ORIGINAL ARTICLE

JIACM 2021; 22(1-2): 35-40

Clinical Determinants and Short-Term Prognosis of Hyponatraemia Present on ICU Admission

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Abstract

Background: Hyponatraemia is one of the most common electrolyte imbalances in hospitalised patients, encountered in 15 - 30% of patients. A major proportion of the data available on this subject is derived from work done outside India. Most of the studies are retrospective in nature and there is wide variation in the findings of different studies.

Objective: To identity the prevalence, aetiology, clinical determinants and outcome of hyponatraemia present on medical Intensive Care Unit (ICU) admission.

Methods: Patients getting admitted to medical ICU over a period of one year meeting inclusion and exclusion criteria were included in this observational, prospective study.

Results: Prevalence of hyponatraemia on ICU admission was 42.7% (n = 128). Prevalence of mild, moderate and profound hyponatraemia was 24%, 17.5% and 12.5%, respectively. Binary logistic regression analysis showed that age > 55 years (p = 0.036), chronic renal failure (p = 0.025) and use of thiazide diuretics (p = 0.010) were independent risk factors for the development of hyponatraemia. Kidney disease was the most common cause of hyponatraemia (29.69%). Fluid restriction was the most common treatment modality (33.59%). There was no significant association of hyponatraemia with increased mortality and adverse outcome.

Conclusions: Hyponatraemia was common on ICU admission, more so in Indian scenario. Old age, chronic renal failure and use of thiazide diuretics were independent risk factors for hyponatraemia. Regular monitoring of serum electrolytes, especially serum sodium, cannot be overemphasised in these specific populations. The association of hyponatraemia with increased mortality and adverse outcome has to be reconsidered in larger, multi-centre studies.

Key words: Hyponatraemia, ICU, risk factors, aetiology, prognosis.

Introduction

The interplay between pituitary (vasopressin/antidiuretic hormone) and renal system (relative salt and water excretion) is mainly responsible for maintaining normal level of sodium in the body. Hyponatraemia is decrease in the relative ratio of sodium (Na^+) to body water. Serum Na^+ < 135 mEq/l has been defined as hyponatraemia and serum Na^+ > 145 mEq/l as hypernatraemia. In the latest European guidelines, hyponatraemia has been further classified as mild (serum sodium between 130 and 134 mEq/l), moderate (serum sodium between 125 and 129 mEq/l) and profound hyponatraemia (serum sodium less than 125 mEq/l[1]. It is one of the most common electrolyte imbalances encountered, reported in 15 - 30% of hospitalised patients[2]. Hyponatraemia is more common in intensive care settings. Frequency of hyponatraemia among patients admitted to intensive care units (ICUs) has been reported to be between 17.7 and 34.3%[3-7]. Hyponatraemia can be hyperosmolar, isoosmolar or hyperosmolar based on the corresponding serum osmolality.

The symptoms of hyponatraemia, mainly caused by brain oedema and/or increased intracranial pressure, vary depending on the time of development of hyponatraemia and the absolute decrease in serum Na^+ level. While mild hyponatraemia is mostly asymptomatic; moderate-to-profound hyponatraemia can cause symptoms ranging from subtle ones like nausea, confusion and headache to severe ones like seizures and coma[1].

In more than one study, hyponatraemia has been reported to be an independent risk factor for poor outcome[5-7]. A major proportion of the data available on this subject is based on work done outside India. Most studies are

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retrospective and there is wide variation in the findings studies. The aim of this prospective study was to identity the clinical determinants and outcomes of hyponatraemia, present on ICU admission.

Objectives

To identity the prevalence, aetiology, clinical determinants, management and outcome of hyponatraemia, present on ICU admission.

Inclusion and exclusion criteria

Successive patients admitted in Medical Intensive Care Unit (MICU) over a period of one year (2017 - 2018) with/without hyponatraemia, with age > 18 years giving consent for participation in the study were included in the study. Patients not giving consent for participation in the study, age less than 18 years, pregnant patients at the time of admission and patients readmitted to MICU during the same hospitalisation were excluded from this study.

Material and methods

Patient's serum sodium level, demographics, volume status, relevant present medical and drug history, APACHE-2 score, SOFA score on day one, two and three of ICU admission, relevant investigations, clinical diagnosis, cause of hyponatraemia, treatment, outcome on transfer out from ICU and hospital discharge, were collected in a specially designed study proforma. Hyponatraemia was classified as mild (serum sodium 130 - 134 mEq/l), moderate (serum sodium 125 - 129 mEq/l) and profound hyponatraemia (serum sodium < 125 mEq/l) acoording to the European guidelines[1]. Chi-square test, Fischer's test, Student's t-test and non-parametric tests, when appropriate, were used for statistical analysis.

Results

In this study, prevalence of hyponatraemia at ICU admission was 42.66% (n = 128). Prevalence of mild, moderate and profound hyponatraemia was 21% (n = 63), 13.33% (n = 40), and 8.33% (n = 25), respectively (Fig. 1).

After univariate analysis, age more than 55 years (p = 0.002), hypertension (p = 0.003), chronic renal failure (p = 0.003), use of thiazide (p = 0.001) and loop diuretics (p = 0.025), and APACHE-2 score more than 12 (p = 0.027) were significant risk factors for hyponatraemia (Table I).

Many of the hypertensive and chronic renal failure patients were taking thiazide and loop diuretics, respectively and most of them belonged to the older age group. Age, along with serum creatinine level, are part of APACHE-2 score.

Binary logistics regression analysis was done to identify the significant independent risk factors. It showed that age more than 55 years (p = 0.036), chronic renal failure (p = 0.025) and use of thiazide diuretics (p = 0.010) were independent risk factors for the development of hyponatraemia (Table II).

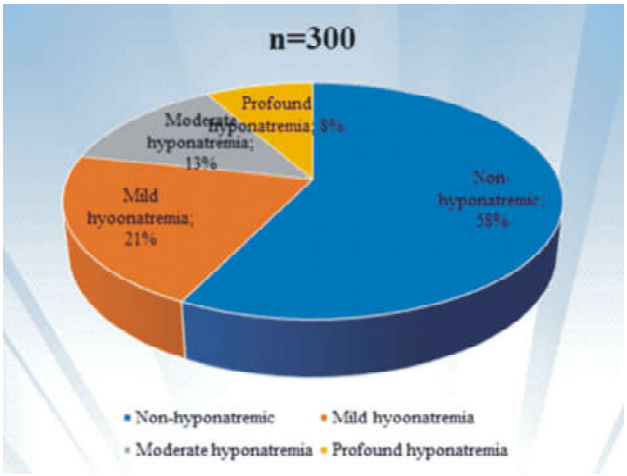
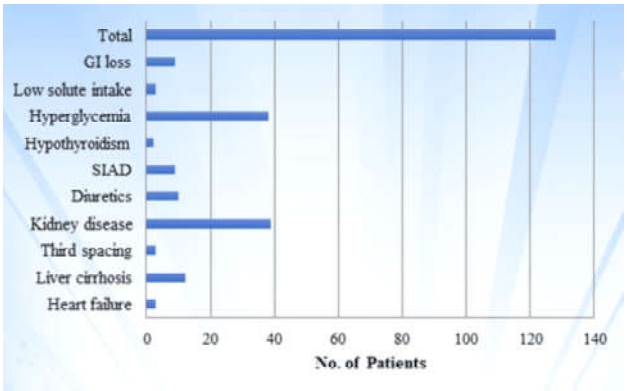


Fig. 1: *Distribution of the cases according to serum sodium level (mEq/l).*

Hypertension (49%) and diabetes mellitus (35.67%) were the most common comorbidities in the study population in both hyponatraemic as well as non-hyponatraemic groups. History of diuretic medications was given by 8.33% (n = 25) of total patients. Mean APACHE-2 score was 14.19 ± 6.57 for the hyponatraemic patients and 12.32 ± 8.20 for the non-hyponatraemic patients (p < 0.05) (Table I).

Kidney disease was the most common cause of hyponatraemia (30.46%, n = 39). It was followed by hyperglycaemia (29.69%, n = 38), liver cirrhosis (9.38%, n = 12), diuretic use (7.81%, n = 10), SIAD (7.03%, n = 9) and gastrointestinal loss (7.03%, n = 9) (Fig. 2).



GI loss: Gastrointestinal loss; SIAD: Syndrome of inappropriate diuresis.

Fig. 2: *Distribution of the cases according to cause of hyponatraemia.*

Table I: Univariate analysis for the risk factors of hyponatraemia.

	Hyponatraemic (n = 128)		Non-hyponataremic (n = 172)		Total (N = 300)	Odds ratio (95% confidence interval)	P value
	No	%	No	%	No		
	128	42.67	172	57.33	300		
Age > 55 years	97	49.24	100	50.76	197	2.253 (1.359 to 3.734)	0.002
Age ³ 55 years	31	30.10	72	69.90	103		
DM	53	49.53	54	50.47	107	1.544 (0.959 to 2.488)	0.095
Hypertension	76	51.70	71	48.30	147	2.079 (1.305 to 3.311)	0.003
Renal failure	26	61.90	16	38.10	42	2.485 (1.271 to 4.861)	0.011
Cardiac failure	1	25.00	3	75.00	4	0.444 (0.046 to 4.315)	0.833
CLD	13	61.90	8	38.10	21	2.317 (0.931 to 5.771)	0.105
Bronchial asthma	3	27.27	8	72.73	11	0.489 (0.127 to 1.881)	0.45
COPD	17	48.57	18	51.43	35	1.310 (0.647 to 2.655)	0.569
Malignancy	5	41.67	7	58.33	12	0.952 (0.295 to 3.072)	0.824
Thiazide diuretics	11	91.67	1	8.33	12	16.077 (2.048 to 126.217)	0.001
Loop diuretics	7	87.50	1	12.50	8	9.893 (1.201 to 81.452)	0.025
K^+ sparing diuretics	4	80.00	1	20.00	5	5.516 (0.609 to 49.958)	0.213
APACHE-II score							
> 12	71	72		143		1.730 (1.090 to 2.745)	0.027
< 12	57	100		157			
Mortality	22	38.60	35	61.40	57	0.812 (0.450 to 1.466)	0.582
Recovery	106	43.62	137	56.38	243		

DM-Diabetes mellitus; CLD-Chronic liver disease, COPD-Chronic obstructive pulmonary disease

Table II: Multivariate analysis for Identifying significant independent predictors for hyponatraemia by binary logistic analysis variables in the equation.

		B	SE	Wald	df	Sig	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1[a]	Renal failure	-.857	.383	5.012	1	.025	.424	.200	.899
	Thiazide diuretics	-2.764	1.066	6.718	1	.010	.063	.008	.510
	Loop diuretics	-2.055	1.085	3.587	1	.058	.128	.015	1.074
	APACHE-II score	-.006	.018	.127	1	.722	.994	.960	1.029
	Age	-.631	.302	4.378	1	.036	.532	.295	.961
	Hypertension	.058	.294	.038	1	.845	1.059	.595	1.885
	Constant	1.022	.400	6.512	1	.011	2.778		

a. Variable(s) entered on step 1: Renal failure, Thiazides, Loop diuretics, Apache 2 score, Age, Hypertension.

Fluid restriction was the most common treatment modality (32.03%), followed by glycaemic control (28.12%) and normal saline (16.40%). Hypertonic saline was used initially in 13.28% of hyponatraemic patients. Tolvaptan was used in 3 patients, being the primary treatment modality in one patient.

Table III: Comparison of outcomes in hyponatraemic patients.

	Non-hyponatraemia		Mild		Moderate		Profound		
	No.	%	No.	%	No.	%	No.	%	Total
Mortality	33	19.19	11	17.46	5	12.5	6	24	53
Recovery	139	80.81	52	82.54	35	87.5	19	76	247
	172	100.00	63	100.00	40	100	25	100	300

Chi-square = 1.668 with 3 degrees of freedom; p = 0.882.

Out of 300 patients, 53 (17.66%) died in the ICU, while 4 patients (1.33%) died after transfer out from ICU. Overall mortality in the study population was 57 (19%). Mortality in hyponatraemic patients was 17.19% (n = 22), with no significant difference from that in the non-hyponatraemic group (20.35%, n = 57) (p = 0.582). Mortality in the mild, moderate and profound hyponatraemia patients was 24% (n = 6), 17.46% (n = 11) and 12.5% (n = 5), respectively (Table III). In the hyponatraemic patients, mean duration of stay in ICU (5.42 ± 5.67 days) was not significantly different as compared with 6.44 ± 8.47 days in the non-hyponatraemic group (p = 0.239). Similarly mean BiPAP (bilevel positive airway pressure) support duration was 4.15 ± 3.31 days as compared with 8.41 ± 9.7 days in the non-hyponatraemic group (p = 0.131). Mean mechanical ventilator support duration was 5.88 ± 7.52 days in the hyponatraemic patients while it was 5.11 ± 6.11 days in the non-hyponatraemic patients (p = 0.644). In patients with profound hyponatraemia (serum sodium < 125), mortality was 24%, which was higher than that in the non-hyponatraemic patients but the association was not significant (p = 0.882).

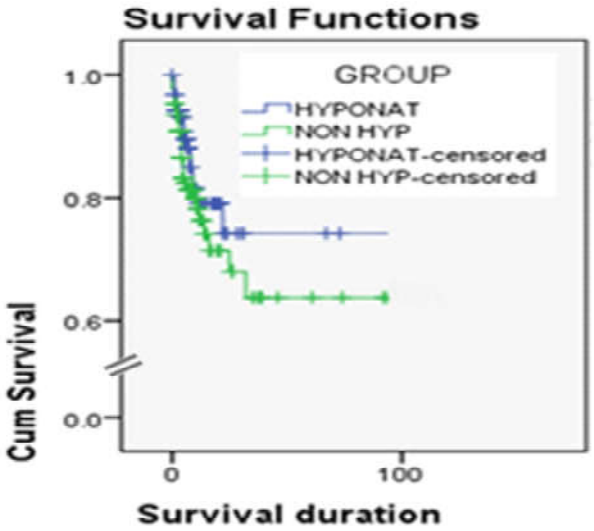


Fig. 3: *Kaplan-Meier survival analysis.*

Discussion

Hyponatraemia is one of the most common electrolyte imbalances seen in hospital ICUs. Yet there is a challenge in managing these patients as hyponatremia is not a single well-defined disease entity and the treatment varies, depending on the aetiology.

Prevalence of hyponatraemia (42.66%) is significantly higher in comparison with other studies, especially the studies done outside India[3-7]. The studies show similar distribution, with profound hyponatraemia having the least prevalence preceded by moderate and mild hyponatraemia. Overall, the prevalence of hyponatraemia on ICU admission appears to be higher in the Indian ICUs as seen in this study and the study done by Padhi *et al*[7]. Hyponatraemia was more common in the elderly patients. Similar trend was observed by Bhattacharjee *et al* where 84% of the patients had age > 84 years[8]. Age is significant risk factor for the development of hyponatraemia due to changes in body metabolism and dietary solute intake with increasing age. Also, comorbidities such as renal failure and hypertension

Kaplan-Meier survival Analysis

Table IV: Means and Medians for Survival Time.

Group	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Hyponatraemia	249.663	35.251	180.570	318.755	373.000	.000	.	.
Non-Hyponatraemia	149.454	14.658	120.724	178.184	228.000	.000	.	.
Overall	222.682	26.286	171.161	274.202	228.000	55.518	119.185	336.815

a. Estimation is limited to the largest survival time if it is censored.

increase with age. There is relatively low consumption of high salt content processed food items by the Indian elderly population, as compared with their Western counterparts. Salt intake is further reduced based on doctor's advice for the control of hypertension. The situation is worsened by use of thiazide diuretics as anti-hypertensive medications, and routine monitoring of serum sodium is rarely done. These may be the possible reasons for higher prevalence of hyponatraemia in Indian ICUs.

Similar to the trend shown by Bhattacharjee *et al*[8], hypertension (49%) and diabetes mellitus (35.67%) were the most common comorbidities in the study population in both hyponatraemic as well as non-hyponatraemic groups. A greater number of patients with hypertension are likely to use diuretics as anti-hypertensive medications and prevalence of diabetes mellitus increases with age. Hyponatraemic hypertensive syndrome is a known clinical entity in which atherosclerosis of arteries in the elderly is associated with development of hyponatraemia[11]. Kidney disease itself is the cause of hyponatraemia due to urinary loss of sodium, so association is causal. Role of thiazide diuretics in hyponatraemia is already well established[1].

Kidney disease was the most common cause of hyponatraemia in this study, followed by hyperglycaemia, liver cirrhosis, diuretic use, SIAD and gastrointestinal loss. In contrast, Padhi *et al* reported SIAD to be the most common cause of hyponatraemia (36.25%)[7] while Bhattacharjee *et al* reported gastrointestinal loss as the most common cause (24%), followed by diuretics (20%), congestive cardiac failure (18%), liver cirrhosis (15%), SIAD (8%) and chronic renal failure (7%)[8]. This may be due to different settings where studies were carried out. Padhi *et al* had patients admitted in the mixed ICU as the study population, while Bhattacharjee *et al* had medicine ward patients as the study population. This study had medical ICU as the study population. As cardiac patients were admitted in a different cardiac ICU, number of patients with cardiac failure was less. More patients with end-stage kidney disease might have been admitted in the ICU. Similar to our study, Agarwal *et al* also reported fluid restriction to be the most common treatment modality (40%) in hyponatraemic patients with serum $Na^+ < 125$ mEq/l[10].

There was no significant difference in mortality in the hyponatraemic and non-hyponatraemic groups. Also, there was no significant difference between the two populations in terms of other parameters like mean duration of stay in ICU, mean BiPAP support duration and mean duration of mechanical ventilator support. This is in contrast to the previous studies where hyponatraemia has been shown to be associated with increased mortality and adverse outcome[5,7]. As compared with this study, hypernatraemic patients were excluded in the studies by Funk *et al*[5] and Padhi *et al*[7]. Hyperglycaemic patients were excluded by Padhi *et al*[7]. Even after adjusting the above two factors, mortality association was not significant. This may be attributed to higher contribution of the other associated diseases and risk factors in the study population, rather than hyponatraemia as the determinant of outcome.

Conclusions

This study shows that hyponatraemia on ICU admission is more common in Indian ICUs (prevalence = 42.66%). Old age, chronic renal failure, and use of thiazide diuretics were important risk factors for hyponatraemia. Emphasis on regular monitoring of serum electrolytes especially serum sodium is of utmost importance in these specific populations. Surprisingly, there was no significant association of hyponatraemia with increased mortality and adverse outcome. Hyponatraemia, when properly and promptly managed in intensive care settings, is a treatable condition with good patient outcomes.

Study limitations

1. As the site of study was adult medical ICU, it doesn't represent other ICUs (e.g., surgical, cardiac and paediatric ICUs).
2. Our hospital, being a private sector tertiary care centre, may not be representative of the lower socio-economic strata of the general population.
3. Further studies with larger sample size, using multivariate analysis, may be needed to substantiate or contradict the findings.

Recommendations

1. Elderly patients, prone to many other diseases, are more likely to develop hyponatraemia. Electrolyte imbalance as cause of presenting complaints in elderly should be given priority.
2. Indiscriminate use of thiazide diuretics for hypertension in older patients should be discouraged. If necessary, frequent monitoring of serum electrolytes especially serum sodium should be done for early detection of electrolyte imbalance.
3. Frequent monitoring of serum sodium, along with other electrolytes and maintenance of fluid balance is recommended in patients with chronic renal failure.
4. Association of hyponatraemia with adverse outcomes needs to be reconsidered with larger studies, in view of the present study findings. Newer diagnostic modalities and better treatment for diseases like chronic renal failure should be taken into account.

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