypernatremia varies from 7% to 38% depending on the population studied, their characteristics, and comorbidities, and prevalence is also significantly high in this population, with studies reporting that one-third of their population developed hypernatremia. (5,6,12)

A study performed by Radant et al. 2020 showed that 52% of their population of patients with ARDS associated with SARS-CoV-2 infection admitted with normal serum sodium levels developed acquired hypernatremia in the ICU. In this group, the incidence of hypernatremia proved to be elevated and was shown to be linked to insensible water losses. (13)

Causes of hypernatremia in patients with acute respiratory failure

In this population, hypernatremia occurs due to multifactorial causes. Sedation, mechanical ventilation, and/or neurologically impaired patients are the causes of a lack of access to free water and its consumption. Mechanical ventilation, tachypnea, and fever increase evaporative losses through the respiratory tract and the skin, all of which are caused by the subsequent lung and general inflammation processes, as well as the increased minute ventilation. Catabolic states promoting urea production, resulting in osmotic diuresis, and aggressive diuretic use for fluid management, especially in patients with acute respiratory distress syndrome (ARDS), cause intense water loss. Finally, an inadequate water replacement plan can lead to patients developing hypernatremia, and iatrogenic sodium can be gained from hypertonic saline, sodium bicarbonate, or other types of maintenance replacement fluids (14–16) (**Figure 1**).

Methodology

A retrospective observational analysis was performed using the National Inpatient Sample (NIS) from 2018 to 2021. (17) The NIS is a large and nationally representative database of the United States hospital discharges. The database includes demographics, diagnoses, procedures, length of stay, outcomes, and hospital characteristics, all stratification factors to represent the national population. To ensure the representativeness, all weights and representative variables were applied correctly.

Patients hospitalized with acute respiratory failure were identified using the ICD-10 code J96.00 (Acute respiratory failure, unspecified whether with hypoxia or hypercapnia). After this, from this same group, we filtered and identified the individuals with hypernatremia using the ICD-10 code E87.0 (Hypernatremia).

Based on the presence or absence of hypernatremia, patients were classified into two groups:

1. Acute respiratory failure with hypernatremia
2. Acute respiratory failure without hypernatremia

The primary outcome assessed was in-hospital mortality, while the secondary outcomes include length of stay (LOS), reported in days, discharge patterns, and demographic associations like sex and race. Descriptive statistics were used to compare baseline characteristics between groups.

Statistical analyses were performed using odds ratios (OR), Mann-Whitney U tests, and 95% confidence intervals (CI) to determine significance. To assess the association between hypernatremia and in-hospital mortality, a multivariable logistic regression model was constructed to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate adjustment was performed to control for potential confounding variables, including age, sex, race, and comorbidity index.

All analyses were performed using IBM SPSS Statistics, with significance set at $p<0.05$.

Results

A total of 136,636,051 hospital cases were analyzed, from which 153,840 cases met the inclusion criteria for further evaluation. The study population had a median age of 64 years [49–77], with 86,225 patients (56%) being males and 67,615 patients (44%) females. Out of the total population, 36,355 (23.6%) died during hospitalization with a median LOS of 7 days [3–14 days]. In the same way, out of the total population, 76,950 patients (50%) were diagnosed with hypernatremia. Within this hypernatremia subgroup, the median age was slightly higher at 66 [52–77], and 44,265 patients (57.5%) were males. In-hospital mortality in the hypernatremia group was observed in 21,685 patients (28.2%), with a notably longer median LOS of 11 days [6–19 days]. On the other hand, the non-hypernatremia group, integrating the patients that met our criteria but without this diagnosis, had a median age of 62 years [44–76], with 41,960 patients (54.5%) being males. Mortality in this group was lower, with 14,570 patients (18.9%) dying during hospitalization, and a shorter median LOS of 5 days [2–9 days] (**Figure 2**).

Patients with hypernatremia demonstrated a significantly higher risk of in-hospital mortality compared to the group without the condition. Specifically, the odds of mortality were 48.9% higher in the hypernatremia group (odds ratio [OR] = 1.489, 95% confidence interval [CI]: 1.432–1.548). This increase in mortality risk was supported by the statistical analysis, which showed a significantly elevated mortality rate in the patients with hypernatremia (28.2%), compared with the patients without this condition (18.9%) (Mann-Whitney U = 137,844, Z = -15.63, $p<0.001$).

Additionally, patients with hypernatremia exhibited greater illness severity, evidenced by their need to be transferred to higher acuity healthcare facilities for more personalized and specialized treatments (OR = 1.273 [CI = 1.225–1.323]). Routine discharges were significantly lower in the hypernatremic group, highlighting the fact that the more severe clinical course and prolonged recovery time are associated with this condition (OR = 0.814 [CI = 0.783–0.846]).

Demographic analysis revealed that Black/African American patients had a 30% higher likelihood of developing hypernatremia, followed by Asian/Pacific islanders with 23% compared to other racial groups (OR = 1.300 [CI = 1.249–1.353]) (**Figure 3**).

To examine the relation between hypernatremia and in-hospital mortality in depth, a multivariable logistic regression model was employed, adjusting for the potential confounders, especially the comorbidity index. The results confirmed that hypernatremia is an independent risk factor for in-hospital mortality (OR = 1.522, 95% CI: 1.480–1.564). Notably, the risk of mortality was significantly higher in patients with comorbidities. Beginning with the fact that patients with diabetes insipidus had a remarkably higher mortality risk (OR = 11.664, 95% CI: 9.977–13.636), followed by those with dementia (OR = 2.192, 95% CI: 2.116–2.271) and acute kidney injury (OR = 1.630, 95% CI: 1.585–1.676) (**Figure 4**). The predictive power of the logistic regression model was moderate, with a Nagelkerke R^2 value of 0.132, providing a reasonable explanation of how factors like age and comorbidities can affect the mortality outcomes, even though other unmeasured factors may have also played a role in the results.

Hypernatremia management in acute respiratory failure

Hypernatremia in ICU settings is usually monitored and measured using blood gases analysis, which uses direct ion-selective electrode (ISE) technology to determine sodium concentration in the blood, providing fast results and the opportunity to take immediate clinical decisions about the management. (18)

The recommended management of hypernatremia in patients with acute respiratory failure consists of the correction of the free water deficit with electrolyte management, usually intravenous 5% dextrose in water (D5W), or enteral water is used. (4,16) Managing this carefully to avoid rapid correction that can cause brain edema, seizures, and even death if not administered correctly. Sodium correction should not exceed 10-12 mmol/L a day to avoid brain edema. Central pontine and extrapontine myelinolysis or osmotic demyelination syndrome can also happen, even though it is more common in the rapid correction of hyponatremia; this can occur in patients with risk factors and present comorbidities. More rapid correction can be considered only in acute conditions with severe symptoms, which is rare to happen in ICU settings. (8,14,19) Proper management of hypernatremia is imperative in patients with acute respiratory failure since being under this condition is linked to longer mechanical ventilation and a greater need for inotropic support, especially in those patients with COVID-19. Proper electrolyte imbalance correction is significantly important to improve the outcomes in these kinds of patients (20) (**Table 1**).

Other options for management are plausible depending on the patient's conditions and comorbidities. The use of loop diuretics (Furosemide, bumetanide, and torsemide) can be considered when sodium overload or positive sodium balance is present in a scenario where the patient is not hypovolemic. This approach can be taken in a situation where the main cause is sodium gain combined with hypotonic fluid administration to reach the correction. (4,26)

In patients with acute kidney injury or when patients require renal replacement therapy, continuous renal replacement therapy (CRRT) is plausible to control sodium and water balance in the context of volume overload when rapid correction is needed due to severe symptoms in an acute episode of hypernatremia. (27)

For situations such as hypernatremia due to sodium overload, like the one caused by iatrogenic sodium administration, hemodialysis can be considered in situations where the patient is already under dialysis or when a life-threatening situation has been reached, where the hypernatremia is not responsive to treatment. (24)

Discussion

This study analyzed 153,840 ICU patients with acute respiratory failure from the NIS. Half of the cohort was selected with hypernatremia (50%) and were linked to more in-hospital mortality (28.2% instead of 18.9%) and had longer stay (11 days instead of 5 days). The condition increased the mortality risk (OR=1.522), especially in patients with comorbidities like diabetes insipidus (OR=11.664), dementia (OR=2.192), or acute kidney injury (OR=1.630). These results align with the other studies demonstrating how hypernatremia worsens outcomes in the ICU and increases the risk of adverse events.

Hypernatremia in this population, as previously shown, comes from multifactorial causes like limited water access, excessive water loss, and sodium overload. In the ICU, routine blood gases and electrolyte test is a common practice, which facilitates the monitoring; however, it is important to keep an eye on changes and watch out for significant alterations and signs of external factors that could worsen the serum sodium values in these patients.

As shown in the results, Black/African American and Asian/Pacific Islander (ORs 1.300 and 1.230, respectively) patients were more likely to develop hypernatremia, and this provides insights into how socioeconomic and genetic factors may play a role in the patient developing the condition. Hypernatremic patients also had fewer discharges, demonstrating that they may have had tougher recovery.

Now the multivariable logistic regression had a moderate model strength (Nagelkerke R^2=0.132), suggesting and confirming the assumptions that other factors may play a role in the results, which opens an opportunity for more research on the topic.

Conclusion

Hypernatremia is an independent risk factor for mortality in ICU patients with acute respiratory failure, increasing the worsening of outcomes, length of stay (LOS), and in-hospital death, especially in patients with comorbidities. These outcomes can worsen depending on multifactorial aspects like race, sex, age, subsequent conditions, and several other factors. What all these outcomes have in common is the imperative need for proper management to improve the patient's condition. It is very important to take into consideration the patient's condition, especially in the ICU. Identifying the underlying cause is a must to develop an appropriate management plan. Particularly because a single mistake can lead to a completely different outcome, and the options for treatments need to be completely personalized. Monitoring the patients through the whole process is very important, as patients' conditions can change quickly, and readjustment of the plan is a day-to-day practice within this population.

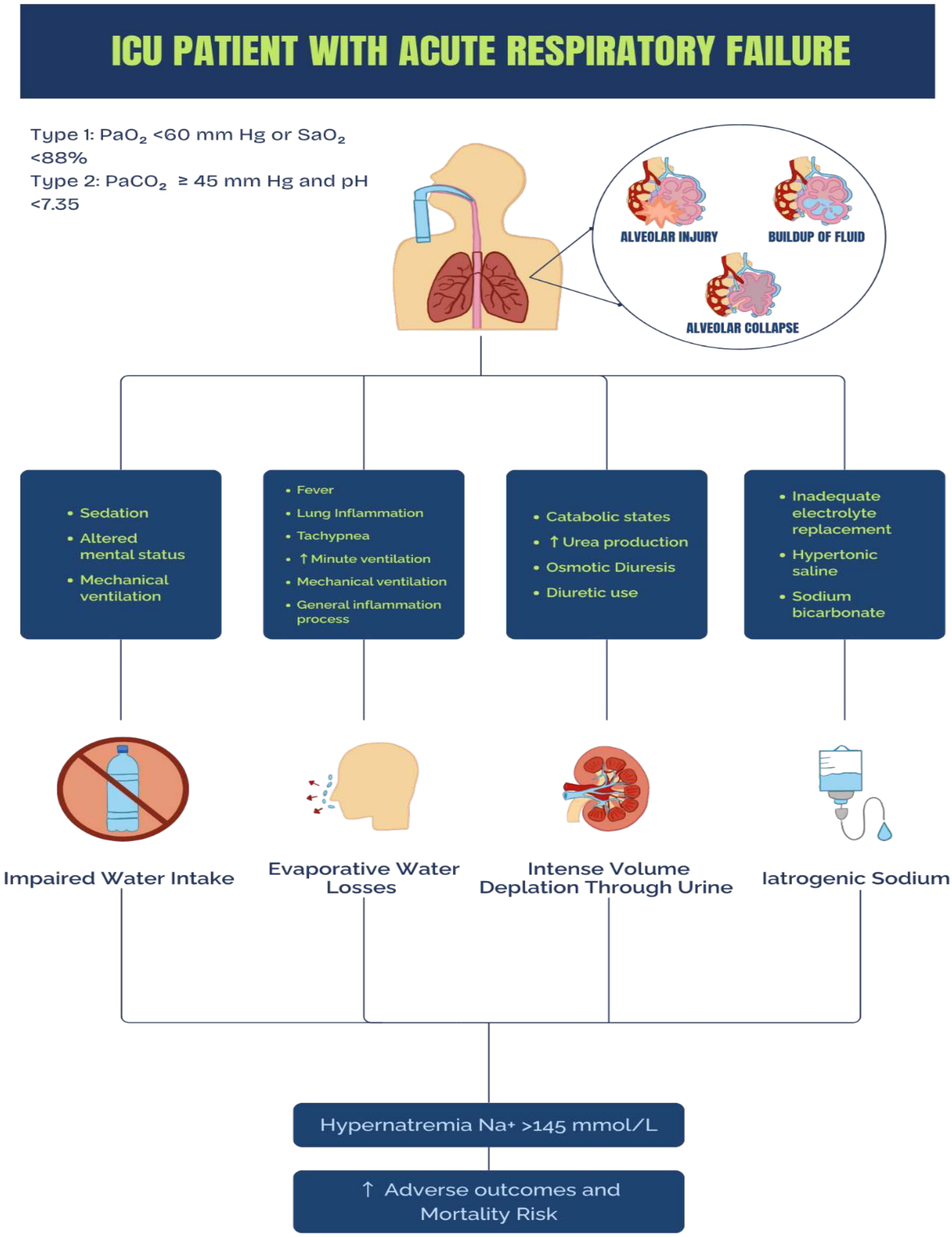
As mentioned before, a day with mismanagement of hypernatremia is practically keeping ICU patients with acute respiratory failure under mechanical ventilation for a longer period and increasing their mortality risk. This is why early recognition and correction of the condition should be a priority in this kind of patient, particularly in those with comorbidities and at-risk patients in risk as older people. The prevention of these sodium imbalances might attenuate and reduce the stay in the ICU and improve the patients' outcomes, which is a promise of bettering the population health, reducing their mortality, and preventing to avoid hospital resource losses, reducing patients' length of stay.

Table 1. Hypernatremia Management in Acute Respiratory Failure

ASPECT	MANAGEMENT OVERVIEW
Underlying Cause	Identify and address causes (e.g., water loss, inadequate intake, renal dysfunction, diabetes). (21) The free water deficit is calculated using the formula: Free Water Deficit = Current TBW × [(Serum Na/140) – 1], where TBW (total body water) ≈ is 0.6 × body weight (kg) for men, 0.5 for women. (22)
Correction Rate	Reduce sodium slowly (≤10–12 mmol/L/day); correction should be gradual to prevent cerebral edema. (21)
Fluid choice	Use hypotonic fluids (e.g., IV 5% dextrose in water or enteral water) for free water replacement. (21) • IV D5W Dosage: Calculate free water deficit; typical starting rate: 3–6 mL/kg/h, adjust based on sodium and volume status. (21) • Enteral water dosage: Calculate free water deficit; administer via feeding tube, matching correction rate to IV fluids. (21)
Fluid Strategy in ARF/ARDS	Adjust rate to avoid rapid correction. In patients with acute respiratory failure, especially those with ARDS, a restrictive fluid strategy is recommended to avoid worsening pulmonary edema. (21,22)
Fluid Management	Balance correction with risk of fluid overload in respiratory failure. (21,22)
Monitoring	Frequent monitoring of serum sodium levels and clinical status is essential during correction. (21) Additional monitoring of plasma and urine osmolality, urine electrolytes, and clinical status should be performed to guide safe and effective management. (3,23) In life-threatening scenarios, rapid correction with dextrose-based hypotonic solutions is also supported but must be closely monitored to avoid complications such as hyperglycemia. (24)
Ventilatory support	Use lung-protective ventilation (low tidal volume, limited plateau pressure); consider prone positioning. (22,25)
ICU Outcomes	Hypernatremia is linked to longer mechanical ventilation, higher inotropic support, and increased mortality. (20)
Comorbidities	Adjust management for diabetes, renal failure, and severe stress. (20)

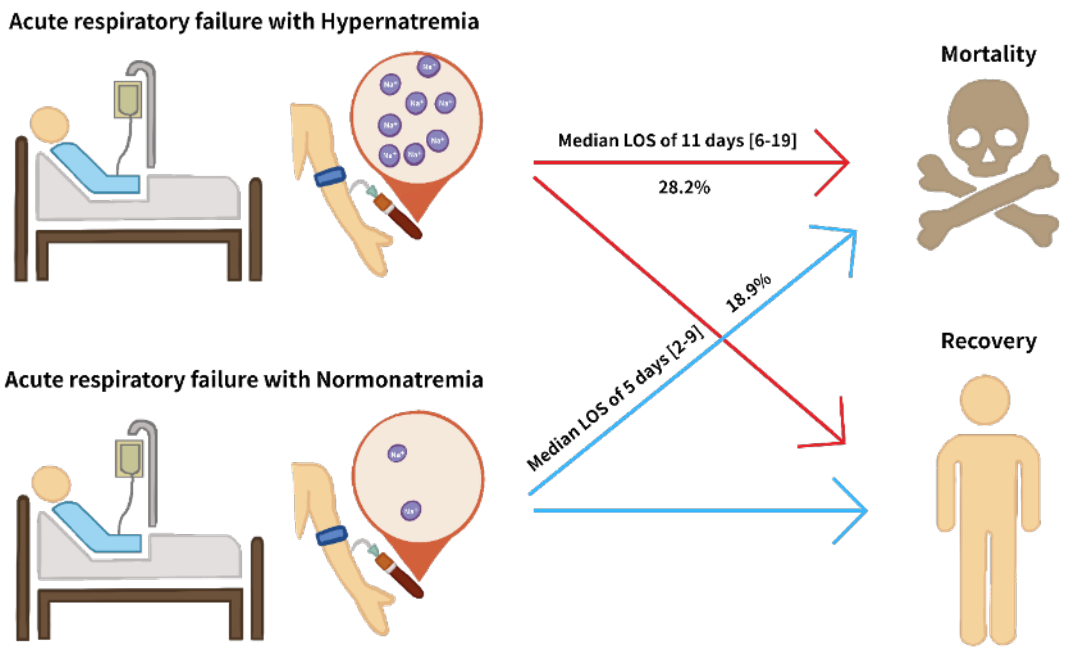
Legend: A summary of every relevant aspect of hypernatremia management in patients with acute respiratory failure. The aspects included are Underlying Cause, Correction Rate, Fluid choice, Fluid Strategy in ARF/ARDS, Fluid Management, Monitoring, Ventilatory support, ICU Outcomes, and Comorbidities. ARF: Acute Respiratory Failure; ARDS: Acute Respiratory Distress Syndrome; TBW: Total Body Water; IV D5W: Intravenous Dextrose 5% Water.

Figure 1. Mechanisms of Acquiring Hypernatremia in ICU Patients with Acute Respiratory Failure



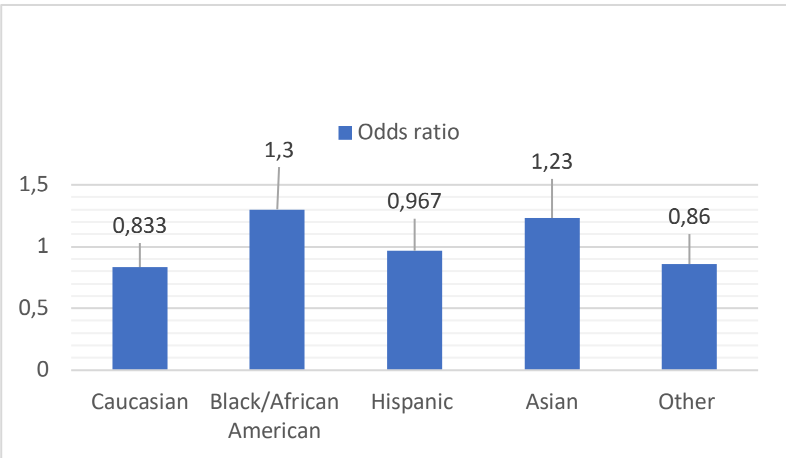
Legend: Diagram of the main causes of hypernatremia in patients of this population. Acute Respiratory Failure (ARF) type 1= hypoxemic and type 2= hypercapnic. The diagram illustrates the risk factors associated with developing the condition, ultimately leading to an increase in adverse outcomes and mortality.

Figure 2. Comparison of groups with and without hypernatremia within the population of ICU patients with Acute Respiratory Failure



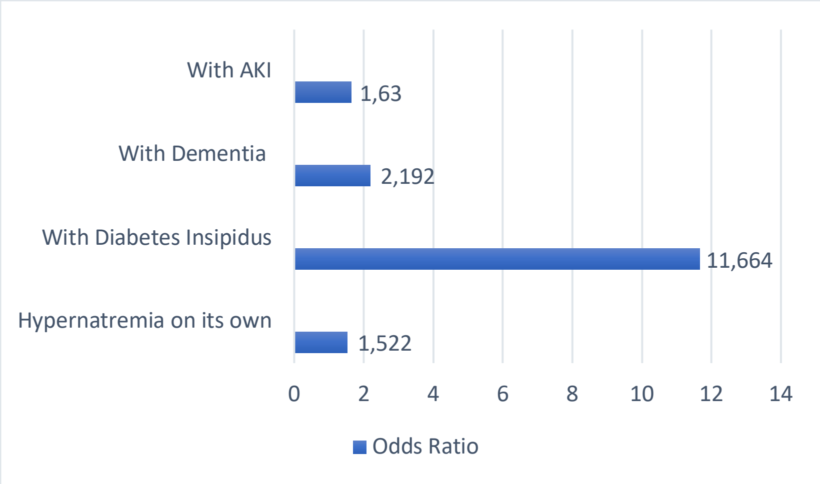
Legend: The figure shows hypernatremia through the elevation of sodium (Na+), and for each group of the population, we have registered the Median Length of Stay (LOS) and the percentage for mortality risk (%).

Figure 3. Likelihood of developing hypernatremia by race



Legend: The X axis represents the race, and the Y axis represents OR. Demonstrating that in order, the races more susceptible to developing hypernatremia are Black/African American (30% more OR=1.3), Asian (23% more OR=1.23), Hispanic (OR=0.967), Other races (OR=0.86), and Caucasian (OR=0.833).

Figure 4. Hypernatremia as an Independent Mortality Factor



Legend: Hypernatremia is, on its own, an independent in-hospital mortality factor by 52% (OR=1.522) in ICU patients with acute respiratory failure; in the study, it increases the mortality risk depending on the subsequent patient comorbidity, being the most elevated Diabetes Insipidus with more than 11 times of mortality risk (OR=11.664), followed by Dementia with twice the mortality risk (OR=2.19) and finally Acute kidney injury (AKI) with 63% more of mortality risk (OR=1.63).

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