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Original Research Article

Prevalence and outcome of hyponatremia in patients admitted with COVID-19

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ABSTRACT

Background: Hyponatremia occurs in up to 30% of patients with pneumonia and is associated with increased morbidity and mortality. The prevalence of hyponatremia associated with coronavirus disease 2019 and the impact on outcome is unknown. We aimed to identify the prevalence, and outcome of patients having hyponatremia admitted with COVID-19.
Methods: This was a retrospective observational study conducted among admitted adult patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Srinivas institute of medical sciences and research centre, Mukka, Surathkal.
Results: This difference in hyponatremia was statistically significant with regard to age ($p<0.001$), respiratory rate ($p=0.002$), SpO_2 ($p=0.029$), total counts ($p=0.03$), CRP ($p=0.005$), and d-dimer ($p=0.015$).
Conclusions: In patients with COVID-19, age, hypotension, respiratory rate, SpO_2, total counts, CRP, and D-Dimer have significant correlation with hyponatremia. Also, patients with COVID-19 and hyponatremia have higher rates of mechanical ventilation and mortality.

Keywords: Coronavirus disease 2019, Hyponatremia, Pneumonia, SARS-CoV

INTRODUCTION

Hyponatremia (sodium <135 mmol/L) occurs in 26-28% of patients.[1,2] With community-acquired pneumonia (CAP) and is associated with increased risk of ICU admission, prolonged length of stay, higher hospital cost, and increased mortality rates.[2-8] Profound hyponatremia can be associated with life-threatening complications, including encephalopathy, cerebral oedema, seizure, coma, and myelinolysis (with overly rapid sodium correction).

The SARS-CoV-2 is part of the beta coronavirus family and causes coronavirus disease 2019 (COVID-19).[9,10] In March 2020, the world health organization (WHO) declared COVID-19 a pandemic, one of the most severe pandemics that humanity has faced over time.[9,10]

Moderate and severe hyponatremia have been described in case reports of SARS-CoV-2 infection.[11,12] The authors of these studies have suggested that hyponatremia at admission may serve as an indicator of potential coronavirus disease 2019 (COVID-19) infection. Data on the prevalence, severity, and impact of hyponatremia in the context of a large COVID-19 cohort is lacking however.[12]

Aims and objectives

In this study, the primary aim was to determine the prevalence and outcome of varying degrees of hyponatremia among patients with SARS-CoV-2 and to identify the association of hyponatremia with in-hospital mortality.

METHODS

This was a retrospective observational study conducted among admitted adult patients with confirmed SARS-CoV-2 infection in Srinivas institute of medical sciences and research centre, Mukka, Surathkal. Data for this study were collected from medical record section using the patient data registry in the period of 3 months from April 2021 to June 2021.

Inclusion criteria

Patients who tested positive for SARS-COV-2 on nasopharyngeal and oropharyngeal polymerase chain reaction testing or rapid antigen testing. Patients who were admitted and received treatment as inpatient for COVID-19 at in Srinivas institute of medical sciences and research centre, Mukka, Surathkal.

Exclusion criteria

Hyponatremia developed during course of hospitalisation, chronic kidney disease. Information obtained included patient demographic and clinical features, laboratory values, and hospital outcomes (length of stay, ICU admission, in-hospital mortality).

Patients were divided into three levels of hyponatremia severity based at admission sodium values: mild (Na 130-134 mmol/L), moderate (Na 121-129 mmol/L), and severe (Na $\leq$ 120 mmol/L) and were compared with patients with normo natremia at admission (Na 135-145 mmol/L). Hyponatremia that developed during the hospital course was not evaluated since iatrogenic causes of hyponatremia would confound analysis of the effect of SARS-CoV-2 on sodium levels. After taking approval from institutional ethics committee clearance.

Statistical analysis

Data was entered into an MS excel sheet to prepare a master chart. Statistical analysis of data was performed using statistical package for social sciences (SPSS for windows, version 21.0 Chicago, SPSS inc.) and Microsoft excel 2010. Results on continuous measurements presented as mean ± SD were compared using an independent t test. Discrete data expressed as numbers (%) and analysed using the chi-square test. For analysis, the statistical significance was fixed at a 5% level ($p<0.05$).

RESULTS

Comparison of age using one way ANOVA test shows that the mean value of severe hyponatremia (69.79) is highest followed by moderate hyponatremia (61.53), mild hyponatremia (57.61) least in normo-natremia (52.1). This difference is statistically significant with a test value of 7.736 and $p<0.001$.

Comparison of respiratory rate using one way ANOVA test shows that the mean value of moderate hyponatremia (28.09) is highest followed by severe hyponatremia (27.43), normo-natremia (25.32) least in mild hyponatremia (23.54). This difference is statistically significant with a test value of 5.013 and p=0.002.

Comparison of SpO_2 using one way ANOVA test shows that the mean value of mild hyponatremia (89.142857) is highest followed by normo-natremia (87.289855), severe hyponatremia (82.5) least in moderate hyponatremia (81.697674). This difference is statistically significant with a test value of 49.168 and p=0.029.

Comparison of total counts using one way ANOVA test shows that mean value of moderate hyponatremia (11985.74) is highest followed by severe hyponatremia (11048.57), normo-natremia (9728.52) least in mild hyponatremia (8187.21). This difference is statistically significant with at lest value of 49.316 and p=0.03.

Comparison of CRP using one way ANOVA test shows that mean value of moderate hyponatremia (140.939535) is highest followed by normo-natremia (111.871449), severe hyponatremia (100.162857) least in mild hyponatremia (85.040926). This difference is statistically Significant with a test value of 4.363 and p=0.005.

Comparison of d-dimer using one way ANOVA test shows that mean value of moderate hyponatremia (3434.501429) is highest followed by severe hyponatremia (2561.969286), normo-natremia (1687.923284) least in mild hyponatremia (1685.343571). This difference is statistically significant with test value of 53.474 and p=0.015.

Correlation between hyponatremia and other parameters in the study (ferritin, number of days of hospital stay, hemoglobin, blood urea and serum creatinine) was not statistically significant ($p>0.05$).

Table 1: Comparison of age, respiratory rate, SpO_2 with degrees of hyponatremia.

Variables	N	Mean	Std. Dev.	Statistics/ mean squares	Df^2 (welch) / F (ANOVA)	P value
Age (Years)						
Normo-natremia	69	52.1	16.125	1607.458	7.736	<0.001
Mild hyponatremia	56	57.61	13.984			
Moderate hyponatremia	43	61.53	13.341			
Severe hyponatremia	14	69.79	9.099			
Total	182	57.38	15.198			

Continued.

Variables	N	Mean	Std. Dev.	Statistics/ mean squares	Df[2] (welch) / F (ANOVA)	P value
Respiratory rate						
Normo-natremia	69	25.32	5.877	186.041	5.013	0.002
Mild hyponatremia	56	23.54	4.917			
Moderate hyponatremia	43	28.09	7.087			
Severe hyponatremia	14	27.43	7.93			
Total	182	25.59	6.291			
SpO_2						
Normo-natremia	69	87.28986	11.29563	3.266	49.168	0.029
Mild hyponatremia	56	89.14286	8.211807			
Moderate hyponatremia	43	81.69767	14.76085			
Severe hyponatremia	14	82.5	17.32828			
Total	182	86.17033	12.22933			

Table 2: Comparison of total counts, CRP, d-dimer with degrees of hyponatremia.

Variables	N	Mean	Std. Dev.	Statistics/ mean squares	Df[2] (welch) / F (ANOVA)	P value
Total counts						
Normo-natremia	69	9728.52	4550.957	3.223	49.316	0.03
Mild hyponatremia	56	8187.21	4070.364			
Moderate hyponatremia	42	11985.74	8595.841			
Severe hyponatremia	14	11048.57	6417.326			
Total	181	9877.53	5893.401			
CRP						
Normo-natremia	69	111.8714	84.60085	25464.74	4.363	0.005
Mild hyponatremia	54	85.04093	64.00181			
Moderate hyponatremia	43	140.9395	79.7273			
Severe hyponatremia	14	100.1629	65.85563			
Total	180	109.8557	78.51777			
D-Dimer						
Normo-natremia	67	1687.923	2494.721	3.811	53.474	0.015
Mild hyponatremia	56	1685.344	2274.575			
Moderate hyponatremia	42	3434.501	3140.289			
Severe hyponatremia	14	2561.969	2265.634			
Total	179	2165.289	2665.203			

Table 3: Comparison of HTN among with patients with different degrees of hyponatremia.

Variables			Serum sodium				Total
			Normo-natremia	Mild hyponatremia	Moderate hyponatremia	Severe hyponatremia	
HTN	Absent	Count	47	37	15	2	101
		% within serum sodium	68.1	66.1	34.9	14.3	55.5
	Present	Count	22	19	28	12	81
		% within serum sodium	31.9	33.9	65.1	85.7	44.5
Total		Count	69	56	43	14	182
		% within serum sodium	100	100	100	100	100
Chi-square tests			**Value**	**Df**	**P value (<0.05 is significant)**		
Pearson chi-square			24.009	3	<0.001		

Table 4: Comparison of need of mechanical ventilation in different degree of hyponatremia.

Variables			Serum Sodium				Total
			Normo-natremia	Mild hyponatremia	Moderate hyponatremia	Severe hyponatremia	
Mechanical ventilation	No	Count	44	39	19	5	107
		% within serum sodium	63.8	69.6	44.2	35.7	58.8
	Yes	Count	0	1	0	0	1
		% within serum sodium	0.0	1.8	0	0	0.5
	Yes	Count	25	16	24	9	74
		% within serum sodium	36.2	28.6	55.8	64.3	40.7
Total		Count	69	56	43	14	182
		% within serum sodium	100	100	100	100	100
Chi-square tests			**Value**	**Df**	**P value (<0.05 is significant)**		
Pearson chi-square			13.187	6	0.040		

Table 5: Comparison of mortality in different categories of hyponatremia.

Variables			Serum sodium				Total
			Normo-natremia	Mild hyponatremia	Moderate hyponatremia	Severe hyponatremia	
Mortality	No	Count	55	49	30	7	141
		% within serum sodium	79.7	87.5	69.8	50	77.5
	Yes	Count	14	7	13	7	41
		% within serum sodium	20.3	12.5	30.2	50	22.5
Total		Count	69	56	43	14	182
		% within Serum sodium	100	100	100	100	100
Chi-square tests			**Value**	**Df**	**P value (<0.05 is significant)**		
Pearson chi-square			10.941	3	0.012		

Correlation between hyponatremia and other parameters in the study (ferritin, Number of days of hospital stay, hemoglobin, blood urea and serum creatinine) was not statistically significant (p>0.05).

DISCUSSION

In infectious diseases (i.e., COVID-19), haemodynamic disorders or an inadequate immune response may cause kidney damage.[13] It is also possible that kidney cells are directly affected by the infection, according to some studies that have demonstrated the presence of viral particles in the proximal tubules and podocytes. Renal cells express receptors and enzymes used by viruses as gateways, such as angiotensin-converting enzyme 2 (ACE2).[13,14] This enzyme is also found in the lungs, heart and intestines, which explains the damage of these organs in COVID-19.[13] Another pathophysiological mechanism that may explain the renal impairment in COVID-19 is inflammatory cytokine-induced impairment. It is known that the cytokine cascade can cause a number of renal pathological changes, as well, such as acute kidney injury (AKI), tubular necrosis, dysfunction of the kidney proximal tubule, glomerulopathy and electrolyte abnormalities.[13-16]

Hyponatremia was identified in approximately 35% of patients with pneumonia.[17] The presence of hyponatremia in patients with pneumonia has been associated with a higher mortality rate, indicating the need for an early diagnosis and proper therapeutic management, to improve the prognosis of these patients.[17] The literature also reports that approximately 60% of patients with COVID-19 and watery diarrhoea have moderate hyponatremia. In this situation, hyponatremia is possibly secondary to viral replication in the intestinal epithelial cells.[18]

In the present study, the mean age of normal, mild, moderate and severe hyponatremia was found to be 52.1, 57.61, 61.53 and 57.38 years. The mean value of respiratory rate among patients in moderate hyponatremia was 28.09 and is highest followed by severe hyponatremia (27.43), normo-natremia (25.32) least in mild hyponatremia (23.54). The mean SpO_2 of mild hyponatremia (89.142857) is highest followed by normo-natremia (87.289855), severe hyponatremia (82.5) least in moderate hyponatremia (81.697674). The mean of SpO_2 of mild hyponatremia (89.142857) was found highest compared to normo-natremia (87.289855), severe hyponatremia (82.5) and least in moderate hyponatremia (81.697674) and statically significant. Whereas in the study of Frontera et al the median age of the normo-natremia, mild, moderate and severe hyponatremia were found to be 71, 66, 64 and 65 years. Patients with moderate or severe hyponatremia were significantly more likely to require invasive mechanical ventilation and were less likely to be discharged home. Additionally, patients with severe hyponatremia had eight-fold higher odds of being encephalopathic than patients with higher sodium levels.[19]

The total counts were high in severe hyponatremia and least in mild hyponatremia, CRP was high in normo-natremia followed by severe and least in mild hyponatremia. The dimer value is high in moderate, followed by severe hyponatremia and found statistically significant. The correlation between hyponatremia and other parameters viz ferritin, number of days of hospital stay, haemoglobin, blood urea serum creatinine was not significant in our study. Frontera et al found that hyponatremia occurred in nearly a third of COVID-19 patients, and was associated with increased risk of encephalopathy, acute respiratory failure requiring mechanical ventilation and was an independent predictor of in-hospital mortality.[19] In the study of Yen et al hypernatremia was independently associated with higher odds of confusion and in-hospital mortality.[20] Despite the common occurrence of hyponatremia in patients with CAP, the underlying mechanisms remain disputed SIADH has been identified as a common aetiology and may be induced by stimuli, including pain, nausea, hypovolemia, and certain medications.[21] Other factors contributing to SIADH in pneumonia are hypoxic pulmonary vasoconstriction with subsequent reduced left atrial filling, leading to increased ADH secretion.[22] Elevated IL-6 levels and inflammation have also been tied to non-osmotic ADH secretion.[23] Since cytokine storming and elevated IL-6 levels in COVID-19 have been well described.[24-31] Hypovolemic hyponatremia may have been common in COVID-19 patients since nausea, vomiting, diarrhoea, insensible losses, and anorexia frequently accompanied more typical pulmonary symptoms

CONCLUSIONS

In patients with COVID 19, age, hypotension, respiratory rate, SpO_2, total counts, CRP, and d-dimer have significant correlation with hyponatremia. Also, patients with COVID 19 and hyponatremia have higher rates of mechanical ventilation and mortality.

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