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Prevalence and Prognostic Impact of Hyponatremia in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Retrospective Observational Study

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ABSTRACT

Background: Few studies determine the prevalence and clinical progress of hospitalized patients having hyponatremia with COPD exacerbation. The objectives were to determine the prevalence of hyponatremia in hospitalized patients of COPD exacerbation, and compare the clinical and laboratory parameters in these patients.

Methodology: Retrospective observational study was carried out among 200 patients admitted with COPD exacerbation over a period of three months from October to December 2024. Patients of CKD, CLD, acute cardiac events, hypernatremia and deaths were excluded. Hyponatremia was defined as serum sodium <136mmol/L. Poor progress was defined as prolonged stay (>8 days), or readmission within one month of previous hospitalization.

Results: 112(56%) cases had hyponatremia (128.98±5.85 vs 138.88±2.22 mmol/L, 95%CI: t=16.45, p<0.001). Patients with hyponatremia were older (71.68±8.093 vs 68.8±7.645 years, 95%CI: t=2.562, p=0.011), had longer hospital stay (11.77±7.263 vs 7.24±2.849 days, 95%CI: t=6.035, p<0.001), lower albumin (95%CI: t=2.798, p=0.006), and a higher chance of being mechanically ventilated (OR=2.39, 95%CI: 1.34-4.22, p=0.003). Patients developing hospital acquired infection were more likely to develop hyponatremia (OR=18.9, 95%CI: 2.48-144, p<0.001). Hyponatraemic patients had poorer progress (OR=4.83, 95%CI: 2.64-8.84, p<0.001) and higher readmission rates (OR=6.07, 95%CI: 2.25-16.4, p<0.001).

Conclusions: Patients of COPD exacerbation have high prevalence of hyponatremia which requires early detection, routine screening, and monitoring for clinical deterioration.

Keywords: Chronic obstructive pulmonary disease, Hyponatremia, Length of stay, Prognosis

INTRODUCTION

Hyponatremia is one of the most common disorders in hospitalized patients, with a varied prevalence ranging from 8% to 51%.[1-7] It is a predictor of poor prognosis in various diseases including heart failure, and chronic kidney and liver disease. Chronic Obstructive Pulmonary Disease is also a significant cause of morbidity and mortality worldwide, with a global prevalence of 10.3%, with an estimated three million deaths, (approximately 5% of

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all global deaths) annually due to COPD. It is the fifth leading cause of poor health (2013), accounting for 74.4 Disability-Adjusted Life Years (2019) and is caused mostly by tobacco smoking (30-40%) and household air pollution in low and middle income countries like India.[8,9] Hyponatremia can occur in COPD patients due to water retention in the presence of underlying comorbidities such as heart and renal failure, or consequent to different drug treatments, adrenal insufficiency or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[4] Though COPD is characterized by airway inflammation, the increased oxidative stress and altered levels of circulating inflammatory mediators in the blood especially Interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)α, contribute to the systemic inflammation.[10] These inflammatory cytokines activate the AVP(ADH)-secreting neurons in the hypothalamus, thus leading to SIADH.[11] Hyponatremia is also an important electrolyte disturbance in heart failure patients, with a prevalence of 11-27%, and it can occur due to SIADH due to low peripheral perfusion, and cardiac output, increased thirst secondary to RAAS activation, or due to diuretic medications.[12] Most patients of COPD have associated cardiac disease, including heart failure to the tune of 20-70%, pulmonary hypertension, and they would be on medications such as Angiotensin-converting enzyme inhibitors (ACEi), and loop diuretics, both of which may contribute to hyponatremia.[8,13] Thus cardiac conditions such as acute heart failure may act as a confounder to the hyponatremia due to COPD alone. A recent study demonstrated that smoking status (ex-smoking), the rate of community acquired pneumonia, anion gap, erythrocyte sedimentation rate, and serum magnesium were independently associated with hyponatremia in COPD exacerbation.[14] Previous studies have shown that hyponatremia is a predictor of poor prognosis in COPD, and post discharge, a new episode of COPD exacerbation within 30 days is seen in more than 20% of patients. However, studies which determine the prevalence and clinical progress of patients with hyponatremia with acute exacerbation of COPD, and those which examine hyponatremia and hospital readmission rates are rather lacking.[3]

The objectives of this study were to determine the prevalence of hyponatremia in patients hospitalized for acute COPD exacerbations, compare hospital length of stay, clinical outcomes (including ventilatory support and readmissions), and laboratory parameters between hyponatremic and normonatremic groups, and to assess the associations between the severity grades of hyponatremia and clinical outcomes.

MATERIALS AND METHODS

A retrospective observational study was carried out among 200 patients admitted and discharged with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD), in the Department of Respiratory Medicine, Goa Medical College, after obtaining permission from the Institutional Ethics Committee (Approval no. GMCIEC/2024/366 dated 16/12/2024). The confidentiality of the collected data was maintained using codes to identify participants. The sample size was calculated the StatCalc tool from the Epi Info™ software. For a confidence level of 95%, minimum sample size was calculated to be 142, accounting for the global prevalence of COPD of 10.3%.[8] Patients of COPD were defined as per the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) criteria (post-bronchodilator ratio of FEV1/FVC <0.7).[8] Data over a period of three months, from October to December 2024, was collected from the IP case papers stored in the Medical Records Department. Baseline demographic details like age, sex, smoking history (past and/or present smoker and non-smoker), history of biomass exposure was collected. History of comorbidities like diabetes mellitus (DM), hypertension, pulmonary artery hypertension (PAH), and ischaemic heart disease (IHD) was also recorded. Patient baseline treatment was identified, including hyponatremia-inducing drugs, such as loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), anti-depressants and anti-psychotics.

On admission, clinical and laboratory investigations were obtained such as whether chest radiograph showed the presence of pneumonia, arterial blood gas analysis at admission [pH, carbon dioxide (pCO2), and bicarbonate (cHCO3) values], total white blood cell (WBC) count, percentage of neutrophils, serum urea, creatinine, and serum sodium, potassium and albumin levels. Presence of a hospital acquired infection which manifested 48 hours after admission during the course of stay in the hospital was also recorded. Duration of hospital stay was recorded, and patients with prolonged stay were identified as those with a stay greater than the median stay of the study population (in our study 8 days).[5] Outcome parameters, i.e. re-admission within one month, and use of long-term oxygen therapy (LTOT) was recorded. Poor progress was defined as follows: prolonged stay (>8 days), or readmission within one month of previous hospitalization.

Patients with hyponatremia (normal sodium levels defined as 136-146 mmol/L, as per the institutional laboratory [MSD Manual Professional Version] [15]) were also classified into grades, viz. mild hyponatremia [130 ≤ , < 136(mmol/L)], moderate hyponatremia [125 ≤ , < 130 (mmol/L)], severe hyponatremia [< 125 (mmol/L)] [13]. Patients were considered to have hyponatremia if serum sodium levels were below 136 mmol/L in at least one of the tests performed from admission to hospital discharge, i.e. the lowest value of serum sodium during hospitalization was considered.

Patients with chronic kidney disease, those on maintenance hemodialysis, chronic liver disease, those with concomitant cardiac events such as acute myocardial infarction and acute left ventricular failure, and patients of hypernatremia, defined as serum sodium levels above 146 mmol/L [5], were excluded from the analysis to avoid confounding factors between the above comorbidities and probable longer duration of hospital stay among these patients. Patients who expired were also not considered in the analysis, due to numerous factors, other than hyponatremia which may have led to death.

The data obtained through statistical analysis are expressed as mean values ± standard deviation (SD) in continuous variables, and as frequencies and percentages in categorical variables. Continuous variables were compared using the independent t test; for categorical variables, the chi-square test was used. Grades of hyponatremia were also compared with the laboratory parameters using One Way Anova and Posthoc tukey test. Multivariable logistic regression was also used to adjust for confounders. Poor prognosis (stay >8 days or readmission within one month) was taken as the dependent variable, and the parameters like age, sex, presence of comorbidities like DM, PAH, IHD, presence of pneumonia at admission, occurrence of HAI during stay, presence of hyponatremia and hypoalbuminemia were taken as the independent variables. Odds ratios with 95% CI were calculated. Variables associated with p <0.05 were considered statistically significant. All analyses were completed with SPSS 20.0.

RESULTS

In the study, 200 patients were enrolled; 112 cases (56% of 200 patients) of hyponatremia were recorded, 64 (57.1%) had mild, 32 (28.6%) had moderate, and 16 (14.3%) patients had severe hyponatremia (Table 1).

Table 1: Grades of Hyponatremia in the Study Population

Grades of Hyponatremia	Cases	With Normal Sodium Levels (N (%))	With Hyponatremia (N (%))
Normal (136 - 146 mmol/L)	88	88 (100)	0 (0)
Mild [130 ≤ , < 136(mmol/L)]	64	0 (0)	64 (57.1)
Moderate [125 ≤ , < 130 (mmol/L)]	32	0 (0)	32 (28.6)
Severe [< 125 (mmol/L)]	16	0 (0)	16 (14.3)

Table 2(a): Age distribution and duration of hospital stay of patients with and without hyponatremia

Variables	Normal Sodium Levels (n=88) (Mean ± SD)	With Hyponatremia (n=112) (Mean ± SD)	t Value	p Value
Age (years)	68.8±7.65	71.68±8.09	-2.562	**0.011**
Number of Days of Hospital Stay	7.24±2.85	11.77±7.26	-6.035	**<0.001**

General and Baseline characteristics of patients with and without hyponatremia [Table 2(a) and 2(b)]:

Patient mean age was 70.41 years (SD = 8). Age was higher in the hyponatremia group, and was statistically significant (p = 0.011). 138 (69%) patients were male. The distribution of hyponatremia was almost equal among females (35 out of 62; 56.45%) and males (77 out of 138; 55.80%). There was no statistically significant association between sex and hyponatremia presence (p = 0.931). Similarly, no significant relationships were observed between hyponatremia and smoking status (past/present) (p = 0.429), biomass exposure (p = 0.466), use of ACE inhibitors/ARBs (p = 0.755), antipsychotics/antidepressants (p = 0.274) and diuretics (p = 0.605). No significant associations were found with diabetes mellitus (p = 0.522), hypertension (p = 0.108), pulmonary artery hypertension (p = 0.742), ischaemic heart disease (p = 0.471), or chest x-ray findings at admission (p = 1.000). However, a strong significant association was noted between occurrence of hospital-acquired infections (HAI) and hyponatremia (χ^2=14.661, OR=18.9, 95%CI: 2.48-144, p<0.001). Patients with HAI had a significantly higher proportion of hyponatremia (20 out of 21; 95.23%) compared to those without HAI (92 out of 179; 51.39%). Significant associations were noted with ventilatory support. Patients requiring non-invasive ventilation (NIV) had a higher prevalence of hyponatremia (70 out of 105; 66.6%) compared to those who did not (42 out of 95; 44.21%) (χ^2=10.207, OR=2.52, 95%CI: 1.42-4.48, p = 0.001). Conversely, patients who did not require any ventilatory support had a higher proportion of normal sodium levels (51 out of 92; 55.43%) compared to those who required mechanical ventilation (37 out of 108; 34.26%) (χ^2=9.041, OR=2.39, 95%CI: 1.34-4.22, p=0.003. Invasive ventilation was not significantly associated (OR=0.387, 95%CI:0.0346-4.34, p=0.426).

Comparison of arterial blood gas parameters showed no significant differences in the pH (p = 0.619, pCO2 (p = 0.919), and bicarbonate (cHCO3) levels (p = 0.223) (table 3). Similarly, there was no statistical significance in total white blood cell count (p = 0.149), percentage of neutrophils (p = 0.23), serum urea (p = 0.171), serum creatinine (p = 0.995) and serum potassium levels (p=0.099) between the two groups. As expected, serum sodium would be lower in the hyponatremia group (138.88±2.22 vs 128.98±5.85 mmol/L; p < 0.001), since the classification was derived from these values, and the difference was statistically significant. Similarly, albumin levels were lower in the hyponatremia group (3.88±0.5 vs 3.66±0.57 g/dL; p = 0.006), and the difference was statistically significant (table 3).

Table 2(b): General, Baseline and Clinical characteristics of patients with and without hyponatremia

Categories	Total cases (n=200)	Sodium levels		Chi square	P value
		With Normal Sodium Levels (n=88 (44%))	With Hyponatremia (n=112 (56%))		
Sex					
Female	62	27 (43.54)	35 (56.45)	0.007	0.931
Male	138	61 (44.20)	77 (55.80)		
History of Smoking					
Non smoker	65	26 (40.0)	39 (60.0)	0.625	0.429
Smoker	135	62 (45.93)	73 (54.07)		
History of Biomass exposure					
Absent	117	54 (46.15)	63 (53.85)	0.531	0.466
Present	83	34 (40.96)	49 (59.04)		
Chest Radiograph shows Pneumonia at Admission					
Absent	175	77 (44.0)	98 (56.0)	0	1
Present	25	11 (44.0)	14 (56.0)		
Occurrence of HAI* during stay					
Absent	179	87 (48.6)	92 (51.4)	14.661	**<0.001**
Present	21	1 (4.76)	20 (95.23)		
Comorbidities					
Diabetes Mellitus					
Absent	120	55 (45.83)	65 (54.17)	0.409	0.522
Present	80	33 (41.25)	47 (58.75)		
Hypertension					
Absent	74	38 (51.35)	36 (48.65)	2.576	0.108
Present	126	50 (39.68)	76 (60.32)		
Pulmonary Artery Hypertension					
Absent	150	65 (43.33)	85 (56.67)	0.108	0.742
Present	50	23 (46.0)	27 (54.0)		
Ischaemic Heart Disease					
Absent	157	67 (42.68)	90 (57.32)	0.52	0.471
Present	43	21 (48.84)	22 (51.16)		
Use of Hyponatremia Causing Drugs					
ACEi†/ARBs‡					
No	164	73 (44.51)	91 (55.49)	0.097	0.755
Yes	36	15 (41.67)	21 (58.33)		
Anti-psychotics/Anti-depressants					
No	195	87 (44.62)	108 (55.38)	1.199	0.274
Yes	5	1 (20.0)	4 (80.0)		
Diuretics					
No	158	71 (44.94)	87 (55.06)	0.268	0.605
Yes	42	17 (40.48)	25 (59.52)		
Ventilatory Settings					
Non-Invasive Ventilation (NIV)					
No	95	53 (55.79)	42 (44.21)	10.207	**0.001**
Yes	105	35 (33.33)	70 (66.67)		
Invasive Ventilation					
No	197	86 (43.65)	111 (56.35)	0.635	0.426
Yes	3	2 (66.67)	1 (33.33)		
No ventilatory support needed					
Required PPV§	108	37 (34.26)	71 (65.74)	9.041	**0.003**
Did not require PPV	92	51 (55.43)	41 (44.57)		

* Hospital Acquired Infection; †Angiotensin Converting Enzyme Inhibitors; ‡ Angiotensin II Receptor Blockers; § Positive Pressure Ventilation.

Table 3: Comparison of Laboratory Investigations of Patients with and without Hyponatremia

Variables	Normal Sodium Levels (n=88) (Mean ± SD)	Hyponatremia Present (n=112) (Mean ± SD)	t Value	p Value
Arterial Blood Gas (ABG) at admission				
pH	7.35±0.08	7.35±0.1	0.499	0.619
pCO2 (mmHg)	55.02±21.45	55.33±21.28	-0.101	0.919
HCO3 (mmol/L)	30.42±13.34	28.63±6.95	1.222	0.223
Blood Investigations				
Total White Blood Cell Count	12143.07±4981.6	13273.75±6057.04	-1.448	0.149
Percentage of Neutrophils	83.05±9.01	84.56±8.72	-1.203	0.23
Serum Urea (mg/dL)	36.91±17.09	41.01±25.04	-1.374	0.171
Serum Creatinine (mg/dL)	0.95±0.33	0.95±0.35	0.006	0.995
Serum Sodium (mmol/L)	138.88±2.22	128.98±5.85	16.448	**<0.001**
Serum Potassium (mmol/L)	3.94±0.57	4.08±0.67	-1.658	0.099
Serum Albumin (g/dL)	3.88±0.5	3.66±0.57	2.798	**0.006**

Among outcome parameters, readmission within one month was significantly associated with hyponatremia (χ^2 = 15.202, OR=6.07, 95%CI: 2.25-16.4, p < 0.001), with 26.8% (30 out of 112) of hyponatremic patients getting readmitted compared to 5.7% (5 out of 88) among those with normal sodium levels. LTOT prescription at discharge was not significantly different (p = 1.000). Progress of patients showed a strong association (χ^2 = 27.603, OR=4.83, 95%CI: 2.64-8.84, p < 0.001), where poor progress was significantly more common among patients with hyponatremia (75 out of 101; 74.26%) compared to those with normal sodium levels (37 out of 99; 37.37%). Lastly, when the duration of stay between the two groups were compared, patients with hyponatremia had longer duration of hospital stay (7.24±2.85 vs 11.77±7.26 days; p < 0.001), and the difference was statistically significant (table 4).

One Way Anova Test was used to compare the grades of hyponatremia with the different parameters (table 5). Statistically significant difference was seen in the mean age among the different groups (p < 0.001), with posthoc analysis of mean age showing significant differences between normal and moderate hyponatremia, normal and severe hyponatremia, mild and moderate hyponatremia, mild and severe hyponatremia groups. Similarly, there was significant difference in the mean duration of hospital stay among the different groups (p < 0.001), with posthoc analysis showing significant differences between normal and mild hyponatremia, normal and moderate hyponatremia, normal and severe hyponatremia groups (table 6). Post hoc analysis of serum albumin showed statistically significant difference between normal sodium and mild hyponatremia groups. The other parameters such as pH, pCO2, bicarbonate levels, total white blood cell counts and neutrophil percentage, serum urea, creatinine, potassium levels did not show statistical significance, hence posthoc analysis was not required.

Table 4: Comparison of Outcome Parameters

Parameters	Cases	Sodium levels		Chi square	P value
		With Normal Sodium Levels (%)	With Hyponatremia (%)		
Total Cases	200	**88 (44%)**	**112 (56%)**		
Hospital Re- admission within one month					
Absent	165	83 (50.30)	82 (49.70)	15.202	**<0.001**
Present	35	5 (14.29)	30 (85.71)		
LTOT* prescribed at discharge					
No	175	77 (44.0)	98 (56.0)	0	1
Yes	25	11 (44.0)	14 (56.0)		
Progress (Median Duration of Stay = 8 Days)					
Good Progress (No readmission, stay ≤8 days)	99	62 (62.63)	37 (37.37)	27.603	**<0.001**
Poor Progress (stay >8 days or Readmission)	101	26 (25.74)	75 (74.26)		

*Long-Term Oxygen Therapy

Table 5: Comparison of the parameters with the grades of hyponatremia using One Way Anova Test

Variables	Normal Sodium Levels (136 - 146 mmol/L)	Mild Hyponatremia [130 ≤ , < 136(mmol/L)]	Moderate Hyponatremia [125 ≤ , < 130 (mmol/L)]	Severe Hyponatremia [< 125 (mmol/L)]	F /welch	P value
Age (years)	68.8±7.645	69.47±7.303	73.81±8.585	76.25±7.452	6.793	<0.001
Number of Days	7.24±2.849	11.14±7.178	13.16±7.846	11.5±6.398	12.041*	<0.001
pH	7.354±0.082	7.342±0.099	7.364±0.105	7.336±0.101	0.555	0.645
pCO2 (mmHg)	55.023±21.45	54.344±22.421	58.156±19.339	53.631±21.012	0.268	0.848
HCO3 (mmol/L)	30.417±13.337	27.836±6.288	31.163±7.144	26.756±8.077	1.46	0.227
Total WBC	12143.07±4981.595	13166.88±6210.377	12538.13±4975.657	15172.5±7299.765	1.062*	0.373
% of Neutrophils	83.045±9.01	83.602±9.521	85.816±6.923	85.9±8.616	1.068	0.364
Urea (mg/dL)	36.906±17.092	40.62±24.054	41.729±25.844	41.136±28.762	0.615*	0.609
Creatinine (mg/dL)	0.952±0.333	0.935±0.313	0.947±0.391	1.028±0.399	0.317	0.813
Sodium (mmol/L)	138.88±2.222	132.63±1.618	127.03±1.379	118.31±7.227	417.059*	<0.001
Potassium (mmol/L)	3.936±0.568	4.122±0.623	4.034±0.778	4.038±0.667	1.082	0.358
Albumin (g/dL)	3.881±0.501	3.692±0.595	3.591±0.529	3.698±0.605	2.863	0.038

Table 6: Post-hoc analysis using Tukey test

Variables	Normal-Mild (Diff (P value)	Normal-Moderate (Diff (P value)	Normal-Severe (Diff (P value)	Mild-Moderate (Diff (P value)	Mild-Severe (Diff (P value)	Moderate-Severe (Diff (P value)
Age	-0.673 (0.951)	-5.017* (0.01)	-7.455* (0.003)	-4.344* (0.047)	-6.781* (0.01)	-2.438 (0.728)
Number of Days	-3.902* (<0.001)	-5.918* (<0.001)	-4.261* (0.035)	-2.016 (0.37)	-0.359 (0.996)	1.656 (0.783)

Diff - Difference

Table 7: Multivariate Logistic Regression to Compare the Prognosis

Step 1a	B	S.E.	Wald	df	P value	Odds ratio	95% CI for Odds Ratio	
							Lower	Upper
Age	-.007	.023	.090	1	0.764	.993	.949	1.039
Sex	.001	.390	.000	1	0.998	1.001	.466	2.150
Diabetes Mellitus	.136	.378	.130	1	0.719	1.146	.547	2.402
PAH	.665	.410	2.624	1	0.105	1.944	.870	4.344
IHD	.117	.422	.077	1	0.781	1.124	.492	2.570
Chest Xray at admission showing pneumonia	.675	.549	1.511	1	0.219	1.964	.669	5.761
Occurrence of HAI during stay	20.713	7866.185	.000	1	0.998	989608861.043	.000	.
Presence of hyponatremia	1.316	.370	12.645	1	0.000	3.729	1.805	7.702
Presence of hypoalbuminemia	-2.697	.798	11.419	1	0.001	.067	.014	.322
No ventilatory support needed	-1.09	.364	8.973	1	0.003	.336	.165	.686
Constant	2.174	1.844	1.391	1	0.238	8.794		

a. Variable(s) entered on step 1: Age, Sex, Diabetes Mellitus, PAH, IHD, Chest Xray at admission showing pneumonia, Occurrence of HAI during stay, Presence of hyponatremia, Presence of hypoalbuminemia, No ventilatory support needed.
Dependent Variable: Poor Prognosis (stay>8 days or Readmission)

In multivariable analysis, lower risk of poor prognosis was independently associated with the absence of ventilatory support and with higher albumin levels. Specifically, patients who did not require ventilatory support had significantly reduced odds of poor prognosis (odds ratio = 0.336, 95% CI 0.165–0.686; p = 0.003). Compared with hypoalbuminemia (albumin <3.2 g/dL), normal albumin levels were strongly protective (odds ratio = 0.067, 95% CI 0.014–0.322; p = 0.001). Hyponatremia independently increased the odds of poor prognosis by approximately 3.7-fold (odds ratio = 3.729, 95% CI 1.805–7.702; p < 0.001) (table 7). Age, sex, DM, PAH, IHD, presence of pneumonia at admission were not statistically significant after adjustment. Occurrence of HAI during stay showed numerical instability with an extremely large standard error and an imprecise confidence bound (odds ratio ≈ 9.0×10^8; p = 0.998), consistent with sparse data or quasi-complete separation.

DISCUSSION

In our study, 56% of the study population had hyponatremia. Similar high percentage was reported by Hawkins RC et al[1], where among 43000 patients, 42.6% of acutely hospitalised patients had hyponatremia (serum sodium <136 mEq/L). Lindner G et al[2], reported 23% prevalence of hyponatremia among 102 COPD exacerbation patients presenting to the emergency department (ED). Similarly, Tokgöz Akyıl F et al[3], reported 22% of hyponatremia in 3274 COPD patients presenting to the ED. However, Chalela R et al[4] reported only 15.8% frequency of hyponatremia among 424 patients of COPD. García-Sanz MT et al[5], reported 10.8% of cases of hyponatremia among 602 patients. Mohan S et al[6], reported a prevalence of 3.87% of hyponatremia in COPD in the general population. Kwok WC et al[7], in a study of outpatient cases of COPD in the stable-state, reported a hyponatremia prevalence of 16.2% among 271 patients. The higher prevalence of hyponatremia in our study could be attributed to the selection of sample population; viz. older age of our study subjects, the smaller sample size, and more acutely ill patients being admitted in our hospital, which is a tertiary care centre, and lastly the higher cut-off for hyponatremia (defined as serum sodium <136 mEq/L), as per institutional laboratory. As previously opined by Chalela R et al[4], the wide range of such prevalence would be consequent to the differences of diagnostic criteria, and due to population differences.

In our study, patients with hyponatremia had higher mean age, with posthoc analysis showing significant difference in the age among the normal sodium group, and the different grades of hyponatremia, oldest age seen in the severe hyponatremia group. This corresponds to the findings by Mohan S et al[6], where prevalence of hyponatremia increased in age with both genders. However, the prevalence of hyponatremia was almost equal in both males and females in our study, which starkly contrasts with the findings by Mohan et al, where hyponatremia was more common in women than men (2.1% vs 1.3%). Hawkins RC et al[1], reported weak association of male sex with hyponatremia, implying that different studies show different prevalence.

In our study, patients of hyponatremia had significantly longer duration of hospital stay, with posthoc analysis showing maximum significance in the duration of hospital stay between the normal sodium levels and the different grades of hyponatremia. This is similar to the findings by Chalela R et al[4], who reported increased hospital stay as the severity of hyponatremia increased. There was also greater need for ventilatory support among hyponatraemic patients. We observed that COPD patients with hyponatremia were more likely to get readmitted within one month of discharge, and thus had significantly poorer progress compared to patients without hyponatremia. This finding corresponded to studies by Chalela R et al[4], García-Sanz MT et al[5], and Al Mawed S et al[16], who reported that a worse outcome is directly related to the severity of the electrolytic disorder. Kwok WC et al[7], also reported an increased rate of hospitalization for the hyponatraemic patients, even in the stable-state. In addition, the annual exacerbation frequency of COPD increased with the severity of hyponatremia (higher frequency in the moderate hyponatremia group). This was similar to the finding by Tokgöz Akyıl F et al[3], who reported an increased ED revisit rate in hyponatraemic patients. However, Lindner G et al[2], found no correlation between dysnatraemia and severity of infection, need for mechanical ventilation nor readmission to the hospital, which could be explained by the smaller absolute number of COPD exacerbation patients (n = 102). Other studies have suggested that hyponatremia is little more than a surrogate for an underlying pathophysiology rather than being an independently detrimental factor, as Mohan S et al[6] demonstrated that the presence of one or more comorbid conditions had a higher hyponatremia prevalence. Conversely, hyponatraemic patients had significantly higher blood pressure, lower protein, and more hospital stays in a year. This is in contrast to our study where there was no significant difference between comorbidities such as diabetes mellitus, hypertension, ischaemic heart disease and pulmonary hypertension between the two groups, which could probably be explained by our smaller sample size.

Mentes O et al[17], in a study of COPD patients admitted in the ICU, reported a "U-shaped" pattern of the relationship between sodium levels and the mortality, with the highest mortality in the hyponatremia (serum sodium <135 mEq/L) and the hypernatremia (serum sodium >145 mEq/L) subset of patients, i.e. abnormal sodium levels led to higher mortality. It was attributed to increased inflammation of sepsis, and acute kidney injury.

The presence of hypoalbuminemia is long known to be associated with prolonged hospital stay during COPD exacerbations, and increased mortality, which is similar to our study. In a meta-analysis by Zinellu E et al[18], serum albumin concentrations were reported to be significantly lower in COPD patients. COPD is a chronic inflammatory disorder of the airways and mediated by pro-inflammatory mediators like IL-1β, IL-6 and TNFα. [10] Park SJ et al[11], also reported that hyponatremia was probably augmented by the elevated levels of inflammatory cytokines, which in turn led to increased levels of circulating ADH (SIADH), thus leading to hypo-osmolar hyponatremia. Albumin is a negative acute-phase protein, which reduces in inflammatory conditions. The decrease may also be due to malnutrition, which is common in COPD patients. From our study, higher albumin levels were found to be a protective factor, probably explained by that subset of patients having a lower level of systemic inflammation. This would also reflect on them having higher sodium levels.

Presence of hospital acquired infections were also more common in hyponatraemic patients, probable causes being the longer duration of hospital stay in hyponatremia, greater chances of being on mechanical ventilation and altered sensorium leading to impaired ability to cough out secretions. However, due to the smaller sample size, multivariate analysis could not be performed. Surprisingly, though pneumonia is an important risk factor for hyponatremia [5], in our study the occurrence of pneumonia at admission was comparable between the two groups.

A meta-analysis by Corona G et al[19], reported a 60% decrease in overall mortality when the hyponatremia was corrected, compared to those with no improvement in their sodium levels. Combined with the fact that hyponatremia was associated with higher number of ED revisits in other studies [3,7], and a higher rate of readmission in our study, it is prudent for routine monitoring of serum sodium levels, and attempts for correction of the hyponatremia, as per the established clinical guidelines.

LIMITATIONS

The limitations of our study included smaller sample size, the cause of hyponatremia not being evaluated as it was an observational study, and the impact of treatment for hyponatremia not being assessed. The retrospective design limited the causality inference; potential unmeasured confounders like fluid intake were not ascertained. Being a single-centre, generalizability was reduced; requiring external validation. We also excluded patients of heart failure, which is one of the most common causes of COPD mortality, to avoid confounding factors. Furthermore, exclusion of deceased patients may also underestimate the prognostic impact of hyponatremia.

CONCLUSION

Hyponatremia affected 56% of patients. These patients were older, had a longer duration of hospital stay, a greater need for ventilatory support, and had a 5-fold increase in readmission within one month. Hyponatremia independently increased the odds of poor prognosis by approximately 3.7-fold. Therefore, it is important that presence of hyponatremia be detected early, and such patients monitored for clinical deterioration. We also need studies to determine the etiology of hyponatremia and the impact of treatment to normalize plasma sodium levels. We also need to implement protocols for early hyponatremia correction in COPD exacerbations.

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