

Clinical and Etiological Profile of Hyponatremia in ICU Patients at Tertiary Care Hospital

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Abstract: ***Aim:** To study the clinical profile of Hyponatremia in acute illnesses and factors associated with mortality in critically ill patients at tertiary care Hospital. **Introduction:** Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is frequently encountered in the intensive care setting.^[1, 6] Treatment varies significantly according to the timing of onset and aetiology of the disorder. Inadequate or improper treatment may lead to brain oedema or demyelination with life-threatening consequences. Appropriate treatment rendered in a timely manner can result in complete recovery in many cases. **Materials and Methods:** Single centric, prospective observational study conducted in Department of Medicine of a tertiary care hospital in period of 18 months (June 2020 till Dec 2021). Total 250 patients diagnosed with hyponatremia (serum sodium < 135 mmol/L), aged more than 12 years with irrespective of gender admitted to Medicine ICUs at our hospital within 48 hours of admission were included in our study. Patients on diuretic therapy, Patients who develop hyponatremia later on during the course in ward (after 48 hours of admission) & patients with pseudo-hyponatremia were excluded. **Results:** The most common cause of hyponatremia was SIADH in our study (66.4%). SIADH was due to infection in (69.8%) of the patients and due to stroke in (30.2%) of the patients. Next most common cause was renal failure (11.6%), severe sepsis (7.2%), trauma (6%), liver failure (3.2%), thiazide diuretics (3.2%) and hypothyroidism (2.4%). The most common precipitating factor in our patients was vomiting (48.4%). The most common presenting complaint of our patients was abnormal behaviour (41.6%). It was observed that (86%) of the patients who died were aged 61 to 80 years, diabetes mellitus and hypertension was more common among patients who died, while 41% of the patients who were discharged were aged 41 to 60 years. In addition, mortality among female patients was significantly higher (p value < 0.01). The severity of hyponatremia was not found to be significantly associated with mortality among the patients (p value = 0.86). **Conclusion:** The most common presenting complaint was abnormal behaviour, 22.4% were drowsy, SIADH was the most common cause, 46.8% had severe hyponatremia, 42.4% were hypervolemic, and 24.4% stayed in ICU for more than 5 days. Mortality rate was 20% and was not associated with severity of hyponatremia, though it was high in patients with severe hyponatremia. Older age, female gender, past medical history of hypertension and diabetes mellitus, high blood pressure, drowsiness at presentation, extensor plantar, pus cells in urine routine, and more than 4 weeks of ICU stay were associated with mortality.*

Keywords: Hyponatremia, ICU (Intensive Care Unit), acute illnesses, Mortality

1. Introduction

The serum sodium level is determined by the relationship of total body exchangeable sodium with total body water. Hyponatremia develops due to primary sodium deficit, primary water excess, or a combination of these conditions.^[2] Diagnosis requires recognition of sometimes subtle neurological symptoms, evaluation of volume status, and analysis of serum and urine sodium levels and osmolality.

Hyponatremia is typically categorized as hypervolemic, euvoletic, or hypovolemic. Causes of Hypervolemic Hyponatremia includes-Renal causes (acute renal failure, chronic renal failure, nephrotic syndrome), Extrarenal causes (congestive heart failure, cirrhosis) & Iatrogenic. Causes of Euvoletic Hyponatremia (TBW increase with stable total body sodium) includes-Drugs (like vasopressin, thiazides, nicotine, antipsychotics, chlorpropamide, cyclophosphamide, nonsteroidal anti-inflammatory drugs), Syndrome of inappropriate antidiuretic hormone (SIADH)^[3], Addison's disease, Hypothyroidism, High fluid intake in conditions like primary polydipsia etc. Causes of Hypovolemic Hyponatremia includes-Gastrointestinal fluid loss (diarrhoea or vomiting), The third spacing of fluids (pancreatitis, hypoalbuminemia, small bowel obstruction), Diuretics, Osmotic diuresis (glucose, mannitol), Salt-wasting nephropathies, Cerebral salt-wasting syndrome (urinary salt wasting, possibly caused by increased brain natriuretic peptide) & Mineral corticoid deficiency. Careful history

and physical examination should determine the time of onset of hyponatremia and the onset of symptoms.

Acute hyponatremia is characterized by onset of symptoms <48h. Patients with acute hyponatremia develop neurologic symptoms resulting from cerebral edema induced by water movement into the brain. These may include seizures, impaired mental status or coma and death. Acute hyponatremia can be corrected more rapidly than chronic hyponatremia because the process of extrusion of organic osmolytes of the brain volume regulatory response has not taken full effect.

Chronic hyponatremia- Hyponatremia developing over >48 h should be considered "chronic." Most patients have chronic hyponatremia. The serum sodium concentration is usually above 120meq/L. Brain adapts itself to hyponatremia by generation of idiogenic osmoles. This is a protective mechanism that reduces the degree of cerebral edema; it begins on the first day and is complete within several days. Hence in chronic hyponatremia patients may appear asymptomatic. Mild hyponatremia is characterized by gastrointestinal tract symptoms nausea, vomiting, loss of appetite. Sometimes, subtle neurologic abnormalities may be present when the serum sodium is between 120 and 130 meq/L. Hyponatremia in the elderly may manifest with frequent falls and gait disturbances.^[4] In chronic hyponatremia very rapid correction can lead to osmotic demyelination syndrome (ODS). Hence, chronic hyponatremia generally needs gradual correction.

The various causes are attributed to hyponatremia in critical ill patients, and one of the important cause of mortality in ICU patients, in the present study included 250 patients from ICU at tertiary care hospital to evaluate the clinical profile of hyponatremia in acute illnesses and factors associated with mortality.

2. Materials and Methods

Study Design

It was a single centric, prospective observational study.

Study Duration

The study was conducted for a period of 18 months (June 2020 till Dec 2021)

Study Site-

The study was conducted in Intensive care unit (ICU) of Department of Medicine at tertiary care hospital.

Sample Size

The sample size calculated was 250.

2.1 Methodology

Ethical Considerations

The study was initiated after obtaining approval from the institutional ethics committee. A written informed consent was taken from the patients, once they were stable.

Selection criteria

Participants were selected based from the following selection criteria

Inclusion criteria

- 1) All the patients irrespective of gender admitted to Medicine ICUs at our hospital within 48 hours of admission.
- 2) Patients diagnosed with hyponatremia (serum sodium < 135 mmol/L).
- 3) Patients aged more than 12 years.
- 4) Patients who are willing to participate in study and giving written informed consent.

Exclusion criteria

- 1) Patient with age <12 years.
- 2) Patients on diuretic therapy.
- 3) Patients who develop hyponatremia later on during the course in ward (after 48 hours of admission)
- 4) Patients with pseudo-hyponatremia (Patients with hyperlipidaemia, paraproteinemias and those having redistributive hyponatremia (mannitol therapy, hyperglycemia).

2.2 Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm SD and median. Normality of data was tested by Kolmogorov-Smirnov test. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

2.3 Study Procedure

The study was initiated after approval from Institutional ethics committee. All the patients presenting to medicine ICU with aged >12 years with hyponatremia patients who meet the inclusion and exclusion criteria were part of the study. Written informed consent in the language understandable was obtained from patients or their legal representative whenever possible.

2.4 Data collection

Demographic information

- 1) Clinical history
 - a) Past history of any pre-existing chronic health conditions
 - b) History of fluid loss
 - c) Presenting complaints
 - d) Medication history
- 2) Clinical examination
 - a) Vitals: pulse, respiratory rate, blood pressures, body temperature
 - b) Hydration status (hypo/eu/hyper-volemia)
 - c) Central Nervous System examination: mental status, focal neurological deficit
- 3) Laboratory investigations
 - a) Complete blood count
 - b) Urine routine and microscopy
 - c) Serum sodium using electrolyte auto-analyser. Hyponatremia was classified:
 - Mild: 130 to 134 mmol/L
 - Moderate: 125 to 129 mmol/L
 - Severe: < 125 mmol/L
 - d) Serum osmolality

$$\text{Serum osmolality} = 2 ([\text{Na}^+] + [\text{K}^+]) + \text{RBS}/18 + \text{BUN}/2.8$$
 mOsm/L
 (RBS in mg/dL, BUN in mg/dL)
 - e) Urine osmolality
 - f) Serum cortisol level (in patients with SIADH, if they satisfied the Bartter and Schwartz criteria)
 - g) Brain imaging and CSF analysis as advised by the treating physician

3. Data Analysis

Qualitative And Quantitative Data Analysis done from collected data In Microsoft Excel Sheet. The data in the proformas of all the 250 patients enrolled in the study was entered into the SPSS software.

Categorical variables in the study were compared using Chi square test. Relative Risk is calculated using odd ratio. P value of <0.05 was significant. Results displayed in Tabular and Graphical form.

3.1 Summary

This was an observational study conducted in the department of medicine at tertiary care hospital after obtaining permission from the institutional ethics committee. The present study included 250 patients diagnosed to have Hyponatremia and admitted in Intensive care unit (ICU) fulfilling the inclusion and exclusion criteria.

Etiology of hyponatremia

- The most common cause of hyponatremia was SIADH in our study (66.4%). Next most common cause was renal failure (11.6%), severe sepsis (7.2%), trauma (6%), liver failure (3.2%), thiazide diuretics (3.2%) and hypothyroidism (2.4%).
- SIADH was due to infection in (69.8%) of our patients and due to stroke in (30.2%) of the patients.

Table 1: Distribution of patients according to Etiological profile

Cause of Hyponatraemia	Frequency	Percent
SIADH	166	66.4
Renal failure	29	11.6
Severe sepsis	18	7.2
Trauma	15	6
Liver failure	8	3.2
Thiazide diuretics	8	3.2
Hypothyroidism	6	2.4
Total	250	100

3.2 Clinical features

- The most common presenting complaint of our patients was abnormal behavior (41.6%). Other presenting complaints were lethargy (26%), postural dizziness (22.4%) and seizures (2.4%). Among these, abnormal behaviour (66% vs 35.5%, p value < 0.01), postural dizziness (38% vs 18.5%, p value < 0.01) and seizure (12% vs 0%, p value < 0.01) were significantly associated with mortality among the patients.
- Among patients who expired, 38% were drowsy and 16% were unconscious, which was significantly higher as compared to those among discharged patients (18.5% drowsy and 1% unconscious), p value < 0.01.
- Extensor planter reflex was observed in 30% of expired and 17.5% of discharged patients (p value < 0.05). Ataxia and cerebellar signs were not observed in any patient.

Table 2: Distribution of patients according to Presentation

Presenting complaints	Patient outcome			Total	p value*
	Death	Discharge			
Lethargy	N	15	50	65	0.44
	%	30.00%	25.00%	26.00%	
Abnormal behaviour	N	33	71	104	< 0.01
	%	66.00%	35.50%	41.60%	
Postural dizziness	N	19	37	56	< 0.01
	%	38.00%	18.50%	22.40%	
Seizure	N	6	0	6	< 0.01
	%	12.00%	0.00%	2.40%	
Total	N	50	200	250	
	%	100.00%	100.00%	100.00%	

*analyzed using chi-square test

Mortality: In our study, (20%) of the patients admitted to ICU with hyponatremia expired.

a) Demography

- (86%) of the patients who died were aged 61 to 80 years, while (41%) of the patients who were discharged were aged 41 to 60 years.
- In addition, it was observed that (80%) of the patients who died were females, while (83%) of the patients who

were discharged were males. Thus, we observed that mortality among female patients was significantly higher (p value < 0.01).

Table 3: Distribution of patients according to their Age

Age groups (years)	Patient outcome		Total
	Death	Discharge	
12 to 20	N	0	7
	%	0.00%	3.50%
21 to 40	N	7	23
	%	14.00%	11.50%
41 to 60	N	0	82
	%	0.00%	41.00%
61 to 80	N	43	84
	%	86.00%	42.00%
More than 80	N	0	4
	%	0.00%	2.00%
Total	N	50	200
	%	100.00%	100.00%

p value* < 0.01

*analyzed using chi-square test

b) Past medical history-

- Diabetes mellitus was significantly more common among patients who died as compared to those who were discharged (76% vs 56.5%, p value < 0.05).
- Hypertension was also significantly more common among patients who died as compared to those who were discharged (50% vs 23%, p value < 0.01).

c) Investigations -

- Mean serum sodium level was 120.72 ± 7.97 and 122.15 ± 7.91 mEq/L among expired and discharged patients respectively.
- Right sided perinephric fat stranding was observed on ultrasound abdomen in 26% of the expired and in 1.5% of the discharged patients (p value < 0.01).
- Pus cells on urine examination were found in 26% of the expired patients and in 1.5% of the discharged patients (p value < 0.01).
- 40% had serum creatine level less than 1 mg/dl, 34.4% between 1 and 2 mg/dl and 25.6% had serum creatinine level more than 2 mg/dl. Serum creatinine levels were not significantly associated with mortality among patients.

d) Severity of hyponatremia

- Mild hyponatremia (13.6%), Moderate hyponatremia (39.6%) & Severe hyponatremia (46.8%)
- The severity of hyponatremia was not found to be significantly associated with mortality among the patients (p value = 0.86).

e) Volume status

- (31.2%) were euvolemic, (42.4%) were hypervolemic and (26.4%) were hypovolemic.
- We did not observe a significant association between volume status and mortality among the patients (p value = 0.46).

Treatment given to patients with severe hyponatremia

- In our study, among those who died, 56% were treated with 3% saline and among those who were discharged,

47% were treated with 3% saline. We observed no significant association between treatment given and final outcome of the patients (p value = 0.73).

Length of ICU stay

- We observed that 24.4% had ICU stay for more than 4 weeks and rest stayed in ICU for up to 4 weeks. It was observed that 90% of the expired patients stayed in ICU for more than 4 weeks, which was significantly more than that among discharged patients (p value < 0.01).

Table 4: Distribution of patients according to length of ICU stay

Length of ICU stay		Patient outcome		Total
		Death	Discharge	
More than 4 weeks	N	45	16	61
	%	90.00%	8.00%	
Up to 4 weeks	N	5	184	189
	%	10.00%	92.00%	75.60%
Total	N	50	200	250
	%	100.00%	100.00%	100.00%
		p value* < 0.01		
*analyzed using chi-square test				

4. Discussion

This prospective observation study was conducted in the Department of Medicine at a tertiary care hospital in Mumbai. In this study, all the patients aged more than 12 years, irrespective of gender admitted to Medicine ICUs at our hospital within 48 hours of admission and diagnosed with hyponatremia (serum sodium < 135 mmol/L) were included. The study was conducted to evaluate the clinical profile of hyponatremia in acute illnesses in and factors associated with mortality. The results of our study are discussed as below.

- Mortality:** In our study, 20% of the patients admitted to ICU with hyponatremia expired. Chatterjee et al reported that 13.5% (15/201) hyponatremic patients died during the hospital stay.^[5] In the study by Padhi et al, 30-day mortality was 19.5%.^[6] The results of the present study are consistent with the above mentioned study.
- Co morbidities:** like Diabetes mellitus, Hypertension, Kidney disease etc also contribute to the mortality of patients. In the study by Uddin et al, commonest co-morbidities among the study subjects were diabetes mellitus (90.5%), followed by hypertension (75.5%), chronic kidney disease (50.5%), ischemic heart disease (38%).^[7]
- Clinical features:** The most common presenting complaint of our patients was abnormal behavior (41.6%). Due to wide spectrum of clinical manifestations, Different studies found different clinical presentation of hyponatremia in Critically ill patients. The most common presenting complaints in the study by Babaliche et al was vomiting (28%) and confusion (26%).^[8] In the study by Paniker and Joseph, confusion was the most common presenting complaint (34%).^[9]
- Etiology of hyponatremia:** The most common cause of hyponatremia was SIADH in our study (66.4%). Next most common cause was renal failure (11.6%) and severe sepsis (7.2%) etc. SIADH was due to infection in

(69.8%) of our patients and due to stroke in 30.2% of the patients. The infection is found to be the most common cause for ICU admission and same infection cause found to be associated with development of SIADH and subsequently Hyponatremia. Padhi et al reported that SIADH (36.25%) was the most common cause of hyponatremia and pneumonia was the most common cause leading to SIADH.^[6] The results of the present study are consistent with the above mentioned study. Similar to our findings, Babaliche et al also reported that SIADH was the most common cause of hyponatremia, reported in 46% of the patients.^[8] On evaluating the cause of SIADH, infections (56.52%) were the predominant cause followed by disorders of CNS (26.08%) and neoplasm (6.52%).

- Severity of hyponatremia:** The severity of hyponatremia was not found to be significantly associated with mortality among the patients (p value = 0.86). Because many other factors are also associated with mortality in critically ill patients with hyponatremia like sepsis, multiorgan dysfunction etc.
- Treatment given to patients with severe hyponatremia:** In our study, among those who died, 56% were treated with 3% saline and among those who were discharged, 47% were treated with 3% saline. We observed no significant association between treatment given and final outcome of the patients (p value = 0.73). In a similar study, Patil et al observed that overall mortality rates during the treatment of hyponatremia was 57% in 0.9% isotonic solution infusion in which death was 14.04%.^[10]
- Length of ICU stay:** It was observed that 90% of the expired patients stayed in ICU for more than 4 weeks, which was significantly more than that among discharged patients (p value < 0.01). Friedman and Cirulli found in a study done in USA, duration of ICU stay was significantly associated with hyponatremia (p < 0.001).^[11] The results of the present study are consistent with the above mentioned study.

5. Limitations

- This being a single centre study with a modest sample, the findings may not be applicable to other populations and geographical locations.
- Ideally, patients' long term outcomes should have been evaluated, which we could not assess due to time constraints.
- In addition, we did not include patients who were not admitted to medical ICU. Many patients with milder forms of hyponatremia could have been excluded in this manner, thereby introducing selection bias.

6. Conclusion

- The most common presenting complaint was abnormal behaviour, 22.4% were drowsy, SIADH was the most common cause, 46.8% had severe hyponatremia, 42.4% were hypervolemic, and 24.4% stayed in ICU for more than 5 days.
- Mortality rate was 20% and was not associated with severity of hyponatremia, though it was high in patients with severe hyponatremia.

- 3) Older age, female gender, past medical history of hypertension and diabetes mellitus, high blood pressure, drowsiness at presentation, extensor plantar, pus cells in urine routine, and more than 4 weeks of ICU stay were associated with mortality.

Hyponatremia is common electrolyte abnormality. Before initiating treatment, the underlying etiology and volume status should be ascertained. For this early identification of hyponatremia is required. Clinically, it may be difficult as majority of the patients have non-specific symptoms and complaints.

After discussing the results and drawing conclusions from the present study, we recommend that:

- 1) Careful history and physical examination should be conducted so as to determine the time of onset and severity of symptoms.
- 2) Patients with severe hyponatremia should be monitored closely in ICU.
- 3) Prospective comparative studies are required in future to determine the role of different treatments in reducing mortality in patients with hyponatremia.

Declaration

I confirm that I have read, understand, and agreed to the submission guidelines, policies, and submission declaration of the journal.

I confirm that all authors of the manuscript have no conflict of interests to declare.

I confirm that the manuscript is the authors' original work and the manuscript has not received prior publication and is not under consideration for publication elsewhere.

On behalf of all Co-Authors, I shall bear full responsibility for the submission.

I confirm that all authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission.

I confirm that the paper now submitted is not copied or plagiarized version of some other published work.

I declare that I shall not submit the paper for publication in any other Journal or Magazine till the decision is made by journal editors

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